

*AAMI Standards*

# Dialysis



**2015**



AAMI Standards  
and  
Recommended Practices

# Dialysis

**2015 Edition**

Includes documents developed under the auspices of the  
AAMI Renal Disease and Detoxification Committee



*Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

**ISBN 1-57020-546-9**

# Contents

## Dialysis (2015 Edition)

|                                                                                                                                                                                                                                | DESIGNATION       | PAGE |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------|
| Introduction.....                                                                                                                                                                                                              |                   | iv   |
| How to use this book.....                                                                                                                                                                                                      |                   | vii  |
| Glossary of equivalent standards.....                                                                                                                                                                                          |                   | viii |
| Guidance for the preparation and quality management of fluids for hemodialysis and related therapies .....<br>(American National Standard)                                                                                     | <b>23500</b>      | 1    |
| Quality of dialysis fluid for hemodialysis and related therapies .....<br>(American National Standard)                                                                                                                         | <b>11663</b>      | 99   |
| Concentrates for hemodialysis and related therapies.....<br>(American National Standard)                                                                                                                                       | <b>13958</b>      | 125  |
| Water for hemodialysis and related therapies .....<br>(American National Standard)                                                                                                                                             | <b>13959</b>      | 161  |
| Water treatment equipment for hemodialysis applications and related therapies .....<br>(American National Standard)                                                                                                            | <b>26722</b>      | 187  |
| Water testing methodologies .....<br>(AAMI Technical Information Report)                                                                                                                                                       | <b>TIR58</b>      | 231  |
| Ultrapure dialysate for hemodialysis and related therapies .....<br>(AAMI Technical Information Report)                                                                                                                        | <b>TIR43</b>      | 289  |
| Cardiovascular implants and extracorporeal systems — Hemodialyzers, hemodiafilters, hemofilters, and hemoconcentrators .....<br>(American National Standard)                                                                   | <b>8637</b>       | 317  |
| Cardiovascular implants and extracorporeal systems — Extracorporeal blood circuit for hemodialyzers, hemodiafilters, and hemofilters .....<br>(American National Standard)                                                     | <b>8638</b>       | 347  |
| Reprocessing of hemodialyzers .....<br>(American National Standard)                                                                                                                                                            | <b>RD47</b>       | 371  |
| Hemodialysis Medical electrical equipment, Part 2-16: Particular requirements for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment .....<br>(American National Standard) | <b>60601-2-16</b> | 437  |
| AAMI Standards Collections .....                                                                                                                                                                                               |                   | A.1  |

# Introduction

**Background.** The Association for the Advancement of Medical Instrumentation (AAMI), founded in 1967, is a unique alliance of engineering, medical, nursing, industry, and government professionals united by the common goal of increasing the understanding and beneficial use of medical instrumentation. AAMI's mission is to assist in the development, evaluation, acquisition, use, and maintenance of medical devices and instrumentation. The association fulfills this mission through continuing education conferences, certification of health care technical specialists, and the publication of technical documents and periodicals.

Accredited by the American National Standards Institute, AAMI is widely recognized as one of the principal voluntary standards organizations in the United States. The consensus standards and recommended practices developed by more than 100 AAMI technical committees, subcommittees, and working groups have earned both national and international acceptance in the health care field.

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**Objectives and Uses of AAMI Standards and Recommended Practices.** It is AAMI's view that standards and recommended practices contribute significantly to the advancement of medical instrumentation, provided that they are drafted with the objectives of increasing the safe and effective application of present-day technologies to patient care and of encouraging new technologies, and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a medical device recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms to the safety and performance criteria and sometimes to compare the performance of different products.

Some standards emphasize information (e.g., performance characteristics, instructions for use, warnings and precautions) that should be provided with the device to ensure its safe and effective use in the clinical environment. “Disclosure” recommendations of performance characteristics often entail the development of special test methods to facilitate uniformity in reporting, and reaching consensus on these tests can be a considerable part of a committee's work. Additionally, a drafting committee may determine that clinical concerns warrant the establishment of *minimum* safety and performance criteria. It must then provide referee tests and give the reasons for the criteria in the Rationale portion of the document.

A *recommended practice* contains guidelines for the use, care, or processing of a medical device or system. Without addressing device performance, *per se*, a recommended practice describes procedures and practices that will help ensure that a device is used safely and effectively, and that its performance is maintained.

Although a medical device standard is primarily directed to the manufacturer, it may also be of value to the potential user in prepurchase evaluations. Most *recommended practices* are written for health care professionals, but some offer guidance to industrial personnel on processing and evaluation techniques. Overall, standards and recommended practices can help manufacturers gain a better understanding of the setting in which a device will be used and can provide health care professionals a clearer picture of industrial practices, in addition to fulfilling their primary purpose.

All AAMI standards and recommended practices are *voluntary* and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary standards and recommended practices are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

Each AAMI standard and recommended practice reflects the collective expertise of health care professionals, representatives of industry, and government officials. The consensus recommendations of the drafting committees, which are intended to respond to clinical needs and to promote the well-being of the patient, are also reviewed nationally. Nevertheless, not all risks and conditions perceived by a committee are relevant to all situations, and for this reason, a standard or recommended practice should *never* replace responsible decision making.

Also, despite periodic review and revision (at least once every five years), a standard or recommended practice is a static document applied to a dynamic field. The reader must carefully review the reasons for a document's development and the rationale for its provisions to determine whether the document remains relevant in particular situations. Although observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be exercised in applying these criteria. No single source of information will serve to identify a particular product as "unsafe." A standard or recommended practice is truly useful only when relied on in conjunction with other sources of information and guidance, knowledge about specific situations, and a framework of professional experience.

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A TIR may be developed because it is more responsive to the underlying safety or performance issues than a standard or recommended practice or because achievement of consensus is difficult. Unlike a standard, a TIR permits the inclusion of differing viewpoints on technical issues, reflecting expert opinion, but not necessarily the formal consensus that characterizes a national standard. An AAMI TIR may be revised or withdrawn at any time. Readers are cautioned to ensure that they have considered any information that may be more recent than the TIR.

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**Document designations:** The official designation of each standard and technical information report appears in the upper right hand corner of the respective title pages and consists of three parts.

| Organization(s) that<br>approved the document | Document number | Year of U.S. <u>approval</u> |
|-----------------------------------------------|-----------------|------------------------------|
| ANSI/AAMI/IEC                                 | 60601-2-16      | 2012                         |

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**Page numbers:** The large page numbers that belong to the reference volume are found at the bottom center of the pages. These are the numbers referred to in the table of contents.

The page numbering of the individual documents has been retained at the bottom outside corners of the pages. References within documents to specific pages relate to these internal page numbers.



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# **Guidance for the preparation and quality management of fluids for hemodialysis and related therapies**

Approved 21 July 2014 by  
**Association for the Advancement of Medical Instrumentation**

Approved 15 August 2014 by  
**American National Standards Institute, Inc.**

**Abstract:** Addresses the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. Includes dialysis water used for the preparation of dialysis fluid and substitution fluid, dialysis water used for the preparation of concentrates at the user's facility, as well as concentrates and the final dialysis fluid and substitution fluid.

**Keywords:** concentrate, microbiological, monitoring, quality, system, validation, water

## AAMI Standard

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-550-7

# Contents

Page

|                                                                               |      |
|-------------------------------------------------------------------------------|------|
| Glossary of equivalent standards.....                                         | v    |
| US deviation to ISO 23500:2014.....                                           | vii  |
| Introduction .....                                                            | viii |
| 1 Scope .....                                                                 | 1    |
| 1.1 General .....                                                             | 1    |
| 1.2 Inclusions .....                                                          | 1    |
| 1.3 Exclusions .....                                                          | 1    |
| 2 Normative references .....                                                  | 1    |
| 3 Terms and definitions.....                                                  | 2    |
| 4 Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663 ..... | 9    |
| 4.1 Dialysis water .....                                                      | 10   |
| 4.2 Requirements for concentrate .....                                        | 12   |
| 4.3 Requirements for dialysis fluid .....                                     | 12   |
| 4.4 Record retention .....                                                    | 13   |
| 5 Critical aspects of system design .....                                     | 13   |
| 5.1 Technical aspects .....                                                   | 14   |
| 5.2 Microbiological aspects .....                                             | 14   |
| 6 Validation of system performance .....                                      | 15   |
| 6.1 Validation plan .....                                                     | 15   |
| 6.2 Installation and operational qualification .....                          | 16   |
| 6.3 Performance qualification.....                                            | 17   |
| 6.4 Routine monitoring and revalidation .....                                 | 17   |
| 7 Quality management.....                                                     | 18   |
| 7.1 General .....                                                             | 18   |
| 7.2 Monitoring of fluid quality.....                                          | 18   |
| 7.3 Monitoring of water treatment equipment .....                             | 19   |
| 7.4 Monitoring of dialysis water storage and distribution.....                | 23   |
| 7.5 Monitoring of concentrate preparation .....                               | 24   |
| 7.6 Monitoring of concentrate distribution .....                              | 25   |
| 7.7 Monitoring of dialysis fluid proportioning .....                          | 25   |
| 8 Strategies for microbiological control .....                                | 25   |
| 8.1 General .....                                                             | 25   |
| 8.2 Disinfection .....                                                        | 26   |
| 8.3 Microbiological monitoring methods .....                                  | 28   |

|           |                                                                                                                                  |           |
|-----------|----------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>9</b>  | <b>Environment</b> .....                                                                                                         | <b>31</b> |
| <b>10</b> | <b>Personnel</b> .....                                                                                                           | <b>31</b> |
|           | <b>Annex A (informative) Rationale for the development and provisions of this International Standard</b> .....                   | <b>32</b> |
|           | <b>Annex B (informative) Equipment</b> .....                                                                                     | <b>36</b> |
|           | <b>Annex C (informative) Monitoring guidelines for water treatment equipment, distribution systems, and dialysis fluid</b> ..... | <b>55</b> |
|           | <b>Annex D (informative) Strategies for microbiological control</b> .....                                                        | <b>62</b> |
|           | <b>Annex E (informative) Validation</b> .....                                                                                    | <b>67</b> |
|           | <b>Annex F (informative) Special considerations for home hemodialysis</b> .....                                                  | <b>70</b> |
|           | <b>Annex G (informative) Special considerations for acute hemodialysis</b> .....                                                 | <b>76</b> |
|           | <b>Bibliography</b> .....                                                                                                        | <b>81</b> |

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#### AAMI Renal Disease and Detoxification Committee

This American National Standard was developed by the AAMI Renal Disease and Detoxification Committee. Approval of the American National Standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the AAMI Renal Disease and Detoxification Committee had the following members:

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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NOTE—Participation by federal agency representatives in the development of this American National Standard does not constitute endorsement by the federal government or any of its agencies.

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## US deviation to ISO 23500:2014

The International Organization for Standardization (ISO) published ISO 23500:2014, *Guidance for the preparation and quality management of fluids for hemodialysis and related therapies* as a revision of ISO 23500:2011 on 2014-04-01. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for guidance on the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. The 2014 ISO revision editorially aligned ISO 23500 with the ISO dialysis fluid standards ISO 11663, ISO 13958, ISO 13959, and ISO 26722 which had been developed serially over several years.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

While considering the US adoption of ISO 23500:2014, the AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) approved a US deviation to the International Standard. ANSI/AAMI 23500:2014 deviates from ISO 23500:2014 in the following aspect:

The following sentence has been added to the end of Subclause 8.3.3.3, Cultivation conditions:

“See USP <1231> for guidance on adoption of alternative methods.”

Also, the following row has been added to Table 5 ,Cultivation techniques:

|                                                                                                                            |       |      |
|----------------------------------------------------------------------------------------------------------------------------|-------|------|
| Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE) | 35 °C | 48 h |
|----------------------------------------------------------------------------------------------------------------------------|-------|------|

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

## Introduction

This International Standard was developed by Working Group 5 of ISO/TC 150/SC 2. The Working Group's objective was to provide users with guidance for handling water and concentrates and for the production and monitoring of dialysis fluid used for hemodialysis. The need for such guidance is based on the critical role of dialysis fluid quality in providing safe and effective hemodialysis, and the recognition that day-to-day dialysis fluid quality is under the control of the healthcare professionals who deliver dialysis therapy.

Quality requirements for the water and concentrates used to prepare dialysis fluid, and for that dialysis fluid, are provided in ISO 13959, ISO 13958, and ISO 11663, respectively. This International Standard does not address clinical issues that might be associated with inappropriate usage of the water, dialysis water, concentrates, or dialysis fluid. Healthcare professionals involved in the provision of treatment for kidney failure should make the final decision regarding the applications with which these fluids are used, for example, hemodialysis, hemodiafiltration, high-flux hemodialysis, and the reprocessing of dialyzers, and need to be aware of the issues that the use of inappropriate fluid quality raises in each of the therapies.

The equipment used in the various stages of dialysis fluid preparation is generally obtained from specialized vendors. Dialysis practitioners are generally responsible for maintaining that equipment following its installation. Therefore, this International Standard provides guidance on monitoring and maintenance of the equipment to ensure that dialysis fluid quality is acceptable at all times. At various places throughout this International Standard, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In those instances in which the equipment is not obtained from a specialized vendor, it is the responsibility of the user to validate the performance of the equipment in the hemodialysis setting and to ensure that appropriate operating and maintenance manuals are available. Annex B provides a general description of the system components that are used for water treatment, concentrate, and dialysis fluid preparation at a dialysis facility. These descriptions are intended to provide the user with a basis for understanding why certain equipment might be required and how it should be configured; they are not intended as detailed design standards. Requirements for water treatment equipment are provided in ISO 26722.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2:2004. For the purposes of this International standard, the auxiliary verb:

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard;
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard;
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.

This International Standard reflects the conscientious efforts of healthcare professionals, patients, and medical device manufacturers to develop recommendations for handling water and concentrates and for the production and monitoring of dialysis fluid for hemodialysis. This International Standard is directed towards the healthcare professionals involved in the management or routine care of hemodialysis patients and responsible for the quality of dialysis fluid. The recommendations contained in this International Standard might not be applicable in all circumstances and they are not intended for regulatory application.

The guidance provided by this International Standard should help protect hemodialysis patients from adverse effects arising from known chemical and microbial contaminants that might be found in improperly prepared dialysis fluid. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysis fluid is correctly formulated and meets the requirements of all applicable quality standards.

The concepts incorporated in this International Standard should not be considered inflexible or static. The recommendations presented here should be reviewed periodically in order to assimilate increased understanding of the role of dialysis fluid purity in patient outcomes and technological developments.

# Guidance for the preparation and quality management of fluids for hemodialysis and related therapies

## 1 Scope

### 1.1 General

This International Standard provides dialysis practitioners with guidance on the preparation of dialysis fluid for hemodialysis and related therapies and substitution fluid for use in online therapies, such as hemodiafiltration and hemofiltration. As such, this International Standard functions as a recommended practice.

### 1.2 Inclusions

This International Standard addresses the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. For the purposes of this International Standard, the dialysis fluid includes dialysis water (see 3.18 for definition) used for the preparation of dialysis fluid and substitution fluid, dialysis water used for the preparation of concentrates at the user's facility, as well as concentrates and the final dialysis fluid and substitution fluid.

The scope of this International Standard includes

- a) the quality management of equipment used to treat and distribute water used for the preparation of dialysis fluid and substitution fluid, from the point at which municipal water enters the dialysis facility to the point at which the final dialysis fluid enters the dialyzer or the point at which substitution fluid is infused,
- b) equipment used to prepare concentrate from powder or other highly concentrated media at a dialysis facility, and
- c) preparation of the final dialysis fluid or substitution fluid from dialysis water and concentrates.

**NOTE** Because water used to prepare dialysis fluid is commonly prepared and distributed using the same equipment as the water used to reprocess dialyzers, water used to reprocess dialyzers is also covered by this International Standard.

### 1.3 Exclusions

This International Standard does not apply to sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use prepackaged solutions, and systems and solutions for peritoneal dialysis.

## 2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11663:2014, *Quality of dialysis fluid for hemodialysis and related therapies*

ISO 13958:2014, *Concentrates for hemodialysis and related therapies*

ISO 13959:2014, *Water for hemodialysis and related therapies*

ISO 26722:2014, *Water treatment equipment for hemodialysis applications and related therapies*

### **3 Terms and definitions**

For the purposes of this document, the following terms and definitions apply.

#### **3.1**

##### **acetate concentrate**

concentrated solution of salts containing acetate, which, when diluted with dialysis water, yields bicarbonate-free dialysis fluid for use in dialysis

Note 1 to entry: Acetate concentrate may contain glucose.

Note 2 to entry: Sodium acetate is used to provide buffer in place of sodium bicarbonate.

Note 3 to entry: Acetate concentrate is used as a single concentrate.

#### **3.2**

##### **acid concentrate**

##### **A-concentrate**

acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term “acid” refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate may contain glucose.

Note 3 to entry: Acid concentrate may be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

#### **3.3**

##### **action level**

concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

#### **3.4**

##### **additive**

##### **spike**

small amount of a single chemical that, when added to the concentrate, will increase the concentration of a single existing chemical by a value labelled on the additive packaging

#### **3.5**

##### **bicarbonate concentrate**

##### **B-concentrate**

concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate may be in the form of a liquid or a dry powder.

Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

### **3.6**

#### **biofilm**

microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

Note 1 to entry: The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

### **3.7**

#### **bulk delivery**

delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery includes containers such as drums, which can be pumped into a storage tank maintained at the user's facility. Alternatively, the drums can be left at the facility and used to fill transfer containers to transfer the concentrate to the dialysis machines. Bulk delivery can also include large containers for direct connection to a central concentrate supply system.

Note 2 to entry: Bulk delivery also includes dry powder concentrates intended to be used with an appropriate concentrate mixer.

### **3.8**

#### **central concentrate system**

system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

### **3.9**

#### **central dialysis fluid delivery system**

system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

### **3.10**

#### **chlorine, combined**

chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

### **3.11**

#### **chlorine, free**

chlorine present in water as dissolved molecular chlorine ( $\text{Cl}_2$ ), hypochlorous acid ( $\text{HOCl}$ ), and hypochlorite ion ( $\text{OCl}^-$ )

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

### **3.12**

#### **chlorine, total**

sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

### **3.13**

#### **colony-forming unit**

#### **CFU**

measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

Note 1 to entry: Colonies can also form from groups of organisms when they occur in aggregates.

### **3.14**

#### **concentrate generator**

system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyzer.

### **3.15**

#### **device**

individual dialysis water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term “component” as used by the US Food and Drug Administration (see Reference [169]).

### **3.16**

#### **dialysis fluid**

#### **dialysate**

#### **dialysis solution**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis

Note 1 to entry: The term “dialysis fluid” is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyzer by the dialysis fluid delivery system. Such phrases as “dialysate” or “dialysis solution” are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyzer is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyzer is referred to as “spent dialysis fluid”.

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as hemodiafiltration and hemofiltration.

### **3.17**

#### **dialysis fluid delivery system**

device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; circulates the dialysis fluid through the dialyzer; monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow, and blood leaks; and, prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system may be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

### **3.18**

#### **dialysis water**

water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in hemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialyzers, preparation of concentrates and preparation of substitution fluid for online convective therapies

### **3.19**

#### **disinfection**

destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

### **3.20**

#### **empty-bed contact time**

##### **EBCT**

time taken by a fluid to pass through an empty volume equal to the volume of a particle bed

Note 1 to entry: EBCT (min) is calculated from the following formula:

$$EBCT = V/Q$$

where

$V$  is the volume of the particle bed, in cubic metres ( $m^3$ );

$Q$  is the flow rate of water through the bed, in cubic metres per minute ( $m^3/min$ ).

Note 2 to entry: EBCT is used as an indirect measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of particles.

### **3.21**

#### **endotoxin**

major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by

fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. [See also *pyrogen* (3.36)].

### **3.22**

#### **endotoxin-retentive filter**

##### **ETRF**

membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

Note 1 to entry: The performance of an endotoxin-retentive filter is usually expressed as the logarithmic reduction value (LRV), defined as  $\log_{10}(\text{inlet concentration})/(\text{outlet concentration})$ .

Note 2 to entry: Endotoxin-retentive filters may be configured in a cross-flow or dead-end mode. Some endotoxin-retentive filters also remove endotoxins by adsorption.

### **3.23**

#### **endotoxin units**

##### **EU**

units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

### **3.24**

#### **feed water**

water supplied to a water treatment system or to an individual component of a water treatment system

### **3.25**

#### **germicide**

agent that kills microorganisms

### **3.26**

#### **hemodiafiltration**

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyzer (predilution hemodiafiltration), after the dialyzer (postdilution hemodiafiltration), or a combination of the two (mixed dilution hemodiafiltration).

### **3.27**

#### **hemodialysis**

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.



### 3.28

#### **hemofiltration**

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the hemofilter (predilution hemofiltration), after the hemofilter (postdilution hemofiltration), or a combination of the two (mixed dilution hemofiltration).

Note 2 to entry: There is no dialysis fluid stream in hemofiltration.

### 3.29

#### **heterotrophic**

not self-sustaining, i.e. a type of nutrition in which organisms derive energy from the oxidation of organic compounds by either consumption or absorption of other organisms

### 3.30

#### ***Limulus* amoebocyte lysate test**

##### **LAL test**

assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachyplesus tridentatus*, may also be used to detect endotoxin.

### 3.31

#### **manufacturer**

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

### 3.32

#### **microbiological contamination**

contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms, such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

### 3.33

#### **nonpyrogenic**

not eliciting a pyrogen reaction

Note 1 to entry: Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

Note 2 to entry: The volume of fluid administered should not exceed the volume that would result in a total dose of endotoxin of  $\geq 5$  EU/kg/h.

Note 3 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 4 to entry: The commonly used gel clot method has a sensitivity limit of 0.03 EU/ml.

### **3.34**

#### **product water**

water produced by a water treatment system or by an individual device thereof

### **3.35**

#### **proportioning system**

apparatus that proportions dialysis water and hemodialysis concentrate to prepare dialysis fluid

### **3.36**

#### **pyrogen**

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.21)].

### **3.37**

#### **sodium hypochlorite**

chemical used for disinfection of hemodialysis systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and javel. These solutions are used for disinfection at concentrations recommended by equipment manufacturers.

### **3.38**

#### **source water**

water entering a dialysis facility from an external supplier, such as a municipal water supply

Note 1 to entry: Source water is sometimes referred to as feed water.

### **3.39**

#### **sterile**

free from viable microorganisms

Note 1 to entry: "Sterile" can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of  $10^{-6}$ , i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, "sterile" can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

### **3.40**

#### **storage tank**

tank at the user's facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

### **3.41**

#### **substitution fluid**

fluid used in hemofiltration and hemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

### **3.42**

#### **total dissolved solids**

##### **TDS**

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of  $\text{CaCO}_3$ , NaCl, KCl, or 442 equivalents, in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

### **3.43**

#### **ultrapure dialysis fluid**

highly purified dialysis fluid that can be used in place of conventional dialysis fluid

Note 1 to entry: A widely accepted specification of ultrapure dialysis fluid is <0.1 CFU/ml and <0.03 EU/ml.

### **3.44**

#### **user**

physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

### **3.45**

#### **validation**

process of documenting that the dialysis water treatment and dialysis fluid production systems, when installed and operated according to the manufacturer's recommendations, consistently produce dialysis water or dialysis fluid meeting the stipulated quality levels

Note 1 to entry: In this context, validation also includes demonstrating that the system is "fit for purpose".

Note 2 to entry: The term "verification" is also used and refers to demonstrating that the system complies with applicable regulations, specifications, or other conditions. A dialysis facility might be interested in both validation and verification of its fluid production systems.

### **3.46**

#### **water treatment system**

collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water for dialysis meeting the requirements of ISO 13959 for hemodialysis applications and deliver it to the point of use

## **4 Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663**

The quality requirements set forth in this clause are reproduced from the 2014 editions of ISO 13958, ISO 13959, and ISO 11663. The latest editions of these International Standards should be consulted to ascertain if there have been any changes to those requirements before implementing the recommendations of this International Standard.

## 4.1 Dialysis water

### 4.1.1 General

The requirements contained in this clause apply to dialysis water at its point of use. As such, these requirements apply to the water treatment system as a whole and not to each of the devices that make up the system. However, collectively, the individual devices shall produce water that, at a minimum, meets the requirements of this clause.

### 4.1.2 Chemical contaminants in dialysis water

Dialysis water shall not contain substances at levels greater than those listed in ISO 13959 (see Tables 1 and 2). The manufacturer or supplier of a complete water treatment system should recommend a system that is capable of meeting these requirements based on a feed water analysis. The system design should reflect possible seasonal variations in feed-water quality. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of ISO 13959 at the time of installation.

**NOTE** The maximum allowable levels of contaminants listed in Tables 1 and 2 include the anticipated uncertainty associated with the analytical methodologies listed in Table 3 of ISO 13959. Other analytical methods can be used, provided that such methods have been appropriately validated and compared to the cited methods.

Following installation of a water treatment, storage, and distribution system, the user is responsible for regular monitoring of the levels of chemical contaminants in the dialysis water and for complying with the requirements of this International Standard.

Tables 1 and 2 are reproduced from ISO 13959:2014.

**Table 1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water<sup>ab</sup>**

| Contaminant                                                                                                  | Maximum concentration (mg/l) <sup>c</sup> |
|--------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Contaminants with documented toxicity in hemodialysis</b>                                                 |                                           |
| Aluminium                                                                                                    | 0.01                                      |
| Total chlorine                                                                                               | 0.1                                       |
| Copper                                                                                                       | 0.1                                       |
| Fluoride                                                                                                     | 0.2                                       |
| Lead                                                                                                         | 0.005                                     |
| Nitrate (as N)                                                                                               | 2                                         |
| Sulfate                                                                                                      | 100                                       |
| Zinc                                                                                                         | 0.1                                       |
| <b>Electrolytes normally included in dialysis fluid</b>                                                      |                                           |
| Calcium                                                                                                      | 2 (0.05 mmol/l)                           |
| Magnesium                                                                                                    | 4 (0.15 mmol/l)                           |
| Potassium                                                                                                    | 8 (0.2 mmol/l)                            |
| Sodium                                                                                                       | 70 (3.0 mmol/l)                           |
| <sup>a</sup> A dialysis facility's Medical Director has the ultimate responsibility for ensuring the quality |                                           |

| Contaminant                                                                                                                    | Maximum concentration (mg/l) <sup>c</sup> |
|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| of dialysis water.                                                                                                             |                                           |
| b The reader is cautioned to refer to the latest version of ISO 13959 to ensure that there have been no changes to this table. |                                           |
| c Unless otherwise noted.                                                                                                      |                                           |

**Table 2 — Maximum allowable levels of other trace elements in dialysis water<sup>a</sup>**

| Contaminant                                                                                                                                                    | Maximum concentration (mg/l) |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Antimony                                                                                                                                                       | 0.006                        |
| Arsenic                                                                                                                                                        | 0.005                        |
| Barium                                                                                                                                                         | 0.1                          |
| Beryllium                                                                                                                                                      | 0.000 4                      |
| Cadmium                                                                                                                                                        | 0.001                        |
| Chromium                                                                                                                                                       | 0.014                        |
| Mercury                                                                                                                                                        | 0.000 2                      |
| Selenium                                                                                                                                                       | 0.09                         |
| Silver                                                                                                                                                         | 0.005                        |
| Thallium                                                                                                                                                       | 0.002                        |
| <sup>a</sup> The reader is cautioned to refer to the latest version of ISO 13959 to ensure that no changes have been made to the maximum concentrations shown. |                              |

#### 4.1.3 Microbiological contaminants in dialysis water

The total viable microbial count and endotoxin concentration in dialysis water shall comply with the maximum allowable levels specified in ISO 13959 (see Table 3). Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on knowledge of the microbial dynamics of the system. Typically, the action level is set at 50 % of the maximum allowable level for bacteria and endotoxins. If a total viable microbial count or endotoxin concentration at or above the action level is observed in the dialysis water, corrective measures should be taken promptly to reduce the level. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of ISO 13959 at the time of installation.

Following installation of a water treatment, storage and distribution system, the user is responsible for regular monitoring of the microbiology of the system and for complying with the requirements of this International Standard, including those requirements related to action levels.

Table 3 is adapted from ISO 13959:2014.

**Table 3 — Maximum allowable levels for total viable microbial count (TVC) and endotoxins in dialysis water<sup>a</sup>**

| Contaminant                                                                                                                                                                                                                                                      | Maximum allowable level | Typical action level <sup>b</sup> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------------------------|
| TVC                                                                                                                                                                                                                                                              | <100 CFU/ml             | 50 CFU/ml                         |
| Endotoxin                                                                                                                                                                                                                                                        | <0.25 EU/ml             | 0.125 EU/ml                       |
| <sup>a</sup> The reader is cautioned to refer to the latest version of ISO 13959 to ensure that there have been no changes to the values presented in this table.<br><sup>b</sup> Typically set at 50 % of the maximum allowable level. Other values may be set. |                         |                                   |

## 4.2 Requirements for concentrate

### 4.2.1 Chemical and microbiological contaminants in concentrate

Concentrates used to prepare dialysis fluid shall comply with the quality requirements specified in ISO 13958.

Bicarbonate concentrate can grow bacteria and caution should be used to limit the bacterial levels in bicarbonate concentrate.

### 4.2.2 Water used to prepare concentrate

Water used to prepare concentrates at a dialysis facility shall meet the requirements of ISO 13959. Any concentrate prepared at a dialysis facility shall permit the dialysis machine to prepare dialysis fluid meeting the requirements of ISO 11663.

## 4.3 Requirements for dialysis fluid

### 4.3.1 General

The requirements contained in this clause apply to a sample of the dialysis fluid collected as close as practicable to the inlet to the dialyzer.

ISO 11663 defines three levels of dialysis fluid: standard dialysis fluid, ultrapure dialysis fluid, and online-prepared substitution fluid. Standard dialysis fluid is considered the minimum acceptable quality for routine hemodialysis. Ultrapure dialysis fluid is recommended for routine hemodialysis.

### 4.3.2 Microbiological requirements for standard dialysis fluid

The total viable microbial count and endotoxin concentration in standard dialysis fluid shall comply with the maximum allowable levels specified in ISO 11663 and reproduced in Table 4. Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on knowledge of the microbial dynamics of the system as specified in ISO 11663. Typically, the action level is set at 50 % of the maximum allowable level for total viable microbial count and endotoxins. If total viable microbial counts or endotoxin concentrations at or above the action levels are observed in the dialysis fluid, corrective measures, such as disinfection and retesting, should promptly be taken to reduce the levels.

Table 4 is adapted from ISO 11663:2014.

**Table 4 — Maximum allowable levels for total viable microbial count (TVC) and endotoxins in standard and ultrapure dialysis fluid<sup>a</sup>**

| Contaminant                                                                                                                                                                                                                              | Standard dialysis fluid |                           | Ultrapure dialysis fluid |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------------------------|--------------------------|
|                                                                                                                                                                                                                                          | Maximum allowable level | Action level <sup>b</sup> | Maximum allowable level  |
| TVC                                                                                                                                                                                                                                      | <100 CFU/ml             | 50 CFU/ml                 | <0.1 CFU/ml              |
| Endotoxin                                                                                                                                                                                                                                | <0.5 EU/ml              | 0.25 EU/ml                | <0.03 EU/ml              |
| <sup>a</sup> The reader is cautioned to refer to the latest version of ISO 11663 to ensure that there have been no changes to this table.<br><sup>b</sup> Typically set at 50 % of the maximum allowable level. Other values may be set. |                         |                           |                          |

### 4.3.3 Microbiological requirements for ultrapure dialysis fluid

The total viable microbial count and endotoxin concentration in ultrapure dialysis fluid shall comply with the maximum allowable levels specified in ISO 11663 and reproduced in Table 4. If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels into an acceptable range. The user is responsible for monitoring the dialysis fluid bacteriology of the system following installation.

**NOTE** Tests for bacterial growth and endotoxins are not required if the system is fitted with an endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires those tests in the instructions for use.

### 4.3.4 Microbiological requirements for online-prepared substitution fluid

The recommendations contained in this clause apply to substitution fluid as it enters the patient's blood.

This fluid shall be sterile and nonpyrogenic according to the recommendations of ISO 11663.

Substitution fluid for convective therapies, such as hemodiafiltration and hemofiltration, or for priming the extracorporeal circuit or bolus administration of fluid during a treatment, may be produced online by a process of ultrafiltration with endotoxin-retentive filters. This online process shall be validated by the manufacturer to produce substitution fluid that is sterile and nonpyrogenic.

The user should follow the manufacturer's instructions for the installation, use, maintenance, and monitoring of the validated system. The function of the validated system should be verified according to the manufacturer's instructions at the time of installation and confirmed by the user with regular monitoring. Monitoring shall include confirmation that the dialysis water and concentrates used by the validated system to prepare the substitution fluid continue to meet the specifications of ISO 13958 and ISO 13959.

## 4.4 Record retention

Records of installation, monitoring, maintenance, and disinfection of the water treatment and dialysis fluid preparation systems, medical observation, and personnel education shall be kept according to national regulations. In the absence of national regulations, it is recommended that these records should be retained for the same period as clinical records.

## 5 Critical aspects of system design

The preparation of dialysis fluid, from inlet municipal water and acquisition of concentrates to discharge of spent dialysis fluid into the drain system, involves numerous components that, together, form a dialysis fluid handling

system. The technical features of the water treatment component of that system should be based on the criteria listed in ISO 26722, with special regard to the aspects related to the dialysis water quality, the optimal use of resources (e.g. water and energy), and the operations of disinfection and maintenance. Concentrates may be obtained from a supplier in a ready-to-use form or prepared at the dialysis facility from dialysis water and prepackaged salts. The technical features of the concentrate preparation and distribution component of the system should be based on the criteria listed in ISO 13958.

## 5.1 Technical aspects

In accordance with the requirements listed in ISO 26722, the system design should specifically address the following points:

- compliance with mandatory local regulations;
- capability to operate with the available feed-water supply and over the anticipated range of variation in the quality of that water, to include both variations arising from changes in the quality of the source water used by the provider of the feed water and variations introduced by the provider in treating that water;

NOTE Source water is assumed to be potable water.

- provision for adequate process monitoring;
- service and maintenance.

If the entire fluid handling system is not obtained from a single supplier, then the user becomes responsible for ensuring that the separate parts of the system are compatible. For example, it is important that the pretreatment section of the water treatment system be designed to supply the main purification device (usually reverse osmosis) with feed water meeting the specifications for that device, i.e. pressure, temperature, flow, and quality (for example, elimination of chemicals which cannot be effectively removed by the main purification device or that could damage it).

The choice of the water treatment system should consider the following aspects concerning the feed-water supply:

- full chemical analysis of the feed water and silt density index (SDI);
- microbiological load, which could lead to the introduction of an additional chlorination step;
- flow rates, pressure, and temperature;
- the treatment techniques used by the provider of the feed water (for example, addition of chloramine, fluoride, aluminium sulfate, etc.). Because treatment techniques can change, ongoing communication with the provider of the feed water is recommended.

## 5.2 Microbiological aspects

The required microbiological quality of the dialysis water and dialysis fluid is achieved by paying adequate attention to the entire water treatment and dialysis fluid preparation cascade. For this reason, the system should be designed to reduce, as much as possible, potential sources of contamination and to allow effective monitoring and disinfection of the critical parts.

When applicable, equipment should be operated on a regular basis to reduce stagnation.

The distribution system should be designed to maintain dialysis water or dialysis fluid quality and, therefore, should fulfil the following criteria:



- the distribution loop should be of the minimum length, and avoid multiple branches and dead ends;
- materials shall be compatible with the different operational conditions (i.e. supply, disinfection, cleaning);
- there should be no release of chemicals and nutrients for microorganisms;
- temperature increases or exposure to sunlight should be minimized.

Suitable sampling ports should be available at the start and the end of the distribution loop.

## 6 Validation of system performance

The validation process should provide documentary evidence that the system will consistently produce dialysis water, dialysis fluid, or substitution fluid meeting the quality requirements of ISO 13959 or ISO 11663. An example of the validation process is presented schematically in Figure 1.

NOTE The rationale for the validation process is given in Annex E.

The validation process consists of the following:

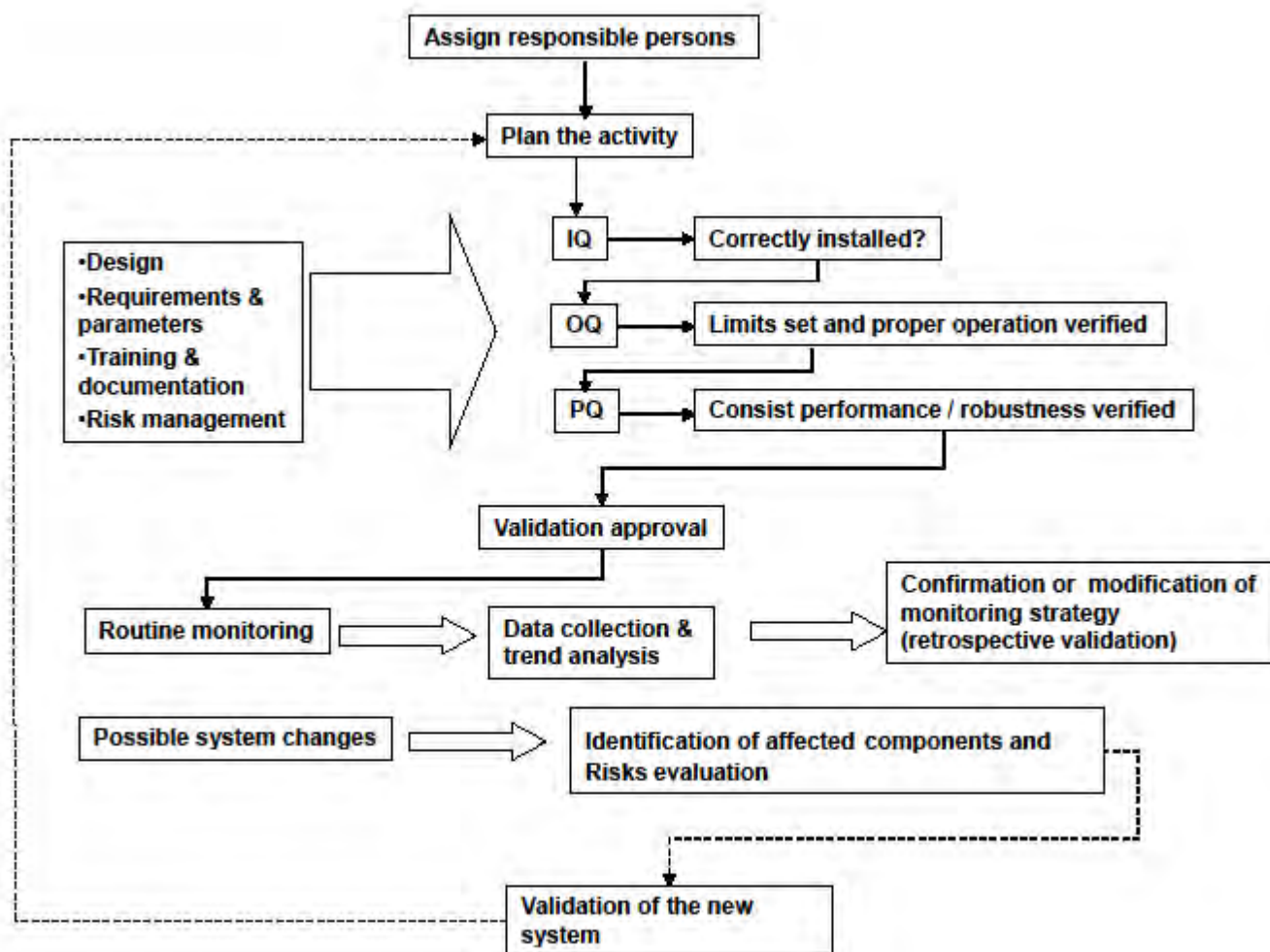
- assignment of operational responsibility;
- assignment of clinical responsibility;
- assignment of legal responsibility;
- validation plan;
- installation and operational qualification;
- performance qualification;
- revalidation as it relates to routine monitoring.

### 6.1 Validation plan

The validation plan should be a clear and concise document covering the following:

- description of relevant systems, equipment, or processes;
- current status of those systems, equipment, or processes;
- procedures for making changes to systems, equipment, or processes;
- planning and scheduling, including the addition of new systems, activities driven by change, and periodic review.

The validation plan should be approved by the person at the dialysis facility with overall responsibility for dialysis fluids.



#### Key

IQ installation qualification

OQ operational qualification

PQ performance qualification

**Figure 1—Example of a validation process for a fluid preparation and distribution system**

## 6.2 Installation and operational qualification

The installation qualification defines and provides the documented proof that the system is installed in accordance with the approved plans and the manufacturer's technical requirements and specifications. Full system documentation should be available on completion of this procedure, including system flow diagrams and layout, log books, and operator's manuals. The installation should be carried out by qualified personnel in line with the manufacturer's recommendations.

The installation qualification should be followed by an operational qualification that verifies the proper operation of the system, including range of operation, set point and interlock testing, and functional testing, and that compares the system performance with the functional specifications of the system. On completion of this phase, the following information should be available:

- test records;
- set-up record;
- calibration schedule;
- sampling procedures;
- maintenance (e.g. disinfection, filter changes, etc.) and monitoring (e.g. conductivity, microbiological analysis) plans;
- record of operator(s) training.

### **6.3 Performance qualification**

The performance qualification should demonstrate the consistency and robustness of the system under local operational conditions. During this phase, information about system behaviour should be collected and action levels should be reviewed or defined. On completion of the performance qualification, the following information should be available:

- test records;
- chemical and microbial analyses;
- key performance indicators [for example, pretreatment efficiency, reverse osmosis (RO) recovery/rejection rate, etc.];
- (initial) trend analysis.

For newly installed systems, the person with overall clinical responsibility for dialysis (possibly supported by technical experts) may authorize use of dialysis fluid for patient treatments once chemical and microbiological analyses are available that show full compliance with the quality requirements of Clause 4, the manufacturer's specifications, and any applicable regulatory requirements.

### **6.4 Routine monitoring and revalidation**

This subclause describes the monitoring activities to be conducted as part of the quality control and quality assurance process.

Routine monitoring should begin following the performance qualification (see 6.3) to ensure ongoing compliance with the dialysis water and dialysis fluid quality requirements set forth in Clause 4. Trend analysis of monitoring data should be used to provide advanced information on system performance, thus enabling a preventive rather than a reactive approach to system maintenance.

Monitoring is achieved with online and offline measurements. Online monitoring of suitable parameters (such as conductivity) provides immediate identification of deviations from normal operating conditions and can identify potential problems in their early stages, and could trigger specific additional offline measurements. A purely time-

based offline sampling regime has inherent limitations for the monitoring of a continuous production process since deviations can occur between samples.

Fluid sampling for microbiological testing should be performed no sooner than 24 h after disinfection to avoid false-negative results. When disinfection is performed on consecutive days, or more frequently, samples should be taken before, and as close as practicable to, a disinfection procedure.

Guidance on parameters that should be monitored is provided in Annex C, Table C.1.

A revalidation should be performed under the following circumstances:

- modification of the maintenance and monitoring plans;
- modification of the system;
- changes in the requirements for dialysis fluid quality.

In the absence of system modification, regular revalidation is still required. This revalidation consists of a retrospective assessment of the routine results of the previous year (no additional tests are required for the revalidation process). The purpose of this review is to prove the adequacy of the maintenance and monitoring plan under the local operating conditions. The revalidation should include a report submitted to, and approved by, the person with overall clinical responsibility for dialysis.

## **7 Quality management**

### **7.1 General**

Quality control and quality assurance procedures should be established to ensure ongoing conformance to policies and procedures regarding fluid quality. This clause defines some of the monitoring activities to be performed at the dialysis facility as part of the quality assurance process. The test methods described in 7.2 do not represent the only acceptable methods available but are intended to provide examples of acceptable methods. The frequency of monitoring is generally recommended by the equipment manufacturer or by local organizations that oversee dialysis facilities. In the absence of a manufacturer's recommendations, guidance on tests to include in a quality assurance monitoring programme can be found in Annex C. This guidance can also be used to supplement the manufacturer's recommendations.

The clinic should establish communications with the feed-water supplier so that the feed-water supplier is aware that the feed water is used for the production of dialysis fluid [i.e. for life-saving treatment on end-stage renal disease (ESRD) patients] and request the establishment of formal procedures to provide the clinic with correct and timely information about any change in the supplied water quality (for example, change of source or type of raw water treatment) or delivery (i.e. water supply interruptions). If such procedures cannot be established, additional monitoring of feed-water quality could be required.

### **7.2 Monitoring of fluid quality**

#### **7.2.1 Monitoring of dialysis water quality**

Dialysis water quality should be monitored on a regular basis for the chemical and microbiological contaminants listed in 4.1.2 and 4.1.3. The monitoring schedule should be based on the results of the system validation. For an established water treatment system operating under stable conditions, chemical contaminants in dialysis water should be monitored at least annually. The exception is for total chlorine, which should be monitored as described in 7.3.5.

Methods for monitoring chemical and microbiological contaminants in dialysis water are given in ISO 13959 (see also 8.3).

For water treatment and distribution systems that are integrated into a single system and that have been validated to produce water meeting the quality requirements of ISO 13959, the manufacturer's recommendations for monitoring may be followed for the manufacturer's recommended maximum period of use according to the instructions for use, provided that there is assurance that the system is being operated under the validated conditions.

### **7.2.2 Monitoring of concentrate quality**

Users do not have to test concentrates to demonstrate compliance with the requirements of ISO 13958 when using commercially available packaged chemicals intended for use in preparing liquid concentrates at a dialysis facility or when using commercially available liquid concentrates, provided that the concentrates are manufactured in accordance with the requirements of ISO 13958. If the user prepares concentrate from raw chemicals, the resulting concentrate should meet the requirements of ISO 13958.

### **7.2.3 Monitoring of dialysis fluid quality**

Dialysis fluid quality should be monitored on a regular basis for the microbiological contaminants listed in 4.3.2 as described in 8.3.1. Methods for monitoring microbiological contaminants in dialysis fluid are described in 8.3.

**NOTE 1** Tests for bacterial growth and endotoxins are not required if the system is fitted with an endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires those tests in the instructions for use.

**NOTE 2** It is not possible to monitor compliance with the bacterial quality requirements for substitution solutions using currently available culturing methods.

Because dialysis fluid is prepared from dialysis water and concentrates meeting the quality requirements of ISO 13959 and ISO 13958, respectively, and since the dialysis water distribution system and dialysis fluid delivery system are required to be constructed of materials that do not contribute chemical contaminants to the water, routine monitoring of chemical contaminants in the dialysis fluid is not required.

## **7.3 Monitoring of water treatment equipment**

### **7.3.1 General**

The following requirements relate to and help explain the guidance provided in Annex C. A brief description of the individual water treatment devices is provided in Annex B.

### **7.3.2 Monitoring of sediment filters**

There is no easy test to determine the effectiveness of a sediment filter; however, pressure drop ( $\Delta P$ ) across the filter can be used to determine when the filter is retaining particulate matter to the point that the filter will no longer allow the required water flow without an excessive reduction in pressure at the outlet of the filter. A backwash cycle is used as a preventive measure to remove particulate matter from the sediment filter and avoid the development of an excessive pressure drop. The frequency of backwashing should follow the manufacturer's recommendations. Sediment filter monitoring should include verification that the timer used to initiate backwashing cycles is set to the correct time of day. A log sheet should be developed to record the pressure drop measurements and timer verifications.

### 7.3.3 Monitoring of cartridge filters

Cartridge filters should be monitored on a regular basis. There is no easy test to determine the effectiveness of a cartridge filter in removing particulate matter; however, pressure drop ( $\Delta P$ ) across the filter can be used to determine when the filter is retaining particulate matter to the point that the filter will no longer allow the required water flow without an excessive reduction in pressure at the outlet of the filter. A marked decrease in  $\Delta P$  without a corresponding decrease in flow rate can indicate a loss of filter integrity. Cartridges are usually replaced when  $\Delta P$  increases to some specified value or at a predetermined interval. A log sheet should be developed to record the pressure drop measurements.

### 7.3.4 Monitoring of softeners

Softener monitoring consists of the following: testing softened water for residual hardness; for automatically regenerating softeners, checking that the brine tank contains a sufficient supply of undissolved sodium chloride; and, for time-controlled softeners, checking that the timer indicates the correct time of day. The frequency of monitoring should be based on the hardness of the feed water and the capacity of the softener. When reverse osmosis is used, monitoring should be used to ensure that hardness limits established by the reverse osmosis machine manufacturer are not exceeded. A temporary rise in hardness will have a minimal effect on the performance of the reverse osmosis system, as calcium and magnesium are removed by reverse osmosis.

Testing for hardness should be performed using an ethylenediaminetetraacetic acid (EDTA) titration test, with “dip and read” test strips, or a similar method. Online hardness monitors are also available. If an online monitor is used, it should be used and maintained in accordance with the manufacturer's instructions. Regardless of the method chosen, users should ensure that test accuracy and sensitivity are sufficient to satisfy the hardness monitoring requirements of the reverse osmosis machine manufacturer when the softener is used as pretreatment for a reverse osmosis system.

When timer-controlled softeners are used, it is recommended that the hardness of the water exiting the softener be measured as near as practicable to the end of the duty cycle. The hardness test at the end of the duty cycle will indicate the overall effectiveness of the water softener under worst-case conditions and will ensure that the softener is sized properly and that the regeneration schedule is adequate. Timers should be checked at the beginning of each day. For volume-controlled duplex softeners, testing for hardness can be performed at any time of the day.

The softener brine tank should be monitored on a regular basis to ensure that enough salt is present in the brine tank to form saturated salt solution of sufficient volume for a minimum of one regeneration cycle. Salt used for regeneration should meet the specifications of the softener manufacturer. In particular, salt designated as rock salt should not be used for softener regeneration since it is not refined and typically contains sediments and other impurities that can damage O-rings and pistons and clog orifices in the softener control head. The frequency of monitoring should be based on the length of the duty cycle.

Water softeners should be fitted with a mechanism to prevent water containing the high concentrations of sodium chloride used during regeneration from entering the product-water line during regeneration.

Water hardness test results and verification of timer settings and the presence of salt pellets should be recorded in a water-softener log.

### 7.3.5 Monitoring of carbon media

The performance of carbon beds is monitored by measuring the total chlorine concentration in the water exiting the carbon bed, or exiting the first carbon bed when a series-connected pair of beds is used. It should be noted that sampling for total chlorine (the sum of free chlorine and chloramine) and allowing a maximum level of 0.1 mg/l of total chlorine is simpler than analysing for free chlorine and chloramine separately.

Testing for total chlorine can be accomplished using the *N,N*-diethyl-*p*-phenylenediamine (DPD)-based test kits, dip-and-read test strips based on Michler's thioketone (MTK or TMK), or other methods where comparable sensitivity and specificity can be demonstrated. Online monitors can also be used to measure total chlorine concentrations. If an online monitor is used, it should be used and maintained in accordance with the manufacturer's instructions. Whichever test system is used, it should have sufficient sensitivity and specificity to resolve the maximum levels described in 4.1.2 (see Table 1).

When offline tests are used, testing for total chlorine should be performed at the beginning of each treatment day prior to the patient's initiating treatment. Where chloramine is used to disinfect the potable water supply at a level of 1 mg/l or more, testing should be repeated prior to the beginning of each patient shift; if there are no set patient shifts, testing should be performed approximately every 4 h during operation. More frequent monitoring could be appropriate during temporary operation with a single carbon bed, which can occur following breakthrough of the first bed. In such instances, testing is performed on water exiting the second carbon bed in a series-connected pair. The decision to change the frequency of monitoring should be based on the past performance of the system and on whether changes in feed-water quality have occurred. Samples should be drawn when the system has been operating for at least 15 min. The analysis should be performed onsite since total chlorine levels will decrease if the sample is not assayed promptly.

Results of monitoring should be recorded on a log sheet.

#### **7.3.6 Monitoring of chemical injection systems**

Systems for chemical injection should be monitored according to the manufacturer's instructions. If a facility designs its own chemical injection system, procedures should be developed to ensure proper preparation of the chemical, adequate mixing of the injected chemical with the water flowing through the pretreatment cascade, and reduction to a safe level of the concentration of any chemical residuals before the point of water use. The facility should also verify that the injected chemical does not degrade the performance of downstream devices, such as the reverse osmosis system. Verification can be accomplished by testing samples from the chemical reservoir and the water line after the point of injection for at least three batches of chemical.

When the chemical to be injected is prepared at a facility from powder or by dilution of a liquid concentrate, the chemical injection reservoir should be labelled with the name of the chemical and its concentration, the date the solution was prepared, and the name of the person who mixed the solution. Each batch of chemical should be tested for correct formulation before use. A batch of chemical should not be used or transferred to the injection system reservoir until all tests are completed. The test results, and verification that they meet all applicable criteria, should be recorded and signed by the trained personnel performing the tests.

Protective clothing and an appropriate environment, including ventilation adequate to meet applicable environmental exposure limits, and national standards or regulations should be provided when chemicals for injection are prepared in a dialysis facility.

#### **7.3.7 Monitoring of reverse osmosis**

Reverse osmosis systems should be monitored using continuously-reading monitors that measure product-water conductivity [sometimes displayed as total dissolved solids (TDS)]. The measurements can be used to calculate rejection of solutes by the reverse osmosis membrane and provide a measure of equipment performance. Per cent rejection is calculated using the Formula (1):

$$\text{Rejection (\%)} = \frac{\text{Feed water conductivity} - \text{Permeate conductivity}}{\text{Feed water conductivity}} \times 100 \quad (1)$$

Many reverse osmosis systems have a direct reading for per cent rejection.

The permeate conductivity and rejection are both affected by a number of factors, such as the salinity and composition of the feed water, the water temperature, the level of dissolved gases, and the pressure in the system. Therefore, neither of them should be regarded as a true indicator of the water's suitability for dialysis. No limits are therefore set for these parameters in ISO 13959. Instead, they should be used to monitor changes in performance over time rather than an absolute measure of the quality. This can only be established by performing a chemical analysis of the product water in accordance with ISO 13959.

NOTE 1 For two-stage reverse osmosis systems, the per cent rejection of the second stage will be lower than that of the first stage because of physicochemical phenomena.

Other parameters that should be measured include product and reject stream flow rates and various internal pressures to the extent permitted by the system's instrumentation. Although these parameters are not directly indicative of treated water quality, monitoring them can help ensure that the system is operating within the manufacturer's specifications and, thus, will aid in maintaining the performance of the reverse osmosis membranes. Flow rates can be used to calculate the per cent recovery of the reverse osmosis system using Formula (2):

$$\text{Recovery (\%)} = \frac{\text{Permeate water flow rate}}{\text{Permeate water flow rate} + \text{Reject water flow rate}} \times 100 \quad (2)$$

NOTE 2 The per cent recovery is also known as the "water conversion factor". The terms are equivalent if none of the reject water stream is recycled to the feed-water stream (see B.2.7). If some of the reject water stream is recycled, Formula (2) provides a measure of overall water utilization by the reverse osmosis system, rather than the recovery of water during a single pass through the membrane module.

NOTE 3 The permeate water flow rate varies with operating pressure and temperature. To enable comparisons to be made under different operating conditions, a normalized permeate flow rate can be calculated. Methods for calculating the normalized permeate flow rate are available from reverse osmosis membrane manufacturers or can be found in ASTM D4516-00 (2010).<sup>[164]</sup>

When reverse osmosis is the final process in the water treatment system for removing chemical contaminants, analysis for the contaminants listed in Tables 1 and 2 should be done when the reverse osmosis system is installed to ensure that the limits specified in 4.1.2 are met. It is also recommended that chemical analyses be done when the following situations occur:

- information is obtained from the water supplier that significant changes in the source water, such as seasonal variations, have occurred;
- significant deviations are observed in process parameters, such as pH, conductivity, chlorine concentration and hardness, that can affect the performance of components of the water treatment system;
- reverse osmosis rejection rates decrease by more than 10 %.

All results of measurements of reverse osmosis performance should be recorded daily in an operating log that permits trending and historical review.

### 7.3.8 Monitoring of deionization

Deionizers shall be monitored continuously using resistivity monitors that compensate for temperatures up to 25 °C and that are equipped with audible and visual alarms. Resistivity monitors shall have a minimum sensitivity of 1 MΩ·cm (1 μS/cm or 0.1 mS/m). If the resistivity of the water at the outlet of a deionizer is less than 1 MΩ·cm, the water shall not be used for dialysis. When deionization is employed as the primary method for removing inorganic contaminants (reverse osmosis is not employed), or when deionization is necessary to polish reverse-osmosis-



treated water, chemical analyses to ensure that the requirements of 4.1.2 are met should be performed when the system is installed. Resistivity monitor readings should be recorded on a log sheet twice each treatment day.

### **7.3.9 Monitoring of endotoxin-retentive filters**

The performance of endotoxin-retentive filters in dialysis water distribution, bicarbonate concentrate distribution, or dialysis fluid delivery systems can be monitored by testing the fluid that is directly exiting the filter for bacteria and endotoxins. Endotoxin-retentive filters should be fitted with a means of assessing filter integrity and fouling. One suitable means is to monitor the pressure drop ( $\Delta P$ ) across the filter at a given product fluid flow rate using pressure gauges on the inlet (feed) and outlet (product) streams. Alternatively, product fluid flow rate can be measured at a given pressure drop. Such monitoring can indicate when membrane fouling has progressed to the point that membrane replacement or cleaning is needed. Monitoring is also necessary to ensure that the device is being operated in accordance with the manufacturer's instructions. Endotoxin-retentive filters operated in the cross-flow mode should also be monitored in terms of the flow rate of fluid being directed to drain at a given pressure drop. Results of pressure measurements and bacteria and endotoxin levels should be recorded on a log sheet.

## **7.4 Monitoring of dialysis water storage and distribution**

NOTE 7.4.1 to 7.4.3 relate to and help explain Table C.1.

### **7.4.1 Monitoring of water storage tanks**

For a system that distributes dialysis water to single-patient proportioning systems, routine monitoring of water storage tank for total viable microbial count and endotoxin concentration is generally accomplished indirectly by monitoring the dialysis water at the first outlet to the distribution loop. For routine monitoring of a storage tank that supplies dialysis water to a central dialysis fluid delivery system, or when direct monitoring of a dialysis water storage tank is performed as part of a troubleshooting process, the total viable microbial count and endotoxin concentration should be determined using samples drawn from a port at the outlet of the storage tank. When a change has been made to an existing storage tank, more frequent testing should be considered to verify that bacteria or endotoxin levels are consistently within the allowed limits. The need for additional testing should be based on the original validation plan (see 6.1) and a risk analysis of the likely impact of the change on system performance. All total viable microbial counts and endotoxin results should be recorded on a log sheet and should be subject to trend analysis.

### **7.4.2 Monitoring of the water distribution systems**

Distribution piping systems used for dialysis water should be monitored for total viable microbial count and endotoxin concentration to demonstrate the adequacy of the disinfection programme described in 8.2. The total viable microbial count and endotoxins shall not exceed the levels specified in 4.1.3. Monitoring should be accomplished by taking samples from the last outlet of the distribution loop and the outlets supplying reuse equipment and bicarbonate concentrate mixing tanks. If the results of this testing are unsatisfactory, the disinfection programme should be re-evaluated and additional testing (for example, endotoxin-retentive filter inlet and outlet, reverse osmosis product water, and storage tank outlet) should be undertaken as part of a troubleshooting strategy to identify the source of contamination, after which appropriate corrective actions can be taken. Total viable microbial counts and endotoxin testing should be conducted on a regular schedule according to system validation data and local regulations and in accordance with 8.3.3 and 8.3.4. When a change has been made to an existing system, more frequent testing should be considered to verify that bacteria or endotoxin levels are consistently within the allowed limits. The need for additional testing should be based on the original validation plan (see 6.1) and a risk analysis of the likely impact of the change on system performance. All bacteria and endotoxin results should be recorded on a log sheet to permit identification of trends and the need for corrective action.

### **7.4.3 Monitoring of bacterial control devices**

#### **7.4.3.1 Monitoring of ultraviolet irradiators**

Ultraviolet irradiators intended for use as a direct means of bacterial control should be monitored for radiant energy output. UV irradiators are available equipped with radiant energy intensity sensors. Either a visual alarm or an output meter is acceptable for determining if the UV lamp is emitting sufficient radiant energy. UV irradiators should be monitored at the frequency recommended by the manufacturer. Because the radiant energy decreases with time, annual lamp replacement is typically required. Periodic cleaning of the quartz sleeve may also be required, depending on the water quality. A log sheet should be used to indicate that monitoring has been performed.

#### **7.4.3.2 Monitoring of ozone generators**

Ozone generators should be monitored for ozone output at a level specified by the manufacturer. The output of the ozone generator should be measured by determining the ozone concentration in the water at the most distal point from the ozone generator. A test based on indigo trisulfonate chemistry, DPD, or the equivalent, or ozone-in-water test strips should be used to measure the ozone concentration. It is recommended that ozone concentration be measured each time disinfection is performed. An ozone-in-ambient-air test should be conducted on a periodic basis, as recommended by the manufacturer, to ensure compliance with National Standards and regulations for the permissible exposure limit. A log sheet should be used to indicate that monitoring has been performed.

#### **7.4.3.3 Monitoring of hot water disinfection systems**

Hot water disinfection systems should be monitored for temperature and time of exposure to hot water, as specified by the manufacturer. The temperature of the water should be recorded at a point farthest from the water heater; that is, where the lowest water temperature is likely to occur. It is recommended that the water temperature be measured each time a disinfection cycle is performed. A record that verifies successful completion of the heat disinfection should be maintained. Successful completion is defined as meeting the temperature and time requirements specified by the equipment manufacturer.

### **7.5 Monitoring of concentrate preparation**

#### **7.5.1 Monitoring of mixing systems**

Systems for preparing either bicarbonate or acid concentrate from powder or other highly concentrated media at a dialysis facility should be monitored according to the mixing system manufacturer's instructions to ensure appropriate dissolution. If a facility designs its own system, procedures should be developed and demonstrated to ensure proper mixing of the concentrate, including establishment of acceptable limits for tests of proper concentration. In this case, verification can be accomplished by testing a sample from each batch prepared over a three-day period.

Acid and bicarbonate concentrates may be tested by measuring conductivity, density with a density meter, or specific gravity with a hydrometer according to the manufacturer's instructions. Although not required, some manufacturers of concentrate powder or other highly concentrated media may provide allowable ranges for either the conductivity, density, or the specific gravity of concentrates prepared from their powder. The use of pH, alone, as an indicator of proper dissolution is inappropriate for both acid and bicarbonate concentrates because large variations in concentration do not produce significant changes in pH. Concentrates should not be used or transferred to holding tanks or distribution systems until all tests are completed. The test results and verification that they meet all applicable criteria should be recorded and signed by the individuals performing the tests.

#### **7.5.2 Monitoring of additives**

When additives are prescribed for a specific patient, the container holding the prescribed concentrates should be labelled with the name of the patient, the final concentration of the added electrolyte, the date and time when the

prescribed concentrate was mixed, and the name of the person who mixed the additive. This information should also be recorded in accordance with the requirements of 4.4. The label should be affixed to the container when the mixing process begins.

## **7.6 Monitoring of concentrate distribution**

A daily check to ensure that the appropriate acid and bicarbonate concentrate is connected to the corresponding concentrate delivery line is recommended if the storage tank is not permanently connected to its distribution piping.

Once a bicarbonate distribution system has been activated, dialysis fluid should be monitored weekly until sufficient data have been obtained to demonstrate the adequacy of the disinfection programme for the bicarbonate distribution system. The frequency of monitoring may then be reduced, but monitoring should be performed at least monthly. If elevated total viable microbial counts or endotoxin levels are found in the dialysis fluid, the disinfection programme for all systems involved in dialysis fluid preparation, including the bicarbonate concentrate distribution system, should be evaluated and revised. The frequency of monitoring should then be increased until it can be demonstrated that the revised disinfection programme is adequate to provide concentrate that allows preparation of dialysis fluid meeting the quality requirements of ISO 11663.

There are no published reports of acid concentrate supporting bacterial growth; therefore, it is not necessary to perform routine testing for total viable microbial count and endotoxins on those systems. However, it should be possible to disinfect these systems.

## **7.7 Monitoring of dialysis fluid proportioning**

Dialysis fluid proportioning should be monitored following the procedures specified by the equipment manufacturer. When the user has specific requirements for monitoring dialysis fluid proportioning, such as when dialysis machine settings are changed to allow the use of concentrates with a different proportioning ratio, the user should develop procedures for routine monitoring of dialysis fluid electrolyte values, such as by monitoring sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), osmotic pressure, or conductivity.

# **8 Strategies for microbiological control**

## **8.1 General**

The strategy for controlling the proliferation of microorganisms in hemodialysis systems primarily involves appropriate system design and operation, and regular disinfection of the entire fluid system. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine), and the dialysis machines (which have their own disinfection circuit and programme). A key concept in ensuring compliance with the requirements of 4.1.3 and 4.3 is that disinfection schedules should be designed to prevent microbial proliferation, rather than being designed to eliminate microorganisms once they have proliferated to an unacceptable level. With this strategy, monitoring levels of microorganisms and endotoxin serves to demonstrate that the disinfection programme is effective, not to indicate when disinfection should be performed.

Microorganisms in fluid colonize surfaces resulting in biofilm formation, even when levels of microbial contamination are low. Microorganisms living within biofilms produce an extracellular polysaccharide or slime matrix, which protects them against disinfection. Microorganisms also excrete both simple and complex metabolites. Their effect on patients, and whether or not they are removed by endotoxin-retentive filters, is largely unknown. All strategies for microbial control of the system should, therefore, be proactive in order to limit biofouling (microbial growth and biofilm formation). It is of utmost importance that the disinfection procedure is applied from the start of the operation of the hemodialysis system. Once formed, biofilm is difficult, if not impossible, to eradicate.

The combined efforts of disinfection and employing strategies for bacterial control make it possible to minimize microbiological growth and biofilm formation.

The information given in this guidance is valid for the following:

- water systems;
- dialyzer reprocessing systems;
- central dialysis fluid delivery systems;
- central sodium bicarbonate concentrate preparation and distribution systems.

## **8.2 Disinfection**

Disinfection is the only effective method of diminishing and inactivating microflora.

First, and most of all, the frequency of disinfection is important. Disinfection should be performed on a regular basis to limit biofouling within the fluid pathways of the system. Depending on the circumstances, different levels of disinfection may be required to comply with the fluid quality requirements of Clause 4.

Second, all surfaces in the circuit should be included in the disinfection procedure. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine), and the dialysis machines (which have their own disinfection circuit and programme).

Third, the disinfection procedure, when applied with a given frequency and with inclusion of all critical areas, should be capable of minimizing the effects of biofouling.

Disinfection can be performed using heat or chemicals. UV lamps can be used to inactivate planktonic cells but are of no value against any biofilm that has formed in the system.

### **8.2.1 Microbiological aspects of fluid system design**

The circuit downstream of the reverse osmosis system, including the clean side of the reverse osmosis membranes, the distribution piping, tanks and filters in the distribution piping, and the inlet lines to the dialysis machines are to be maintained and disinfected so that it is possible to fulfil the microbiological requirements of ISO 11663 and ISO 13959.

Examples of good system design include

- use of a recirculation-type system,
- avoidance of dead ends and dead space areas,
- a high-quality finish to joints and connections,
- use of materials compatible with the planned methods of disinfection, and
- avoidance of storage tanks. If a storage tank is necessary it should be designed and constructed in such a manner that it can be cleaned and disinfected.

Once the water treatment system has been installed, water flow should be maintained to limit biofilm formation. The system design should also take into consideration preventive maintenance of the fluid distribution system, as well as education and training of staff in order to create awareness about disinfection and microbiological control.

The disinfection programme could compensate for a weakness in system design but will not totally prevent the formation of biofilm, which can become difficult to eradicate.

## **8.2.2 Disinfection frequency**

### **8.2.2.1 General**

A key concept in ensuring compliance with the requirements of 4.1.3, 4.2.1, and 4.3.2 is that disinfection schedules should be designed to prevent bacterial proliferation, rather than being designed to eliminate bacteria once they have proliferated to an unacceptable level (i.e. above the action level). With this strategy, monitoring levels of bacteria and endotoxins serves to demonstrate that the disinfection programme is effective, not to indicate when disinfection should be performed.

A proper disinfection strategy is to be preventive and this should be applied from the start of operation. The disinfection strategy may be modified based on results obtained during validation and revalidation activities.

The disinfection frequency should not be based only on findings obtained during the first month of operation because microbiological growth in a fluid system starts as surface growth (biofilm formation) and little or nothing could be seen in fluid samples taken from a fluid system during that time, even if no disinfection is performed.

### **8.2.2.2 Dialysis water storage and distribution systems**

Storage and distribution systems should be disinfected on a schedule that allows the water quality recommendations of 4.1.3 to be met routinely. For integrated treatment and distribution systems, the manufacturer's instructions for disinfection should be followed, provided routine monitoring shows that they are adequate to meet the requirements of 4.1.3. For systems assembled from individual components, the frequency of disinfection necessary to minimize biofouling will vary with the design of the system and, in the case of existing systems, the extent to which any biofouling has already occurred.

### **8.2.2.3 Concentrate mixing systems**

Concentrate mixing equipment should be either

- a) completely emptied, cleaned, and/or disinfected according to the manufacturer's instructions, or
- b) cleaned and/or disinfected using a procedure demonstrated by the facility to be effective in routinely producing concentrate that allows the recommendations of 4.2.1 to be met.

The mixing and disinfection data should be recorded for each mix and disinfection cycle using a dedicated log.

### **8.2.2.4 Concentrate distribution systems**

Piped bicarbonate concentrate distribution systems should be disinfected either according to the manufacturer's instructions or using a procedure that has been demonstrated by the facility to be effective in routinely producing concentrate that allows the recommendations of 4.2.1 to be met. The disinfection interval should not exceed 1 week. If the manufacturer does not supply disinfection procedures, the user should develop and validate a disinfection protocol. It is recommended that monitoring of concentrate distribution systems be performed on a routine basis. When reusable concentrate containers are used to distribute bicarbonate concentrate, the containers and pick-up tubes should be disinfected at least weekly. Bicarbonate concentrate containers should be rinsed with treated water

and stored inverted at the end of each treatment day. Pick-up tubes should also be rinsed with treated water and allowed to air dry at the end of each treatment day. Because there are no published reports of acid concentrate supporting bacterial growth, disinfection of acid concentrate distribution systems is not normally required. However, it should be possible to disinfect these systems.

### **8.3 Microbiological monitoring methods**

#### **8.3.1 General**

The fluid system should be routinely monitored in order to verify that the microbiological quality indicators (bioburden represented by total plate count and endotoxin concentration) are being met.

The frequency of sampling should meet applicable local recommendations. If no such recommendations exist, the following are recommended.

- a) Water system: The number of samples and positions of sampling should be based on the complexity and size of the water system. The frequency will depend on the analysis of the data collected during the validation and revalidation activities. Monthly monitoring is most frequently adopted but less frequent monitoring may be possible based on data collected during the validation and revalidation.
- b) Dialysis fluid/hemodialysis machines without a validated bacteria- and endotoxin-retentive filter: Machines should be sampled on a regular basis to provide verification of the effectiveness of the disinfection process. The schedule of sampling will depend on the type of disinfection process being used. Each machine should be sampled at least once per year and different machines should be sampled on each occasion. Monthly monitoring is most frequently adopted.
- c) It is not necessary to take samples of ultrapure dialysis fluid or substitution fluids if their production paths are fitted with bacteria- and endotoxin-retentive filters validated by the manufacturer and operated and monitored according to the manufacturer's instructions. It could be necessary to sample the dialysis fluid entering such bacteria- and endotoxin-retentive filters depending on the manufacturer's instructions for use of the filters; for example, when the instructions for use specify the quality of the fluid entering the filter. (See also Annexes D and E.)

The results of testing should be subjected to trend analysis. When results exceed the action levels, or in the case of a patient's pyrogenic reaction or suspected bacteremia/fungemia, an investigation and follow-up should be initiated. This investigation could include additional sampling and extra disinfection procedures carried out as per the manufacturer's recommendations.

#### **8.3.2 Sample collection**

##### **8.3.2.1 Dialysis water sample sites**

Samples are to be taken at outlets of the distribution system.

Prior to sampling, the inside of the outlet can be disinfected, especially if no hemodialysis machine is attached. The reason for such disinfection is that, over time, residual water in an outlet will support microbial growth. The disinfection can be made by flushing the inside of the outlet with 70 % ethanol or isopropanol. A sterile cotton swab wetted with alcohol can also be used. Exposure time is to be >15 s. In principle, it is sufficient to let out enough water to rinse off the alcohol (200 ml to 500 ml) prior to sampling. Alternatively, hoses can be disconnected from the tap and the taps opened and allowed to flush for 2 min to 3 min before aseptically collecting a sample. Other sampling methods may be appropriate, provided they have been validated.

Sample volumes of 5 ml to 1 000 ml or a volume as specified by the laboratory should be used. Containers used for samples to be cultured should be sterile and endotoxin free.

#### **8.3.2.2 Dialysis fluid samples**

Samples should be collected from the dialysis fluid line according to the sampling instructions provided by the manufacturer of the dialysis fluid delivery system.

**NOTE** Where the dialysis fluid delivery system is equipped with a dialysis fluid sampling port that can be accessed using a syringe, the sample port can be disinfected with alcohol and allowed to air dry. A sterile syringe can then be used to aspirate dialysis fluid out of and into the port before filling the syringe. The filled syringe is discarded and a fresh sample of dialysis fluid collected using a new sterile syringe. For sample ports consisting of a simple septum penetrated with a needle, the use of a second syringe is not necessary.

Alternatively, if the hemodialysis machine permits, samples can be collected immediately after the dialyzer by disconnecting the effluent connector and aseptically collecting a “free/clean” catch sample after allowing dialysis fluid to run for 30 s to 60 s.

Sample volumes of 5 ml to 1 000 ml or a volume as specified by the laboratory should be used. Containers used for samples to be cultured should be sterile and endotoxin free.

#### **8.3.3 Heterotrophic plate count**

##### **8.3.3.1 Storage of samples**

Microbial analysis of any fluid sample should be conducted as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analyzed within 4 h of collection, follow the laboratory's instructions for shipping. Samples intended for colony counts should not be frozen.

Storage of samples for endotoxin analysis may be different from what is given above, provided the complete procedure follows the manufacturer's instructions for use of the LAL assay.

##### **8.3.3.2 Analytical methods**

###### **8.3.3.2.1 Membrane filtration**

Membrane filtration is filtration of the sample through a membrane filter with pore diameter of 0.45 µm or less. Membrane filtration is a method used when the sample is to be concentrated to detect low levels of contamination (usually <1 CFU/ml). The volume to be filtered should be determined by the suspected level of contamination and should be between 10 ml and 1 000 ml.

###### **8.3.3.2.2 Spread-plate technique**

A pipette is used to apply 0.1 ml to 0.3 ml of a sample to a Petri dish (typically 90 mm in diameter) containing agar medium and spread over the surface of the agar. The detection limit of this technique is 5 CFU/ml when 0.2 ml of sample is used as the inoculum.

###### **8.3.3.2.3 Pour-plate technique**

A sample (typically 1 ml) is placed in a Petri dish and 15 ml to 20 ml of molten medium is added. The sample and medium are mixed carefully by gentle rotation and allowed to set. The time between addition of the sample and addition of the molten medium should not exceed 15 min. The plate is inverted and incubated. If 1 ml of sample is used, the detection limit of this technique is 1 CFU/ml.

Molten media should be <45 °C at the time the plate is poured.

#### 8.3.3.2.4 Dip samplers

Currently available dip samplers are not suitable for use in dialysis applications.

#### 8.3.3.3 Cultivation conditions

A cultivation method has three elements: the cultivation medium, the incubation temperature, and the incubation time. Suitable cultivation conditions can be found in Table 5. Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods.

**Table 5 — Cultivation techniques**

| Cultivation medium                                                                                                         | Incubation temperature | Incubation time |
|----------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------|
| Tryptone glucose extract agar (TGEA)                                                                                       | 17 °C to 23 °C         | 7 d             |
| Reasoner's agar no. 2 (R2A)                                                                                                | 17 °C to 23 °C         | 7 d             |
| Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE) | 35 °C                  | 48 h            |

NOTE 1 It is not necessary to use both media for routine monitoring.

For central sodium bicarbonate preparation and distribution systems, the cultivation medium should be supplemented with 4 % sodium bicarbonate.

NOTE 2 If dehydration of culture plates is a concern, then plates can be sealed using Petri-plate seals or placed in closed plastic bags during incubation.

NOTE 3 Colony counts of microbes in fluid distribution systems and other environmental samples are only relative counts. Counts will vary depending on the length of incubation and culture conditions. No matter what different conditions are used, not all viable cells will grow on artificial media [for example, viable but not culturable (VBNC)].

#### 8.3.4 Bacterial endotoxin test

Bacterial endotoxins are assayed using the *Limulus* amoebocyte lysate (LAL) test. Current pharmacopoeias [United States (USP), European, and Japanese pharmacopoeias] acknowledge six different testing techniques.

Endotoxin testing requires education and should be performed by fully trained personnel.

Valid tests have to follow official applicable requirements and manufacturer's instructions.

NOTE It is important to use correct types of sample containers, labelled or validated for storage of endotoxin samples. Appropriate containers are usually specified by the testing laboratory or the manufacturer of the LAL testing kit.



## 9 Environment

The water treatment and storage system should be located in a secure area that is readily accessible only to personnel authorized by the dialysis facility. The location should be chosen with a view to minimizing the length and complexity of the distribution system. Access to the treatment system should be restricted to those individuals responsible for monitoring and maintenance of the system.

The layout of the water treatment system should provide easy access to all components of the system, including all meters, gauges, and sampling ports used for monitoring system performance. An area for processing samples and performing onsite tests is also recommended. Critical alarms, such as those associated with deionizer exhaustion or low water levels in a storage tank, should be configured to notify staff in the patient treatment area, as well as in the water treatment room.

Water systems should include schematic diagrams that identify components, valves, sample ports and flow direction. Additionally, piping should be labelled to indicate the contents of the pipe and direction of flow. The use of text labels, such as “RO Water”, and colour-coded “arrow tape” provides a convenient means of identifying the pipe content and flow direction.

If water system manufacturers have not done so, users should identify major water system components and describe their function. How performance is verified, and what actions to take in the event that performance is not within an acceptable range, should be readily available to the user.

## 10 Personnel

Policies and procedures that are understandable and accessible are mandatory, along with a training programme that includes quality testing, the risks and hazards of improperly prepared concentrate, and bacterial issues. Operators should be trained in the use of the equipment by the manufacturer or should be trained using materials provided by the manufacturer. Additional training may be provided using materials from other sources. The training should be specific to the functions performed (i.e. mixing, disinfection, maintenance, and repairs). Periodic audits of the operator's compliance with procedures should be performed. The user should establish an ongoing training programme designed to maintain the operator's knowledge and skills.

## **Annex A**

### **(informative)**

## **Rationale for the development and provisions of this International Standard**

### **A.1 Scope**

This clause provides the rationale for the requirements in Clause 1. It has long been known that chemical and microbiological contamination of dialysis fluid places hemodialysis patients at risk of acute and chronic adverse events. From the beginning, it was recognized that there was a problem with including fluid quality requirements in an International Standard directed at manufacturers of water treatment equipment or hemodialysis machines. Although a manufacturer might be responsible for providing equipment that, when assembled as a system, provides water, concentrate, or dialysis fluid that meets certain quality requirements, that manufacturer has no control over the equipment once it is installed. For example, the treated water quality could change if a water treatment system is not well maintained or if there is some change in the municipal water feeding the system. Therefore, fluid quality standards were established independent of the standards for the equipment used to prepare those fluids. Since the day-to-day responsibility for maintaining fluid quality lies with the healthcare professionals at each dialysis facility under the leadership of the facility's Medical Director, this International Standard was prepared to provide guidance to those healthcare professionals on how to manage fluid preparation systems so as to comply with the requirements of the fluid quality standards.

### **A.2 Chemical contaminants in dialysis water**

This clause provides the rationale for the requirements in 4.1.2. ISO 13959 sets forth maximum levels of chemical contaminants in three categories: chemicals with documented toxicity in hemodialysis patients, electrolytes normally included in dialysis fluid, and trace elements. The rationale for including particular chemicals in ISO 13959, and for setting their maximum levels, is set forth in Annex A of ISO 13959:2014.

### **A.3 Microbiological contaminants in dialysis water**

This clause provides the rationale for the requirements in 4.1.3. ISO 13959 sets forth maximum levels of bacteria and endotoxins in dialysis water, along with action levels for these contaminants. The rationale for the maximum levels of bacteria and endotoxins is set forth in Annex A of ISO 13959:2014.

### **A.4 Requirements for concentrate**

The rationale in this clause addresses the requirements in 4.2. Requirements for commercially available concentrates are given in ISO 13958. It was decided not to recommend limits on bacteria and endotoxins for concentrate prepared at a facility, even for bicarbonate concentrate. This decision was based on the difficulty of performing cultures and endotoxin assays in samples with high concentrations of salts. High concentrations of bicarbonate require special culturing techniques and are inhibitory in the LAL assay. It was determined that it was unreasonable to require an individual dialysis facility to meet the special conditions required for proper testing of bicarbonate concentrate and that patients would be adequately safeguarded by the quality recommendations for the water used to prepare the concentrate and for the final dialysis fluid. For users who are interested in determining bacterial levels and endotoxin concentrations as part of a troubleshooting investigation, guidelines on performing cultures and endotoxin assays in bicarbonate concentrate are included in 8.3.3.3 and A.10.

## A.5 Microbiological contaminants in dialysis fluid

The rationale in this clause addresses the requirements in 4.3. ISO 11663 sets forth maximum levels of bacteria and endotoxins in three categories of dialysis fluid: standard dialysis fluid, ultrapure dialysis fluid, and online-prepared substitution fluid. Where appropriate, action levels for bacteria and endotoxins are also given. The rationale for the maximum levels of bacteria and endotoxins is set forth in Annex A of ISO 11663:2014.

ISO 13959 sets a maximum allowable level for endotoxins in dialysis water of 0.25 EU/ml, while ISO 11663 sets a maximum allowable level for endotoxins in dialysis fluid of 0.5 EU/ml. The level for dialysis fluid is set higher than that for dialysis water in recognition that powder concentrates can contribute endotoxins, but not volume, to the final dialysis fluid. No such accommodation is made for bacteria since most bacteria will not survive in a viable form in powder concentrate.

## A.6 Monitoring of carbon media

The rationale in this clause addresses the requirements in 7.3.5. Intensive monitoring of carbon beds is recommended because of the long history of adverse events related to chloramine contamination of dialysis fluid.<sup>[38]</sup> Chloramine concentrations in municipal water can change from day to day and the capacity of carbon beds to remove chloramine can vary with the pH and temperature of the water, the nature of the chloramine compounds present, and the presence of other substances in the water. The dependence of chloramine removal on multiple factors makes the performance of carbon beds unpredictable. Therefore, patient safety can only be ensured by intensively monitoring the performance of the carbon bed. Configuring carbon beds in series and sampling from a port located between the two beds provides one margin of protection against chloramine breakthrough. When chloramine is first detected in the effluent from the first bed, the second bed will still have some capacity for chloramine removal. This reserve capacity allows the user to conveniently replace the exhausted bed without risk to patients. The exhausted bed is discarded, the second bed is moved into the first position, and a new bed is placed in the second position. A new bed of virgin carbon should be used for replacement. Continuous monitoring with an online monitor provides the best protection of the patient. The online monitor should be capable of activating a means of diverting the water from the reverse osmosis system, for example by shutting down the reverse osmosis system, should the total chlorine level exceed 0.1 mg/l.

In situations where chloramine is not used to disinfect the water, and the ammonia level in the water is low, one carbon bed or a carbon cartridge filter with a shorter EBCT could be sufficient. Carbon cannot be regenerated in a dialysis facility, and the use of regenerated carbon is prohibited. Backwashing of carbon beds does not regenerate the carbon, although it can allow more efficient use of the bed's capacity by removing channels that can form in the bed during routine operation. The recommendation that the water purification system should operate for at least 15 min, before samples of water from a carbon bed are drawn, is to guard against inadvertently sampling water that has been in the bed for an extended period.

## A.7 Strategies for microbiological control

The rationale in this clause addresses the requirements in 8.1. All microbial growth in a fluid system involves growth on surfaces. In most cases, the microbial growth starts on surfaces and consequently little or nothing of the microbial development in the fluid system is recorded by taking fluid samples. The surface growth occurs in patches in the earlier stages and is difficult to analyze.

No testing is able to show a complete picture of bacterial growth and the tests described and referred to in this International Standard do not measure many microbial contaminants, including: cell wall fragments from microorganisms; nucleic acids DNA and RNA; and metabolites of various kinds.

For this reason, a proactive disinfection programme is recommended to combat bacterial growth in the dialysis water and dialysis fluid systems.

## A.8 Heterotrophic plate count

The rationale in this clause addresses the requirements in 8.3.3. Sensitive culturing methods should be used to measure the low total viable microbial counts permitted for water used for hemodialysis applications. The membrane filter technique is particularly suited for this application because it permits large fluid volumes to be assayed. Because the membrane filter technique might not be readily available in clinical laboratories, the spread plate assay or the pour plate assay can be used as an alternative for water and standard dialysis fluid.<sup>[112]</sup> If the spread plate assay is used, a calibrated loop should not be used to apply sample to the plate. The sensitivity of an assay performed with a calibrated loop is low. A standard calibrated loop transfers 0.001 ml of sample to the culture medium so that the minimum sensitivity of the assay is 1 000 CFU/ml. This sensitivity is unacceptable when the maximum allowable limit for microorganisms is 100 CFU/ml. Therefore, when the spreadplate method is used, a pipette should be used to place 0.2 ml to 0.5 ml of water or dialysis fluid on the culture medium. The pour-plate method may be used as an alternative method to the spread-plate method. If a sample volume of 1 ml is used, the detection limit of the pour-plate method is 1 CFU/ml.

Culture results obtained using the methods outlined in this International Standard are only a relative indicator of the bioburden in dialysis water or dialysis fluid and do not provide a measure of the absolute bacterial burden. The original clinical observations on which the microbiological requirements were based used standard methods agar (SMA), a medium containing relatively few nutrients.<sup>[75]</sup> Later, the use of trypticase soy agar (TSA), a general-purpose medium for isolating and cultivating fastidious organisms, was recommended because it was thought to be more appropriate for culturing bicarbonate-containing dialysis fluid. However, several studies have shown that the use of nutrient-poor media, such as tryptone glucose extract agar (TGEA) or Reasoner's agar no. 2 (R2A), results in an increased recovery of bacteria from water.<sup>[110][113][115][116]</sup> Extending the culturing time up to 7 d and using incubation temperatures of 23 °C to 28 °C have also been shown to increase the recovery of bacteria compared to incubation for 48 h at 35 °C to 37 °C.<sup>[110][113][116]</sup>

When monitoring for microbial contamination in ultrapure dialysis fluid, the maximum allowable level of bacteria requires that culturing be performed using the membrane filtration method with a minimum of 10 ml of ultrapure dialysis fluid being passed through the filter. The use of larger volumes (up to 1 000 ml) will provide greater sensitivity, but the improved sensitivity needs to be balanced against the increased risk of contamination in collecting and handling the sample. The addition of 2 % to 8 % sodium bicarbonate to the medium can enhance the recovery of organisms.<sup>[114]</sup> Even with these more sensitive techniques, compliance with the stringent requirement that online-prepared substitution fluid be sterile cannot be demonstrated by culturing; it has to be ensured by use of a validated process. Monitoring of the production of online-prepared substitution fluid will depend on the production system and should be performed according to the manufacturer's instructions.

Furthermore, the culturing conditions recommended in this International Standard could fail to identify the presence of some organisms. Specifically, the recommended methods might not detect the presence of various nontuberculous mycobacteria that have been associated with several outbreaks of infection in dialysis units.<sup>[78][85]</sup> Also, the recommended methods will not detect fungi and yeast, which have been shown to contaminate water used for hemodialysis applications.<sup>[82]</sup>

The microbiological purity of packaged liquid concentrates and dry powder cartridges is the responsibility of the manufacturer. Monitoring of bicarbonate concentrate produced at a dialysis facility from powder and water, though not required routinely, may be undertaken as part of a troubleshooting investigation. The sodium content of TSA is sufficient for use in culturing bicarbonate concentrate without supplementation. However, salt tolerance studies showed that optimal growth of organisms found in bicarbonate concentrate occurred when the sodium chloride concentration was approximately 3 % to 6 %.<sup>[81]</sup> Therefore, if a low-salt medium, such as Reasoner's 2A or TGEA, is used to monitor microbial contamination in bicarbonate concentrate, it should be supplemented by the addition of 4 % sodium bicarbonate.

## A.9 Cultivation conditions

The rationale in this clause addresses the requirements in 8.3.3.3. Since dialysis is not stopped between sampling and obtaining the results of the tests, a long incubation time of 7 d is of no disadvantage or practical importance. However, significant contamination might be detected earlier by performing intermediate counts (e.g. every 2 d).

## A.10 Bacterial endotoxin test

The rationale in this clause addresses the requirements in 8.3.4. Bicarbonate concentrate inhibits the LAL assay. Inhibition is caused by the high concentration of solutes in the concentrate and the pH. In the gel-clot assay, this inhibition results in a failure of the positive control to clot. In kinetic assays, inhibition results in a failure to recover the positive control to within -50 % to +200 % of the nominal value.

Dilution of the bicarbonate concentrate with water is the usual method for overcoming inhibition. A minimum dilution of 1:16 is necessary; however, higher dilutions are recommended for more sensitive assays. For example, a 1:20 dilution is recommended when using an assay with a sensitivity of 0.03 EU/ml. Dilution reduces the detection limit of the assay. In kinetic methods, the sensitivity is the lowest concentration used to construct the standard curve. A kinetic assay is recommended for monitoring the quality of online-prepared substitution fluid because kinetic assays generally are more sensitive than gel-clot assays.

Standard gel-clot tests are incubated at 37 °C for the time recommended by the manufacturer. At the end of the recommended time, the tubes are inverted to detect the presence of a clot. A positive test will have a clot, which will remain in the end of the tube as long as it is not shaken or bumped. A negative test will not have a clot and will tend to flow out of the tube, when inverted. A clot that is semisolid and flows slowly is classified as a negative clot. For example, when bicarbonate concentrate is tested using a gel-clot assay with a sensitivity of 0.03 EU/ml and the concentrate is diluted 1:20 (1.0 ml concentrate plus 19 ml LAL reagent water or equivalent), the positive control sample should clot, indicating that there is no inhibition of the assay. If the diluted bicarbonate concentrate sample clots, it indicates that the sample contains at least 0.6 EU/ml of endotoxins. A new version of the gel-clot assay has a matched positive control, which simplifies the testing and increases the reliability of the results.

## **Annex B (informative)**

### **Equipment**

#### **B.1 General**

This annex provides a brief description of the different components that may be included in systems to treat and distribute dialysis water and dialysis fluid and to prepare and distribute concentrates for hemodialysis applications. Two types of systems are used: systems in which dialysis water is distributed to a dialysis machine at an individual patient treatment station, which prepares and controls the dialysis fluid for use at that station; and central dialysis fluid delivery systems, which prepare dialysis fluid centrally and supply it to multiple-patient treatment stations. Since feed-water quality and product-water requirements can vary from facility to facility, not all of the components described in the following clauses will be necessary in every water treatment and distribution system. Also, not every dialysis facility will prepare concentrate at the dialysis facility. Requirements for water treatment equipment used for hemodialysis and related therapies can be found in ISO 26722 and requirements for equipment used to prepare concentrates at a dialysis facility can be found in ISO 13958.

Routine dialysis requires a well-functioning water treatment and distribution system, since dialysis cannot be performed without an adequate supply of water. In addition, certain components of the water treatment and distribution system are critical to its operation. An example of such a critical component is the circulating pump in an indirect feed system. A dialysis facility should develop contingency plans to cover the failure of its water treatment and distribution system or a critical component of that system. Such contingency plans should describe how to deal with events that completely prevent dialysis from being performed, such as failure of the facility's municipal water supply or electrical service following a natural disaster or water main break. Other plans should address how to deal with sudden changes in municipal water quality, as well as with failure of a critical component of the water treatment and distribution system. Similar contingency plans should be developed to deal with the failure of concentrate preparation systems.

#### **B.2 Water treatment systems**

##### **B.2.1 General**

Water treatment systems consist of three basic sections: a pretreatment section that conditions the water supplied to the primary purification device, which may be followed by other devices that increase final water quality. The pretreatment section commonly includes a sediment filter, cartridge filters capable of retaining particles of various sizes, a softener, and carbon beds. The primary purification process most commonly used is reverse osmosis, which may be followed by deionization and ultrafiltration for polishing the product water from the reverse osmosis system. Whether a particular device is included in an individual water treatment system will be dictated by local conditions.

This clause provides a brief description of the principal equipment used to purify water used in hemodialysis applications. Devices used to treat water for hemodialysis should comply with the requirements of ISO 26722, including certain design and performance specifications for individual water treatment devices.

B.2.2 to B.2.9 provide general information. Design and instrumentation of individual water treatment devices may vary from these general descriptions. For example, softeners may be configured as a single resin bed that is regenerated outside the normal operating hours of the dialysis unit, or they may have a dual-bed configuration that allows one bed to be regenerated while the other is used to provide water for normal dialysis operations.

Depending on the feed-water quality and product-water requirements, not every component in this clause might be required in a given facility. Likewise, additional components can be required in certain circumstances. For example, carbon might not provide adequate chloramine removal if the water contains substances, such as polyphosphates, that mask the reactive sites on the carbon particles. In those circumstances, other processes, such as infusion of sodium bisulfite, can be required to achieve product water that meets the requirements of 4.1.2.

Users are encouraged to obtain detailed descriptions of all water treatment components, together with operating manuals and maintenance procedures, from the manufacturer or the supplier of the water treatment and distribution system.

### **B.2.2 Sediment filters**

Permanent, backwashable sediment filters, also known as “bed filters”, are frequently located at or near the beginning of hemodialysis water treatment systems and are intended to remove relatively coarse particulate materials from incoming water. Although a single filtration medium may be used, bed filters known as multimedia filters are more commonly selected. These units contain multiple layers, each layer retaining progressively smaller particles. In this way, the bed is used to its fullest extent; the largest particles are removed in the first layer contacted by the water and the smallest in the final layer.

As the bed accumulates particulate material, open passages begin to clog and resistance to the water flowing through the filter increases. Ultimately, the increased resistance to flow will lead to a reduction in water supply to downstream components. To prevent this situation from occurring, bed filters are cleaned by periodic backwashing, which is accomplished either manually or by using a timer-activated control valve. Sediment filters should have an opaque housing or other means to inhibit proliferation of algae. Bed filters should be fitted with gauges to measure the hydrostatic pressure at the filters' inlet and outlet. These values can be used to determine the dynamic pressure drop across the filter (delta pressure or  $\Delta P$ ), which serves as an index of resistance to flow and provides a basis, together with the manufacturer's recommendations, for setting the frequency of backwashing.

### **B.2.3 Cartridge filters**

Cartridge filters consist of a cylindrical cartridge of the filter medium with a central drainage core. The cartridge is contained within a filter housing with seals to separate the feed and product-water streams. In the pretreatment cascade, transparent filter housings can be useful because they allow any carbon or resin leakage to be seen without the need to break the integrity of the system. The housing can be cleaned to remove any algae growth when the filter cartridge is changed. For this reason, use of opaque housings for cartridge filters is recommended, but not required. If transparent housings are used, they should not be exposed to natural light, in order to minimize proliferation of algae. Cartridge filters should be fitted with gauges to measure the hydrostatic pressure at the filters' inlet and outlet. Although cartridge filters may be installed at the inlet to a water treatment system, their usual application is as a final filtration step prior to reverse osmosis. Resistance to flow through the filter increases as the cartridge accumulates particulate material, as indicated by an increase in  $\Delta P$ . When the maximum  $\Delta P$  recommended by the filter manufacturer is reached, the cartridge should be replaced according to the manufacturer's instructions.

### **B.2.4 Softeners**

Water that contains calcium or magnesium can form relatively hard deposits and is called “hard water”. Water that has had these elements replaced by sodium ion exchange is called “soft water”, hence the term “softener” is used. Softeners also remove other polyvalent cations, most notably iron and manganese, although they are somewhat limited in this regard. However, if significant concentrations of iron and manganese are present, special procedures should be implemented in order to reduce those concentrations to levels that do not interfere with the softening process or cause membrane fouling. The primary use of softeners in hemodialysis water systems is to prevent hard water deposits from fouling reverse osmosis membranes.

A softener is a cylinder or vessel that contains insoluble spheres or beads, called “resin”, to which sodium ions are attached. During operation, exchangeable sodium ions in the resin are progressively replaced by calcium and magnesium ions. When all the sodium ions have been used, the resin bed has reached a condition referred to as “exhaustion”. Prior to exhaustion, softeners should be restored; that is, new exchangeable sodium ions are placed on the resin by a process known as “regeneration”, which involves exposure of the resin bed to a highly concentrated sodium chloride solution. The concentrated sodium chloride solution is prepared in a separate brine tank, from which the solution is drawn during the regeneration process. A control valve on the softener regulates the regeneration and service cycles.

Automatically regenerated water softeners should be fitted with a mechanism to prevent water containing the high concentration of sodium chloride used during regeneration from entering the product-water line during regeneration. For softeners with a time-controlled regeneration cycle, the face of the timer should be visible to the user. Operating controls should be positioned so as to minimize inadvertent resetting.

### **B.2.5 Carbon media**

Carbon systems, often referred to as carbon filters, are the principal means of removing both free chlorine and chloramine. Removal of chloramine to a maximum level of 0.1 mg/l and removal of free chlorine to a maximum level of 0.5 mg/l are necessary to protect hemodialysis patients from red blood cell hemolysis. In addition, free chlorine can also degrade some reverse osmosis membranes, depending on the membrane material. Determining the level of chloramine typically involves measuring both total chlorine and free chlorine and assigning the difference in concentrations to chloramine. To permit a single test to be used, a maximum allowable level for total chlorine was set at the maximum allowable level for chloramine (0.1 mg/l).

In addition to removing free chlorine and chloramine, carbon also adsorbs a wide variety of other substances, including both naturally occurring and synthetic organic compounds. The capacity of carbon to remove free chlorine and chloramine can be reduced when other substances “mask” reactive sites on the carbon media. In addition, the rate of free chlorine and chloramine removal is reduced as pH increases or as temperature decreases. The net effect of those variables is that the finite capacity of carbon beds to remove free chlorine and chloramine cannot be predicted with any certainty. Therefore, their performance needs to be monitored frequently.

Carbon systems should be adapted specifically to the maximum anticipated water flow rate of the system. When carbon is used for the removal of chloramine at a level of 1 mg/l or more, two carbon beds should be installed in a series configuration. A means should be provided to sample the product water from the first bed. A sampling port should also be installed following the second bed for use in the event of total chlorine breaking through the first bed. In situations where chloramine is not used to disinfect the water, and the ammonium level in the water is low, one carbon bed or carbon cartridge filters could be sufficient. Exhausted carbon media should be discarded and replaced with new media, according to a replacement schedule determined by regular monitoring. For example, when testing between the beds shows that the first bed is exhausted, the second bed should be moved into the first position, the second bed replaced with a new bed, and the exhausted bed discarded. When samples from the first sampling port are positive for total chlorine, operation may be continued for a short time (up to 72 h) until a replacement bed is installed, provided that samples from the second sampling port remain negative. It was recognized that it might not be practical to rotate the bed positions in installations that use large, backwashable carbon beds. However, there was concern that the capacity of the second bed could decrease unpredictably and no longer provide adequate backup if there was breakthrough of the first bed. For this reason, replacing both beds if bed rotation was not possible was recommended.

Granular activated carbon with an iodine number greater than 900 is considered optimal for chlorine/chloramine removal. When granular activated carbon is used as the medium for the removal of chloramine from water containing >1 mg/l chloramine, each bed should have an empty-bed contact time (EBCT) of at least 5 min at the maximum product-water flow rate (a total EBCT of at least 10 min). Some source waters, such as those with a high organic content, could require alternative types of carbon that are more resistant to organic fouling. These types of carbon may have iodine numbers less than 900. When other forms of carbon or granular activated carbon with an



iodine number of less than 900 are used, the manufacturer should provide performance data to demonstrate that each bed has the capacity to reduce the total chlorine concentration in the feed water to less than 0.1 mg/l when operating at the maximum anticipated flow rate for the maximum time interval between scheduled testing of the product water for total chlorine. Regenerated carbon should not be used. Some granular activated carbon contain aluminium, which can elute from the carbon and add to the burden of aluminium to be removed by reverse osmosis or ion exchange. The use of acid-washed carbon minimizes this source of aluminium in the water.

Where practical, portable dialysis systems supplied with water known to contain chloramine should include two carbon beds in series, which together provide a 10 min EBCT. Where that is not practical, alternative technologies can be used provided there is a redundant means of chloramine removal and that a total chlorine concentration of less than 0.1 mg/l is verified in a sample collected after the primary device before each treatment. Possible alternatives include: a granular activated carbon bed followed by a dense carbon block; and two carbon block filters in series.

Carbon beds used for free chlorine and chloramine removal are sometimes arranged as series-connected pairs of beds so that they need not be overly large. The beds within each pair are of equal size and water that flows through them are parallel. For removal of chloramine from water containing >1 mg/l, each pair of beds should have a minimum empty bed contact time of 5 min at the maximum flow rate through the bed. When series-connected pairs of beds are used, the piping should be designed to minimize differences in the resistance to flow from inlet and outlet between each parallel series of beds to ensure that an equal volume of water flows through all beds.

Although treatment of water by carbon is the method usually used to meet the requirement of 4.1.2 for total chlorine, it was recognized that, in certain situations, carbon might not adequately remove chloramine. Inadequate removal of chloramine might occur when chloramines in the form of naturally occurring N-chloramines are present or when practices such as the use of high pH or the inclusion of orthophosphate or polyphosphates are used. If the pH of the incoming water is out of the range specified by the manufacturer, the carbon might not function properly and deplete rapidly. In other situations, such as acute dialysis with portable water treatment systems, it could be impractical to use the volume of carbon required to ensure adequate chloramine removal. In such circumstances, other strategies for chloramine removal may be needed to supplement carbon. Acid injection can be used to decrease pH (see B.2.6), anion exchangers (also known as organic scavengers) can be installed before carbon beds to remove organic matter and other substances that might foul carbon beds, and dealkalizers can be used to reduce alkalinity. It is known that adding sodium bisulfite prior to the reverse osmosis system has been successful in eliminating chloramine in hemodialysis applications. Ascorbic acid has also been added to the acid concentrate used to eliminate chloramine from the final dialysis fluid.<sup>[38]</sup> It should be noted that a minimum contact time is required for ascorbic acid to neutralize chloramine in water. If ascorbic acid is being used to neutralize chloramine, and if unexplained red blood cell destruction or anemia occurs, the effectiveness of the ascorbic acid neutralization of chloramine should be investigated. Other means of removing chloramine, such as redox alloy media and ultraviolet irradiation, are used in the pharmaceutical and electronics industries. These processes are currently being evaluated for hemodialysis applications. The final choice of a system for chloramine removal in hemodialysis settings will depend on local conditions and might need to include more than one of the processes outlined above.

#### **B.2.6 Chemical injection systems**

Chemical injection systems may be used in the pretreatment section of a water purification system to supplement the physical purification processes described in the previous clauses. Applications of chemical injection include the addition of sodium bisulfite to remove chloramine and the addition of acid to adjust pH.

Chemical injection systems consist of a reservoir that contains the chemical to be injected, a metering pump, and a mixing chamber located in the main water line. Chemical injection systems also include some means of regulating the metering pump to control the addition of a chemical. This system should be designed to tightly control the addition of the chemical. The control system should ensure that a chemical is added only when water is flowing through the pretreatment cascade and that it is added in fixed proportion to the water flow or based on some continuously monitored parameter, such as pH, using an automated control system. If an automated control system is used to

inject the chemical, the controlling parameter should be independently monitored. There should also be a means of verifying that the concentrations of any residuals arising from the chemical added to the water are reduced to a safe level before the water reaches its point of use.

When acid is added to adjust pH, a mineral acid should be used; organic acids can act as a nutrient and allow bacteria to proliferate.

Reservations were expressed about the addition of chemicals to the water. However, it was recognized that the addition of chemicals could be necessary, in some circumstances, if a facility is to meet the maximum contaminant levels set forth in 4.1.2. For example, if the municipal water contains high levels of *N*-chloramines or chloramine in the presence of orthophosphate or polyphosphate, injection of sodium bisulfite can be one of the few options available for chloramine removal.

If chemical injection is used in the pretreatment cascade, users should ensure that the addition of the chemical does not interfere with the operation of subsequent purification processes, including the primary purification process. For example, the performance of thin-film composite reverse osmosis membranes might be affected by the pH of the feed water. At pH levels below 7, the rejection of fluoride can be substantially reduced, compared to its rejection at a pH of 8.

### **B.2.7 Reverse osmosis**

Reverse osmosis (RO) systems have become widely used in hemodialysis water treatment systems, largely because these devices remove dissolved inorganic and organic solutes, as well as bacteria and bacterial endotoxins.

The following requirements apply to reverse osmosis systems.

- a) When used to prepare water for hemodialysis applications, either alone or as the last chemical purification stage in a water treatment system, reverse osmosis systems should be shown to be capable, at installation, of meeting the requirements of ISO 13959, when tested with the typical feed water of the user.
- b) Reverse osmosis devices should be equipped with online monitors that allow the determination of rejection rates and product-water conductivity. The product-water conductivity monitor should activate audible and visual alarms when the product-water conductivity exceeds the preset alarm limit. The alarms should be capable of notifying staff in the patient care area when reverse osmosis is the last chemical purification process in the water treatment system. Monitors that measure resistivity may be used in place of conductivity monitors.

The RO membrane separation process components are a semipermeable membrane, typically in a spiral-wound configuration, a pump, and various flow and pressure controls to direct the flow of water through the system. In operation, feed water is pressurized by the RO pump and is then directed along the surface of the semipermeable membrane. A portion of the water is forced through the membrane; a process that removes inorganic and organic solutes, bacteria and bacterial endotoxins. The remainder of the water continues along the membrane surface and is directed to the drain. Water passing through the membrane is referred to as “product water” or “permeate”. The water that flows along the membrane surface and to the drain is known as “reject water” or “concentrate”. This flow configuration, known as “cross-flow filtration”, prevents a progressive build-up of materials on the membrane surface that would eventually lead to fouling and membrane failure. In some reverse osmosis systems, a portion of the reject water stream is recycled to the feed-water stream. This recycling allows higher velocities across the membrane surface, which can help reduce membrane fouling, as well as allowing higher overall use of water. RO systems may operate in a single-stage or two-stage (double-pass) configuration depending on feed-water quality and/or local requirements and preferences. In a two-stage RO, the product water from the first stage acts as the feed water for the second stage.

**NOTE** The rejection rate of the second stage in a two-stage reverse osmosis system can be significantly lower than the rejection rate of the first stage. One reason for the difference in rejection rates is due to dissolved CO<sub>2</sub>.

RO systems may also be fitted with flowmeters, usually in the product water and the rejected water streams, to monitor the output of the RO system and gauges to monitor the pressure at various points in the system. Although not indicative of treated water quality, monitoring flow rates and pressures can help ensure that the system is operating within the manufacturer's specifications and thus will help ensure RO reliability.

In addition, it is recommended that, when a reverse osmosis system is the last chemical purification process in the water treatment system, means should be incorporated to prevent patient exposure to unsafe product water in the event of a product-water conductivity alarm. Such means could include diversion of the product water to the drain, in addition to activating the audible and/or visual alarms that should be situated to ensure a prompt response by personnel in the patient care area.

Depending on membrane configuration and materials of construction, RO systems are sensitive to various feed-water conditions that can lead to diminished performance or premature failure. To avoid such problems, users should carefully follow the manufacturer's instructions for feed-water treatment and monitoring to ensure that the RO is operated within its design parameters.

### **B.2.8 Deionization**

Deionization (DI) is an ion exchange process that removes both anions (negatively charged ions) and cations (positively charged ions) from water. During the exchange process, hydroxyl ions replace other feed-water anions, and hydrogen ions replace other feed-water cations; the hydroxyl and hydrogen ions then combine to form pure water. DI systems may contain anion and cation resin in separate vessels, known as “dual-bed systems”, or may have both resin types mixed together in a single vessel, known as “mixed-bed” or “unibed systems”.

Deionizers are an effective means of removing ionic contaminants from water. However, they do not remove nonionic contaminants and they can contribute bacterial contaminants to the water rather than remove them. The inability of deionizers to remove nonionic contaminants could limit aluminium removal by deionization, since aluminium is an amphoteric substance that changes from being cationic to being anionic as the pH varies from acidic to basic.<sup>[12]</sup> At neutral pH, aluminium is present mostly as colloidal aluminium, which does not carry a charge and is not removed by deionization.<sup>[4]</sup> Furthermore, deionizers have a finite capacity for contaminant removal. Once the deionizer is depleted of hydrogen and hydroxyl ions, the next least avidly bound ions will be displaced by more avidly bound ions. For example, once the hydroxyl ions are depleted, anionic contaminants in the water will displace fluoride ions from the anion exchange resin.<sup>[26]</sup> This phenomenon has led to high levels of fluoride in the product water, with subsequent patient injury and death.<sup>[25][21]</sup> Deionization, even in combination with an endotoxin-retentive filter, does not remove certain low-molecular-weight toxic bacterial products, such as microcystins. For the above reasons, use of deionization as the primary means of treating water supplying multiple dialysis machines is strongly discouraged. Deionization may be used to polish product water from a reverse osmosis system or may be used as a standby if the reverse osmosis system fails. Many believe that a two-stage reverse osmosis system operated in a redundant configuration is preferable to a combination of reverse osmosis and deionization.

The most common configuration for DI is to have two mixed beds in series, with resistivity monitors being placed downstream of each bed. Upon exhaustion of the first bed, reliance for water of sufficiently high resistivity shifts to the second bed, and dialysis operations may be continued for a short time until a replacement bed is installed, provided that the product water from the second tank has a specific resistivity of 1 MΩ·cm or greater.

DI has a finite capacity that, when exceeded, will cause dangerously high levels of contaminants in the product water. Therefore, DI systems, when used to prepare water for hemodialysis applications, should be monitored continuously to produce water of 1 MΩ·cm or greater specific resistivity (or conductivity of 1 μS/cm or less) at 25 °C. An audible and visual alarm should be activated when the product-water resistivity falls below this level and the product-water stream should be prevented from reaching any point of use, for example by being diverted to drain. The alarm should be capable of notifying staff in the patient care area. Under no circumstances should DI be used when the product water of the final bed has a resistivity below 1 MΩ·cm.

Feed water for deionization systems should be pretreated with activated carbon, or a comparable alternative, to prevent nitrosamine formation.

If a deionization system is the last process in a water treatment system, it should be followed by an endotoxin-retentive filter or other bacteria- and endotoxin-reducing device. The tendency for deionizers to contribute bacterial contaminants to the water is greater when deionizers are kept as a backup for a reverse osmosis system, particularly if there is no flow through the deionizers. Some facilities counter this tendency by connecting the deionizers in parallel to the main water line and by maintaining a low flow through them. An alternative approach is to contract with a local supplier to provide backup deionizers on demand.

**NOTE** The requirements given above for deionization might not apply to electrodeionization (EDI) technology, which can be used as an alternative to deionization following reverse osmosis in hemodialysis applications.

### **B.2.9 Endotoxin-retentive filters**

Endotoxin-retentive filters are membrane-based separation devices that may be used to remove both bacteria and endotoxins. Endotoxin-retentive filters should be placed in dialysis water systems at locations downstream of deionization. They may also be used at the end of the purification cascade and in dialysis water or central dialysis fluid distribution systems. Endotoxin-retentive filters can also be used in the dialysis fluid line of individual dialysis machines as a final barrier against bacteria and endotoxins. These filters are considered part of the dialysis machine and might not be subject to all the recommendations that follow.

**NOTE** Endotoxin-retentive filters do not remove low-molecular-weight microbial metabolites.

Endotoxin-retentive membranes used for hemodialysis applications are typically in either a spiral-wound configuration or a hollow-fibre configuration. Spiral-wound ultrafilters are usually operated in a cross-flow mode, with a fraction of the feed water being forced through the membrane and the remainder being directed along the membrane surface to drain. As with reverse osmosis, cross-flow filtration is intended to minimize membrane fouling. Hollow-fibre endotoxin-retentive filters are typically housed in vessels similar to those used for cartridge sediment filters and may be operated in a cross-flow or a dead-end (no cross-flow) mode. When used in a water purification system for hemodialysis applications, an endotoxin-retentive filter should be shown to reduce the concentrations of bacteria and endotoxins entering the filter by factors at least as great as those specified in the manufacturer's labelling.

Endotoxin-retentive filters should be fitted with a means of assessing filter integrity and fouling. One suitable means is to monitor the pressure drop ( $\Delta P$ ) across the filter at a given product-water flow rate using pressure gauges on the inlet (feed) and outlet (product) water lines. Alternatively, product-water flow rate can be measured at a given pressure drop. Such monitoring will indicate when membrane fouling has progressed to the point at which membrane replacement or cleaning is needed. Monitoring also ensures that the device is being operated in accordance with the manufacturer's instructions. Endotoxin-retentive filters should be included in routine disinfection procedures to prevent uncontrolled proliferation of bacteria in the filter. If bacterial proliferation is not controlled, bacteria can "grow through" the membrane and contaminate the product-water compartment of the filter. Endotoxin-retentive filters operated in the cross-flow mode should also be fitted with a flowmeter to monitor the flow rate of water being directed to the drain.

## **B.3 Dialysis Water storage and distribution**

### **B.3.1 General**

The function of the water storage and distribution system is to distribute dialysis water from the treatment cascade to its points of use, including individual hemodialysis machines, proportioning systems used to prepare dialysis fluid centrally, dialyzer reprocessing equipment, and concentrate preparation systems. A water storage and distribution system typically contains a large volume of water exposed to a large surface area of piping and storage tank walls.

Because chlorine and chloramine are removed in the purification process, the water does not contain a bacteriostatic agent. This combination of circumstances predisposes wetted surfaces to bacterial proliferation and biofilm formation. Therefore, any dialysis water storage and distribution system should be designed specifically to facilitate bacterial control, including measures to prevent bacterial colonization and to allow for easy and frequent disinfection.

### **B.3.2 Water storage**

When used, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Storage tanks should have a tight-fitting lid and be vented through a hydrophobic 0.22 µm to 0.45 µm air filter. The filter should be changed on a regular schedule according to the manufacturer's instructions or if it becomes wet. A means should be provided to effectively disinfect any storage tank installed in a water distribution system. Internal spray mechanisms can facilitate effective disinfection and rinsing of a storage tank.

### **B.3.3 Water distribution**

Two types of water distribution systems are used: direct feed systems and indirect feed systems. In a direct feed system, dialysis water flows directly from the last stage of the purification cascade to the points of use. In an indirect feed system, dialysis water flows from the end of the purification cascade to a storage tank. From there, it is distributed to the points of use. The water storage and distribution system chosen for a particular situation should provide the simplest possible flow path and contain the smallest volume of water consistent with the operating needs of the dialysis unit. The simplest system is generally a direct feed system. However, direct feed systems can be impractical. For example, the pressure at the end of the purification cascade could be insufficient to provide adequate flow and pressure at the points of use without a booster pump. If a direct feed system is used, it is also necessary to size the water treatment cascade to provide sufficient water to meet the peak demand. For these reasons, an indirect feed system with a storage tank may be used. Since storage tanks provide a large surface area for potential biofilm formation, their volume should be kept to a minimum in order to maximize water turnover in the tank. Whichever type of system is used, water distribution systems should be configured as a continuous loop and designed to minimize bacterial proliferation and biofilm formation (see Clause 8). A centrifugal pump made of inert materials is necessary to distribute the dialysis water and aid in effective disinfection. A multistage centrifugal pump is preferred for this purpose.

Direct feed distribution systems typically return unused dialysis water to the feed side of the reverse osmosis unit. If the pressure at the end of the distribution loop decreases to a value below the water pressure at the inlet to the reverse osmosis pressurizing pump, retrograde flow of untreated water into the distribution loop can occur. To minimize this risk, it is recommended that dual check valves or a break tank at the inlet to the reverse osmosis system with an air gap on the lines from the pretreatment cascade and the distribution loop be used to prevent retrograde flow and that the pressure at the end of the distribution loop be monitored.

Distribution systems for dialysis water should be constructed of materials that do not contribute chemicals, such as aluminium, copper, lead, and zinc, or bacterial contaminants to dialysis water. The choice of materials used for a water distribution system will also depend on the proposed method of disinfection. Table B.1 provides some guidance on the compatibility of different materials and disinfection agents. Whatever material is used, care should be taken to select a product with properties that provide the least favourable environment for bacterial proliferation, such as smooth internal surfaces.

**Table B.1 — Guidance on piping materials used in dialysis water distribution systems and their compatibility with common disinfectants**

| Material                                                                                                                                                                                                                                                                   | Sodium hypochlorite (bleach) | Peracetic acid | Formaldehyde | Hot water | Ozone <sup>a</sup> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|----------------|--------------|-----------|--------------------|
| PVC                                                                                                                                                                                                                                                                        | X                            | X              | X            |           | X                  |
| CPVC                                                                                                                                                                                                                                                                       | X                            | X              | X            |           | X                  |
| PVDF                                                                                                                                                                                                                                                                       | X                            | X              | X            | X         | X                  |
| PEX                                                                                                                                                                                                                                                                        | X                            | X              | X            | X         | X                  |
| SS                                                                                                                                                                                                                                                                         |                              | X              | X            | X         | X                  |
| PP                                                                                                                                                                                                                                                                         | X                            | X              | X            | X         |                    |
| PE                                                                                                                                                                                                                                                                         | X                            | X              | X            |           | X                  |
| ABS                                                                                                                                                                                                                                                                        |                              | X              |              |           |                    |
| PTFE                                                                                                                                                                                                                                                                       | X                            | X              | X            | X         | X                  |
| Glass                                                                                                                                                                                                                                                                      | X                            | X              | X            | X         | X                  |
| NOTE 1 X denotes probable compatibility.                                                                                                                                                                                                                                   |                              |                |              |           |                    |
| NOTE 2 PVC = polyvinylchloride, CPVC = chlorinated polyvinylchloride, PVDF = polyvinylidene fluoride, PEX = cross-linked polyethylene, SS = stainless steel, PP = polypropylene, PE = polyethylene, ABS = acrylonitrile butadiene styrene, PTFE = polytetrafluoroethylene. |                              |                |              |           |                    |
| <sup>a</sup> Ozone refers to ozone dissolved in water, not ozone gas.                                                                                                                                                                                                      |                              |                |              |           |                    |

Table B.1 is not intended as an exhaustive compilation of all possible compatible combinations of piping material and disinfectant. Considerations of compatibility should include any joint materials and pipe fittings, as well as the actual piping material. The concentration of germicide and the duration, frequency, and conditions (flow, pressure, temperature) of exposure should also be taken into account.

Users should verify compatibility between a given germicide and the materials of a piping system with the supplier of that piping system and/or the disinfectant supplier before using the germicide.

If the length of a connection exceeds three times the pipe diameter, it should be exposed to germicide during routine disinfection.

### **B.3.4 Bacterial control devices**

#### **B.3.4.1 General**

Traditionally, chemical disinfection has been used to prevent bacterial proliferation in dialysis water storage and distribution systems. One consequence of the increased attention being paid to bacterial control in the dialysis water storage and distribution system is an interest in alternatives to traditional chemical disinfection, including ultraviolet irradiators, ozone generators, and hot water disinfection systems. Both ozone and hot water can allow more frequent disinfection of the dialysis water storage and distribution system because prolonged rinsing is not needed to remove residual disinfectant from the system before dialysis is recommenced. The use of ozone or hot water is possible only if the systems are constructed from appropriately resistant materials. This limitation applies not only to the piping and any storage tank that may be in the system but also to all pumps, valves, and other fittings, including any O-rings and seals they may contain. Ultraviolet irradiation can be used to kill planktonic cells, but it has no impact on bacteria

located in biofilm. In order to achieve an effective and preventive disinfection with the respective system, the user should refer to the recommendations given by the manufacturer of the device or system.

#### **B.3.4.2 Ultraviolet irradiators**

When used to control bacterial proliferation in dialysis water storage and distribution systems, UV irradiation devices should be fitted with a low-pressure mercury lamp which emits light at a wavelength of 254 nm and provides a dose of radiant energy of  $30 \text{ mW} \cdot \text{s}/\text{cm}^2$ . If the irradiator includes a calibrated ultraviolet intensity meter, the minimum dose of radiant energy should be at least  $16 \text{ mW} \cdot \text{s}/\text{cm}^2$ . The device should be sized for the maximum anticipated flow rate according to the manufacturer's instructions. It is recommended that UV irradiators be followed by an endotoxin-retentive filter to remove pyrogens.

The recommendations provided in this clause concern UV irradiator used specifically for bacterial control. UV irradiators may also be used for other applications in a water purification and distribution system.

Ultraviolet irradiation can also be used to control bacteria in the pretreatment section of a water treatment system, such as the following carbon beds to reduce the bacterial burden presented to a reverse osmosis unit.

UV irradiators should be equipped with a calibrated ultraviolet intensity meter, as described above, or with an online monitor of radiant energy output that activates a visible alarm, which indicates that the lamp should be replaced. Alternatively, the lamp should be replaced on a predetermined schedule according to the manufacturer's instructions to maintain the recommended radiant energy output.

When ultraviolet irradiators are dipped in the storage tank to control bacteria, they should be designed to keep the required energy at the farthest position in the tank, considering the flow situation during operation.

#### **B.3.4.3 Ozone disinfection systems**

When used to control bacterial proliferation in dialysis water storage and distribution systems, an ozone disinfection system should be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. When ozone disinfection systems are used, it is recommended that an ambient air ozone monitor be installed in the area of the ozone generator.

Ozone generators convert oxygen to ozone using a corona discharge or ultraviolet irradiation. The ozone is then injected into the water stream. An ozone concentration of 0.2 mg/l to 0.5 mg/l, combined with a contact time of 10 min, measured at the end of the distribution loop, is capable of killing bacteria, bacterial spores, viruses, moulds, and yeast in water. Destruction of established biofilm could require longer exposure times and/or higher concentrations of ozone. Ozone can also degrade endotoxins.

Ozone can degrade many plastic materials, including PVC and elastomeric O-rings and seals. Therefore, ozone can be used for bacterial control only in systems constructed from ozone-resistant materials (see B.3.3).

#### **B.3.4.4 Hot water disinfection systems**

Hot water may be used to control bacterial proliferation in dialysis water storage and distribution systems. The exposure time should be according to the manufacturer's instructions. The water heater of a hot water disinfection system should be capable of delivering hot water at the temperature and for the exposure time specified by the manufacturer at any site in the dialysis water storage and distribution system. The manufacturer's instructions for using hot water disinfection systems should be followed. If no manufacturer's instructions are available, the effectiveness of the system can be demonstrated by verifying that the system maintains a specified temperature for a specified time and by performing ongoing surveillance with bacterial cultures and endotoxin testing.

NOTE 1 The ability of hot water to disinfect a distribution system is a function of water temperature and time of exposure. For example, the minimum exposure time for hot water disinfection at 80 °C is 10 min.

NOTE 2 The concept  $A_0$  can be used for quantification of heat disinfection between 65 °C to 100 °C (see ISO 15883-1). Temperature and time can be combined to yield a number representing a dose capable of achieving the required reduction in viable organisms.

$$A_0 = \sum 10^{(T-80)/z} \cdot \Delta t$$

where

$T$  is the temperature in °C;

$z$  is equal to 10 °C;

$\Delta t$  is the selected time period in seconds.

An  $A_0$  value of 1 is defined as an exposure to 80 °C for 1 s. Thus,  $A_0 = 600$  represents 10 min at 80 °C, 1 min at 90 °C, or 100 min at 70 °C.

Hot water disinfection systems can be used only in systems constructed from heat-resistant materials, such as PVDF (polyvinylidene fluoride), PEX (cross-linked polyethylene), SS (stainless steel), PP (polypropylene), and PTFE (polytetrafluoroethylene) (see B.3.3).

## B.4 Concentrate preparation

### B.4.1 General

Dialysis fluid is customarily prepared from two concentrates: the bicarbonate concentrate, which contains sodium bicarbonate (and sometimes additional sodium chloride), and the acid concentrate, which contains all remaining ions, acetic acid, and sometimes glucose. Some systems have also been developed that prepare acid concentrate from individual components, such as from a sodium chloride cartridge and a concentrated solution of the remaining minor electrolytes.

Acid concentrate can be supplied by the manufacturer in bulk or in single-use containers. In some cases, the manufacturer will pump the acid concentrate from bulk delivery containers into a holding tank at the dialysis facility. Systems have recently been introduced that allow a user at a dialysis facility to prepare acid concentrate from packaged powder and dialysis water using a mixer. If the acid concentrate is pumped into a bulk storage tank at the dialysis facility, the user is responsible for maintaining the concentrate in its original state and to ensure that the correct formula is used according to the patient's prescription. Acid concentrate prepared at the dialysis facility from powder and dialysis water is also the responsibility of the user.

Bicarbonate concentrate can be supplied by the manufacturer in one of the following three ways:

- a) in powder cartridges that are used to prepare concentrate online at the time of dialysis;
- b) as packaged powder that is mixed with dialysis water at the dialysis facility;
- c) in single-treatment containers of liquid concentrate.

Dialysis fluid can also be prepared from a single concentrate that contains acetate. The buffer is provided to the patient in the form of acetate, which is metabolized to yield bicarbonate. Acetate-based dialysis fluid is now rarely used in clinical practice. In general, acetate-based concentrate is handled in a similar manner to that of acid concentrate, except that acetate-based concentrate systems use only one concentrate which is mixed with dialysis water. The labels of acetate-based concentrate are colour-coded white.



#### **B.4.2 Materials compatibility**

All components used in concentrate preparation systems (including mixing and storage tanks, pumps, valves, and piping) should be fabricated from materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the concentrate to affect its purity, or with the germicides or germicidal procedure used to disinfect the equipment. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, zinc, galvanized material, lead, and aluminium, are specifically prohibited.

#### **B.4.3 Labelling**

##### **B.4.3.1 General**

Labelling strategies should permit positive identification by anyone using the contents of concentrate mixing tanks, bulk storage/dispensing tanks, and small containers intended for use with a single hemodialysis machine. Requirements for such positive identification will vary among facilities, depending on the differences between concentrate formulations used and on whether single or multiple dialysis fluid proportioning ratios are used. The use of multiple dialysis fluid proportioning ratios in a single facility is strongly discouraged.

In addition to the container labelling described below, there should be permanent records of all batches of concentrate produced at a dialysis facility. These records should include the concentrate formula produced, the volume of the batch, the lot numbers of powdered concentrate packages, the manufacturer of the powdered concentrate, the date and time of mixing, any test results, the person performing the mixing, the person verifying mixing and test results, and the expiration date, if applicable.

Although it is the responsibility of facilities to develop and use labelling to positively identify the contents of mixing tanks, bulk storage/dispensing tanks, and concentrate containers, the guidelines in the following subclauses are suggested.

##### **B.4.3.2 Mixing tanks**

Prior to batch preparation, a label should be affixed to the mixing tank that includes the date of preparation and the chemical composition or formulation of the concentrate being prepared. This labelling should remain on the mixing tank until the tank has been emptied. Using a photocopy of the concentrate manufacturer's package label provides a convenient and comprehensive means of identifying the chemical composition or formulation of the concentrate; however, the lot number and expiration date should be marked out because they apply only to the dry powder.

##### **B.4.3.3 Bulk storage/dispensing tanks**

These tanks should be permanently labelled to identify the chemical composition or formulation of their contents. As with mixing tanks, bulk storage/dispensing tank labelling can be conveniently accomplished by affixing a copy of the concentrate manufacturer's package label.

##### **B.4.3.4 Concentrate containers**

Concentrate containers may be nondisposable vessels provided by hemodialysis machine manufacturers and having a capacity sufficient for one or two hemodialysis sessions. The extent of labelling for these containers depends on the variety of concentrate formulations used and on whether the facility uses dialysis machines with different proportioning ratios; the latter practice is strongly discouraged. At a minimum, concentrate containers should be labelled with sufficient information to differentiate the contents from other concentrate formulations used at the facility. If a chemical spike is added to an individual container to increase the concentration of an electrolyte, the label should show the added electrolyte, the date and time added, and the name of the person making the addition (see B.4.5).

The additional information may be simple or extensive, but in all cases it should permit users to positively identify the container's contents.

#### **B.4.4 Concentrate mixing systems**

##### **B.4.4.1 General**

Concentrate mixing systems require a source of dialysis water, a suitable drain, and a ground-fault-protected electrical outlet. Protective measures should be used to ensure a safe work environment. For example, ventilation and personal protective equipment should be used to handle any residual dust that is introduced into the atmosphere as powdered concentrates are added to the system and to handle any additional heat produced by the device. Structural issues, such as the facility's weight-bearing capacity, should be addressed if systems are to be installed above ground level. Operators should at all times use appropriate personal protective equipment, such as face shields, masks, gloves, gowns, and shoe protectors, as recommended by the manufacturer.

If a concentrate mixing system is used, the preparer should follow the manufacturer's instructions for mixing the powder with the correct amount of dialysis water. The number of bags or the weight of powder added should be determined and recorded.

The manufacturer's recommendations should be followed regarding any preventive maintenance and disinfection procedures. Records should be maintained indicating the date, time, person performing the procedure, and results (if applicable).

##### **B.4.4.2 Acid concentrate mixing systems**

Acid concentrate mixing tanks should be designed to allow the inside of the tank to be completely emptied and rinsed according to the manufacturer's instructions when concentrate formulas are changed. Use of a tank with a sloping bottom that drains from the lowest point is one means of facilitating this process. Because concentrate solutions are highly corrosive, mixing systems should be designed and maintained to prevent corrosion. Acid concentrate mixing tanks should be emptied completely and rinsed with dialysis water before mixing another batch of concentrate. If another batch of concentrate is not to be mixed promptly, the mixing tank should be rinsed again with dialysis water before the next batch is mixed.

##### **B.4.4.3 Bicarbonate concentrate mixing systems**

Bicarbonate concentrate mixing tanks should be designed to drain completely; for example, they should have a sloping bottom and a drain at the lowest point. High- and low-level alarms can prevent overfilling and air damage to the pump. Because concentrate solutions are highly corrosive, mixing systems should be designed and maintained to prevent corrosion. Mixing tanks should have a tight-fitting lid and should be designed to allow all internal surfaces to be disinfected and rinsed. A translucent tank allows users to see the liquid level; the use of sight tubes is not recommended because of the potential for microbial growth, such as bacteria, algae, and fungi.

Once mixed, bicarbonate concentrate should be used within the time specified by the manufacturer of the concentrate. The concentrate should be shown to routinely produce dialysis fluid meeting the recommendations of 4.3.2. Overagitating or overmixing of bicarbonate concentrate should be avoided, as this can cause CO<sub>2</sub> loss and can increase pH. (Systems designed for mixing dry acid concentrates may use methods that are too vigorous for dissolving dry bicarbonate.)

The mixing tank should be either

— completely emptied and disinfected according to the manufacturer's instructions, or

- disinfected using a procedure demonstrated by the facility to be effective in routinely producing dialysis fluid that allows the recommendations of 4.3.2 to be met.

#### **B.4.5 Additives**

Manufacturers provide acid concentrates with a wide range of electrolyte compositions for different proportioning ratios. Most typical dialysis fluid prescriptions can be obtained by using one or more of these commercially available concentrates. If particular formulations are not available, manufacturers provide additives that can be used to adjust the level of potassium or calcium in the dialysis fluid. These additives are commonly referred to as “spikes”.

NOTE The use of additives is not approved in some countries.

Concentrate additives should be mixed with liquid acid concentrates according to the manufacturer's instructions, taking care to ensure that the additive is formulated for use in concentrates of the appropriate dilution ratio. When liquid additives are used, the volume contributed by the additive should be considered when calculating the effect of dilution on the concentration of the other components in the resulting concentrate. When powder additives are used, care should be taken to ensure that the additive is completely dissolved and mixed before the concentrate is used.

### **B.5 Concentrate storage and distribution**

#### **B.5.1 Materials compatibility**

All components used in concentrate distribution systems (including concentrate containers, storage tanks, and piping) that contact the fluid should be fabricated from nonreactive materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the concentrate to affect its purity. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, zinc, galvanized material, lead, and aluminium, are specifically prohibited.

#### **B.5.2 Bulk storage tanks (acid concentrate)**

Procedures should be in place to control the transfer of the acid concentrate from the delivery container to the storage tank to prevent the inadvertent mixing of different concentrate formulations. If possible, the tank and associated plumbing should form an integral system to prevent contamination of the acid concentrate. The storage tanks and inlet and outlet connections, if remote from the tank, should be secure and labelled clearly.

#### **B.5.3 Distribution systems**

Concentrate may be distributed from a central preparation point using reusable concentrate containers that contain sufficient concentrate for one to two treatments, or it may be distributed through a piping system that provides concentrate connections at each treatment station. A combination of these two systems may also be used, with some concentrates distributed by concentrate container and others through a piping system. Two common configurations used for distributing concentrate through a piping system are gravity feed and pressurized. Gravity feed systems require an elevated tank; pressurized systems deliver the concentrate using a pump and motor and do not require an elevated tank. The maximum allowable concentrate delivery pressure is specified by the manufacturer of the dialysis fluid delivery machine and should not be exceeded.

Elevated tanks are usually smaller than those used for preparing concentrates. Elevated tanks for bicarbonate concentrate distribution should be equipped with conical or bowl-shaped bottoms, tight-fitting lids, a spray mechanism, and high- and low-level alarms. Any air vents should have 0.45 µm hydrophobic vent filters.

### **B.5.3.1 Acid concentrate distribution systems**

Acid concentrate delivery piping should be labelled and colour-coded red at the point of use (at the container filling station or the dialysis machine connection). More than one type of acid concentrate may be delivered, and each line should clearly indicate the type of acid concentrate it contains. Even though there are no published reports of acid concentrate supporting bacterial growth, every effort should be made to keep the system closed to prevent contamination and evaporation. If the acid system remains intact, no rinsing or disinfection is necessary.

### **B.5.3.2 Bicarbonate concentrate distribution systems**

Bicarbonate concentrate delivery piping should be colour-coded blue at the point of use (at the concentrate container filling station or dialysis machine connection). All joints should be sealed to prevent leakage of concentrate.

Because bicarbonate concentrates provide excellent media for bacterial proliferation,<sup>[80][81]</sup> bicarbonate concentrate delivery systems should be disinfected on a regular basis to ensure that the dialysis fluid routinely achieves the level of bacteriological purity recommended in 4.3.2. The manufacturer's instructions can provide an initial disinfection schedule. However, this schedule might need to be adjusted on the basis of the user's bacteriological monitoring. For piped distribution systems, the entire system, including patient station ports, should be purged of bicarbonate concentrate before disinfection. Each patient station port should be opened and flushed with disinfectant and then rinsed; otherwise, it would be a "dead leg" in the system. Also, prompt use of bicarbonate concentrates prepared in dialysis facilities from powder and dialysis water is strongly recommended.

When reusable concentrate containers are used to distribute bicarbonate concentrate, they should be rinsed free of residual concentrate before disinfection.

All chemical disinfectants (e.g. sodium hypochlorite and peracetic acid products) that are compatible with dialysis machines can be used to disinfect bicarbonate concentrate distribution systems. However, some disinfectants attack biofilm better than others. Appropriate dwell times and concentrations should be used as recommended by the manufacturer of the concentrate system. If this information is not available, sodium hypochlorite solutions, such as bleach, may be used at a dilution of 1:100 and proprietary disinfectants at the concentration recommended by the manufacturer for disinfecting piping systems. In the event that precipitation or salt build-up impedes flow through a piping system, cleaning with a 1:34 solution of 5 % acetic acid (e.g. distilled white vinegar) is recommended. Some manufacturers supply bicarbonate concentrate systems with UV irradiation or ozone systems for bacterial control.

UV irradiation devices that are used to control bacterial proliferation in the pipes of bicarbonate concentrate distribution systems should be fitted with a low-pressure mercury lamp that emits light at a wavelength of 254 nm and provides a dose of radiant energy of 30 mW·s/cm<sup>2</sup>. The device should be sized for the maximum anticipated flow rate according to the manufacturer's instructions and be equipped with an online monitor of radiant energy output that activates a visual alarm indicating that the lamp should be replaced. Alternatively, the lamp should be replaced on a predetermined schedule according to the manufacturer's instructions to maintain the recommended radiant energy output. It is recommended that UV irradiators be followed by an endotoxin-retentive filter. Disinfection of the bicarbonate concentrate distribution system should continue to be performed routinely.

When used to disinfect the pipes of a bicarbonate concentrate distribution system, an ozone generator should be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. When ozone disinfection systems are used, ambient air should be monitored for ozone according to national standards and regulations.

When heat is used to disinfect the bicarbonate distribution system, the time and temperatures should be validated by the manufacturer.

Overagitation or mixing of bicarbonate concentrate can result in loss of CO<sub>2</sub> from the solution. Loss of CO<sub>2</sub> results in an increase in pH and favours the formation of carbonate that can lead to precipitation of calcium carbonate in the fluid pathways of the dialysis machine following dialysis fluid proportioning.

### **B.5.3.3 Concentrate outlets**

For piped concentrate distribution systems, each treatment station is equipped with a concentrate outlet for bicarbonate, one or more outlets for acid concentrate, and a dialysis water outlet for connection to the inlet line of the dialysis machine (optional). To prevent mix-ups with delivery of two or more types of acid concentrate, each concentrate should have its own outlet. Concentrate outlets should be compatible with the dialysis machine and have a means of minimizing the risk that the wrong concentrate will be connected to an outlet. The dispensing outlets should be labelled with the appropriate symbol (see Table B.2) indicating the proportioning ratio for the dialysis machine, if required, and should be colour-coded blue for bicarbonate and red for acid.

## **B.6 Dialysis fluid proportioning**

Essentially, all dialysis fluid is produced with three fluid streams: dialysis water, acid concentrate, and bicarbonate concentrate. This three-stream combination produces a highly buffered dialysis fluid with a pH between 6.9 and 8.0. Dialysis fluid can also be prepared from a single concentrate that contains acetate to provide a dialysis fluid in which buffer is provided to the patient in the form of acetate, which is subsequently metabolized to yield bicarbonate. However, acetate-containing dialysis fluid is now rarely used in clinical practice.

Different manufacturers of dialysis machines use different methods of controlling the proportions of the concentrates. These can be generally grouped into two categories: “fixed proportioning” and “servo-control”. With both methods, the operator can select a desired sodium and bicarbonate level, or conductivities corresponding to defined sodium and bicarbonate levels, and the machine will make the necessary adjustments to achieve the selected levels. Both types use a redundant system of controls and monitoring. With fixed proportioning systems, the pumps are set to established volumes, and the final conductivity is verified. With servo-control machines, the individual concentrates are added until the conductivity achieves the expected value. A final redundant conductivity monitor monitors the conductivity. Some machines also monitor the pH of the dialysis fluid as an additional safeguard against gross errors in dialysis fluid formulation. A different type of machine with a batch tank and dedicated concentrates is also available.

It is important that the acid and bicarbonate concentrates be matched with respect to the proportioning ratio and with the model and setup configuration of the dialysis machine. Several types of three-stream concentrates are available, with different ratios of acid concentrate to bicarbonate concentrate to dialysis water (see Table B.2). The different proportioning types are not compatible with one another. Generally, bicarbonate is available in one or two forms for each proportioning type (in liquid, cartridge, or dry powder, and in various sizes). Each proportioning type has numerous acid concentrate formulations (“codes”) with different amounts of potassium, calcium, and magnesium ions, plus glucose. To help differentiate between concentrates of different proportioning types, ISO 13958 recommends that the manufacturer include a geometric symbol on the labels, along with acid/base colour coding.

**Table B.2 — Symbols and colour coding for different concentrate proportioning ratios**

| Concentrate type                                                | Acid proportioning ratio <sup>a</sup><br>(red colour coding) | Geometric symbol | Bicarbonate concentrate<br>(blue colour coding) | Comments                                                                                                                                  |
|-----------------------------------------------------------------|--------------------------------------------------------------|------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 35X                                                             | 1:34 <sup>a</sup>                                            | Square           | Dry, liquid, or cartridge                       |                                                                                                                                           |
| 36.83X                                                          | 1:35.83 <sup>a</sup>                                         | Circle           | Dry or liquid                                   | Bicarbonate concentrate contains some NaCl.                                                                                               |
| 45X                                                             | 1:44 <sup>a</sup>                                            | Triangle         | Dry, liquid, or cartridge                       |                                                                                                                                           |
| 36.1X                                                           | 1:35.1 <sup>a</sup>                                          | Diamond          | Cartridge                                       | Powder cartridges may be used for other proportioning ratios, except for 36.83X, in which the bicarbonate concentrate also contains NaCl. |
| NOTE      Acetate-containing concentrate is colour-coded white. |                                                              |                  |                                                 |                                                                                                                                           |
| <sup>a</sup> Acid: bicarbonate and water.                       |                                                              |                  |                                                 |                                                                                                                                           |

Some models of dialysis machines can use concentrates of only one type of proportioning ratio, but others may be set up or calibrated for use with concentrates of more than one proportioning type. (Note that changing from one proportioning ratio to another requires recalibration for some models of dialysis machines.) Thus, for those machines, the type of concentrate should be labelled on the machine or clearly indicated by the machine display. It is strongly recommended that facilities configure every machine to use only one type of concentrate.

Injuries related to improper dialysis fluid are rare, but they can and do happen when all procedures are not followed. Frequently, when the error occurs, several patients have been exposed before the facility recognizes the mistake. For example, because one of the concentrates is acidic and the other is basic, connecting the wrong concentrates to the machine could result in dialysis fluid that could harm the patient. Thus, it is necessary for the operator to follow the manufacturer's instructions regarding dialysis fluid conductivity, including measuring the approximate pH with an independent method before starting the treatment of the next patient, if recommended by the dialysis machine manufacturer.

Even though a single concentrate is used to prepare acetate dialysis fluid, consideration should be given to checking both conductivity and pH because mix-ups involving acid concentrate and other chemicals can result in an acceptable conductivity with an incorrect pH.

Dialysis fluid is usually prepared by a proportioning system that sequentially adds acid concentrate and bicarbonate concentrate to dialysis water. These systems produce a buffered physiologic dialysis fluid with a pH between 6.9 and 8.0. Current dialysis machines are also capable of supplying acetate dialysis fluid. For acetate dialysis fluid, dialysis water is mixed with a single acetate concentrate to produce the dialysis fluid. This system is not buffered, so the pH can vary depending on the supply water. More recently, systems have been developed that use three concentrates (bicarbonate, sodium chloride, and an acid concentrate containing the remaining electrolytes) to allow more sophisticated variation of the dialysis fluid composition during dialysis.

## B.7 Central dialysis fluid storage and delivery systems

### B.7.1 General

Dialysis fluid may be prepared centrally and distributed to dialysis consoles at the treatment stations using a central dialysis fluid delivery system (CDDS). Central dialysis fluid delivery systems incorporate many of the features found in dialysis water storage and distribution systems (see B.3) and concentrate preparation systems (see B.4) and most of the recommendations in those clauses are applicable to central dialysis fluid delivery systems; however, there are additional factors to be considered.

### B.7.2 Design and maintenance

Central dialysis fluid delivery systems are usually designed as single-pass systems, although a distribution loop can also be used.

If a distribution loop is used, it is necessary to pay attention to preventing calcium carbonate precipitation and an increase in pH resulting from loss of CO<sub>2</sub> and an increase in temperature as the dialysis fluid is circulated.

Central dialysis fluid delivery systems should be disinfected daily to limit biofilm formation using a chemical disinfectant or hot water. Such disinfection should include the tubing connection to the hemodialysis console as well as the dialysis console.

Microbiological monitoring of central dialysis fluid delivery systems should be similar to that described in 8.3. Monitoring should include the dialysis consoles located at each treatment station, as well as the dialysis fluid distribution system. Sampling should include samples collected from the inlet to dialysis fluid proportioning system and the inlet to dialysis consoles. The frequency of monitoring should meet applicable local recommendations; if no such recommendations exist the following are suggested.

- a) Water system: The number of samples and positions of sampling should be based on the complexity and size of the water system. The frequency will depend on the analysis of the data collected during the validation and revalidation activities. Monthly monitoring is most frequently adopted but less frequent monitoring may be possible based on data collected during the validation and revalidation.
- b) Dialysis fluid/hemodialysis machines without a validated bacteria- and endotoxin-retentive filter: Machines should be sampled on a regular basis to provide verification of the effectiveness of the disinfection process. The schedule of sampling will depend on the type of disinfection process being used. Each machine should be sampled at least once per year and different machines should be sampled on each occasion. Monthly monitoring is most frequently adopted.
- c) It is not necessary to take samples of ultrapure dialysis fluid or substitution fluids if their production paths are fitted with bacteria- and endotoxin-retentive filters validated by the manufacturer and operated and monitored according to the manufacturer's instructions. It could be necessary to sample the dialysis fluid entering such bacteria- and endotoxin-retentive filters depending on the manufacturer's instructions for use of the filters; for example, when the instructions for use specify the quality of the fluid entering the filter. (See also Annexes D and E.)

The results of testing should be subjected to trend analysis. When results exceed the action levels, or in the case of a patient's pyrogenic reaction or suspected bacteremia/fungemia, an investigation and follow-up should be initiated. This investigation could include additional sampling and extra disinfection procedures carried out as per the manufacturer's recommendations.

### **B.7.3 Dialysis fluid storage**

Central dialysis fluid delivery systems usually include a dialysis fluid storage tank. The tank should be designed to drain completely; for example, it should have a sloping bottom and a drain at the lowest point, and be ventilated through a hydrophobic 0.45 µm air filter.

### **B.7.4 Materials compatibility**

All components used in dialysis fluid storage and delivery systems (including storage tanks, pumps, valves and piping) should be fabricated from materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the dialysis fluid to affect its purity, or with the germicides or germicidal procedure used to disinfect the system. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, zinc, galvanized material, lead, and aluminium, is specifically prohibited.



## Annex C (informative)

### Monitoring guidelines for water treatment equipment, distribution systems, and dialysis fluid

#### C.1 Monitoring systems

Table C.1 provides guidelines on monitoring systems used for preparing and distributing dialysis fluid. The recommendations given in Table C.1 can be used as a starting point for developing a quality management programme for dialysis fluid when the manufacturer or supplier of the system does not provide adequate instructions. Not every item listed in Table C.1 will be required in all dialysis facilities and the frequency of monitoring may differ depending on the nature of the water supplied to the dialysis facility; for example, whether or not the water supply is disinfected using chloramine. The actual quality management programme for a given facility will depend on the components used in that facility's water treatment system, the purposes for which the fluids are to be used, the results of validation procedures, and any applicable local regulations.

NOTE Refer to footnotes <sup>a</sup> and <sup>b</sup> for an explanation of the use of Xs in the "Typical range of values" column.

**Table C.1 — Suggested framework for monitoring water treatment equipment,  
distribution systems, and dialysis fluid**

| Item to monitor                   | What to monitor                                | Typical range of values                                                     | Typical interval | Comments |
|-----------------------------------|------------------------------------------------|-----------------------------------------------------------------------------|------------------|----------|
| Sediment filter                   | Pressure drop across the filter (see 7.3.2)    | Pressure drop less than XXXX                                                | Daily            | NA       |
| Sediment filter backwashing cycle | Backwash cycle timer setting (see 7.3.2)       | Backwash clock set to XX:XX                                                 | Daily            | NA       |
| Cartridge filter                  | Pressure drop across the filter (see 7.3.3)    | Pressure drop less than XXXX                                                | Daily            | NA       |
| Water softener                    | Residual hardness of product water (see 7.3.4) | Hardness as specified by the manufacturer of the reverse osmosis equipment. | Daily            | NA       |
| Water softener brine tank         | Level of undissolved salt in tank (see 7.3.4)  | Salt level at XXX                                                           | Daily            | NA       |
| Water softener regeneration cycle | Regeneration cycle timer setting (see 7.3.4)   | Regeneration cycle timer set to XX:XX                                       | Daily            | NA       |

| Item to monitor             | What to monitor                                                                                                      | Typical range of values                                                         | Typical interval                            | Comments                                                                                                                                                                                                                                                          |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Carbon beds                 | Product-water total chlorine between the beds (see 7.3.5)                                                            | $\leq 0.1$ mg/l of total chlorine                                               | Daily                                       | Prior to each patient shift if chloramine is present in the feed water at 1 mg/l or more (see 7.3.5 for exceptions to these typical intervals). (Note that use of an online monitor can provide continuous monitoring and avoid the need for offline monitoring.) |
| Chemical injection system   | Level of chemical in the reservoir, injector function, value of the controlling parameter (e.g. pH) (see 7.3.6)      | Chemical level in reservoir $\geq$ XXX; controlling parameter in range XX to XX | Daily (continuous monitoring is preferable) | NA                                                                                                                                                                                                                                                                |
| Reverse osmosis             | Product water conductivity, total dissolved solids (TDS), or resistivity and calculated rejection (see 7.3.7)        | Rejection $\geq$ XX %<br>Conductivity $<$ XX $\mu$ S/cm                         | Daily (continuous monitoring is preferable) | NA                                                                                                                                                                                                                                                                |
| Reverse osmosis             | Product and reject flow rates, and calculated recovery (see 7.3.7)                                                   | Product water flow rate $\geq$ X,X l/min<br>XX % $<$ recovery $<$ XX %          | Daily (continuous monitoring is preferable) | NA                                                                                                                                                                                                                                                                |
| Deionizers                  | Product water resistivity or conductivity (see 7.3.8)                                                                | Resistivity $\geq$ 1 M $\Omega$ ·cm<br>Conductivity $\leq$ 1 $\mu$ S/cm         | Continuous monitoring                       | NA                                                                                                                                                                                                                                                                |
| Endotoxin-retentive filters | Pressure drop across the filter at a fixed flow rate or product-water flow rate at a fixed pressure drop (see 7.3.9) | Pressure drop less than XXXX or flow rate greater than XXX                      | Daily                                       | NA                                                                                                                                                                                                                                                                |

| Item to monitor                    | What to monitor                                                     | Typical range of values                                                                                                                                                  | Typical interval                                                                                                                     | Comments                                                                                                                                                                                                                                    |
|------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Water system chemical contaminants | Chemical contaminants as listed in Tables 1 and 2 of ISO 13959:2014 | <p>Maximums as listed in Tables 1 and 2</p> <p>The parameters to be monitored should be defined by the validation process on the basis of the expected contaminants.</p> | Yearly                                                                                                                               | These recommendations apply to dialysis water. However, chemical analysis of source water (or analysis results from the water supplier) is necessary to evaluate the overall performance of the water treatment system.                     |
| Dialysis water storage tanks       | Bacterial growth and endotoxins (see Clause 8)                      | <p>Total viable microbial count &lt; action level (typically 50 CFU/ml); (see 4.1.3)</p> <p>Endotoxin &lt; action level (typically 0.125 EU/ml); (see 4.1.3)</p>         | Monthly, or as defined by the results of the validation process for storage tanks supplying a central dialysis fluid delivery system | Specific testing at this location is performed to troubleshoot contamination of the distribution system for tanks connected to a water distribution piping system until a pattern of consistent compliance with limits can be demonstrated. |
| Water distribution piping system   | Bacterial growth and endotoxins (see 4.1.3)                         | <p>Total viable microbial count &lt; action level (typically 50 CFU/ml); (see 4.1.3)</p> <p>Endotoxin &lt; action level (typically 0.125 EU/ml); (see 4.1.3)</p>         | Monthly, or as defined by the validation process results                                                                             | NA                                                                                                                                                                                                                                          |
| UV irradiators                     | Energy output and/or the lamp life span (see 7.4.3.1)               | <p>Light output &gt; XXX</p> <p>Lamp life span &lt; XXXX</p>                                                                                                             | Monthly                                                                                                                              | NA                                                                                                                                                                                                                                          |

| Item to monitor                | What to monitor                                                                     | Typical range of values                                                                                                                                            | Typical interval                                                                                                                                                 | Comments                                                                                                  |
|--------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Ozone generators               | Concentration in the water and contact time (see 7.4.3.2)                           | Ozone concentration > XXX<br><br>Contact time > XXX<br><br>Residual ozone after disinfection < X,XX mg/l                                                           | During each disinfection                                                                                                                                         | NA                                                                                                        |
| Hot water disinfection systems | Temperature and time of exposure of the system to hot water (see 7.4.3.3)           | Temperature not less than XX °C; minimum exposure time at temperature ≥ XX min                                                                                     | During each disinfection                                                                                                                                         | This information might be available from the data logs of automated systems.                              |
| Chemical disinfection systems  | Concentration of germicide in water and contact time                                | Germicide concentration > X,X mg/l; residual germicide concentration < X,XX mg/l after rinsing                                                                     | During each disinfection                                                                                                                                         | NA                                                                                                        |
| Dialysis fluid                 | Conductivity, pH, electrolyte concentrations                                        | XX,X mS/cm < conductivity < XX, X mS/cm<br><br>pH in the range 6.9 to 8.0 for dialysis fluid containing bicarbonate, or as otherwise specified by the manufacturer | In accordance with local regulations or as specified by the manufacturer of the dialysis fluid delivery system (continuous monitoring for proportioning systems) | pH monitoring is necessary only if recommended by the manufacturer of the dialysis fluid delivery system. |
| Standard dialysis fluid        | Bacterial growth and endotoxin concentration in standard dialysis fluid (see 4.3.2) | Total viable microbial count < action level (typically 50 CFU/ml); (see 4.3.2)<br><br>Endotoxin < action level (typically 0.25 EU/ml); (see 4.3.2)                 | Monthly, rotated among machines so that each machine is tested at least once per year and different machines are sampled on each occasion                        | The sample should be collected at worst-case time (for example, Monday morning) if possible.              |

| Item to monitor          | What to monitor                                                                                                   | Typical range of values                                                                               | Typical interval                                                                                                                                                                                                                                                                                                | Comments |
|--------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Ultrapure dialysis fluid | Bacterial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyzer (see 4.3.3)             | Total viable microbial count < 0.1 CFU/ml; endotoxin < 0.03 EU/ml (see 4.3.3) (see 8.3.1 and Annex E) | Before the first use to validate the system and monthly thereafter<br><br>Bacterial growth and endotoxin tests are not necessary if the system is fitted with a bacteria- and endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions. | NA       |
| Substitution fluid       | Bacterial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyzer (see 8.3.1 and Annex E) | Sterile and nonpyrogenic (see 8.3.1 and Annex E)                                                      | Bacterial growth and endotoxin tests are not required if the system is fitted with a bacteria- and endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions.                                                                            | NA       |

<sup>a</sup> It is not possible to specify universally acceptable operating ranges for each device listed in the table since some of the specifications will be system-specific. In those cases, the facility should define an acceptable operating range based on the manufacturer's instructions or measurements of system performance.

<sup>b</sup> The actual interval for monitoring, testing, cleaning, and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6 and 8.2.2).

## C.2 Cleaning/disinfection strategies

See Table C.2.

NOTE Refer to the manufacturer's instructions for more detail prior to referring to the "Typical interval" column.

**Table C.2 — Summary of cleaning/disinfection strategies for dialysis water treatment systems, dialysis water storage and distribution systems, concentrate distribution systems, and dialysis fluid distribution systems**

| Item for cleaning/disinfection                 | Element(s) to be cleaned/disinfected                                                                             | Cleaning/disinfection              | Typical interval                                                      | Comments                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reverse osmosis                                | The membrane module should be disinfected, paying particular attention to the product side<br><br>(See 8.1, 8.2) | Disinfection                       | Monthly, or according to manufacturer's instructions<br><br>(See D.1) | The product side of the membrane is considered to be a part of the dialysis water distribution system. It should be disinfected at an interval sufficient to routinely produce dialysis water meeting the quality requirements of Clause 4. (See D.1, 3rd paragraph.) If needed, the feed side of the membrane should be cleaned periodically to remove foulants that can degrade membrane performance. |
| Water storage tanks                            | Tanks and pipes<br>(See 8.2.2.2)                                                                                 | Disinfection                       | Monthly, or according to manufacturer's instructions                  | More frequent disinfection might be necessary if indicated by microbiological testing results.                                                                                                                                                                                                                                                                                                          |
| Water distribution piping system               | Piping system<br>(See 8.1, 8.2, D.1)                                                                             | Disinfection                       | Monthly, or according to manufacturer's instructions                  | More frequent disinfection might be necessary if indicated by microbiological testing results.                                                                                                                                                                                                                                                                                                          |
| UV irradiators                                 | Quartz sleeve<br>(See 7.4.3.1)                                                                                   | Periodic cleaning<br>(See 7.4.3.1) |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                         |
| Concentrate mixing systems                     | Tanks and piping<br>(See 8.2.2.3)                                                                                | Cleaning and/or disinfection       |                                                                       | Disinfection is usually not needed for acid concentrate mixing systems.                                                                                                                                                                                                                                                                                                                                 |
| Concentrate distribution systems (bicarbonate) | Tanks and piping<br>(See 8.2.2.4, B.5.3.2)                                                                       | Disinfection                       | Weekly<br>(See D.1, last paragraph)                                   | If using sodium hypochlorite for disinfection, a concentration of 0.5 % to 1 % is recommended.<br><br>If cleaning with acetic acid, a concentration of approximately 0.15 % acetic acid is recommended. (See B.5.3.2, 4th paragraph.)<br><br>Disinfection is usually not needed for acid concentrate distribution systems.                                                                              |

|                                                                                                                                                                              |                                                                      |              |                                                |                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------|------------------------------------------------|--------------------------------------------------------------------------------|
| Dialysis machine                                                                                                                                                             | System<br>(See 8.1)                                                  | Disinfection | According to<br>manufacturer's<br>instructions | By its own disinfection circuit and<br>programme. (See 8.2, 3rd<br>paragraph.) |
| Central dialysis<br>fluid delivery<br>system, CDDS                                                                                                                           | Dialysis fluid delivery<br>system<br>Dialysis console<br>(See B.7.2) | Disinfection | Daily<br>(See B.7.2)                           | Use chemical disinfectant or hot<br>water. (See B.7.2, 3rd paragraph.)         |
| NOTE      The actual interval for cleaning and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6 and 8.2.2). |                                                                      |              |                                                |                                                                                |

## Annex D (informative)

### Strategies for microbiological control

#### D.1 General

The strategy for controlling the proliferation of microorganisms in hemodialysis systems primarily involves proper system design and operation, and regular disinfection of water treatment system and hemodialysis machines. A key concept in ensuring compliance with the requirements of 4.1.3 and 4.3 is that disinfection schedules should be designed to prevent bacterial proliferation, rather than being designed to eliminate bacteria once they have proliferated to an unacceptable level. With this strategy, monitoring levels of bacteria and endotoxins serves to demonstrate that the disinfection programme is effective, not to indicate when disinfection should be performed. Gram-negative water bacteria, their associated lipopolysaccharides (bacterial endotoxins), and nontuberculous mycobacteria (NTM) most frequently come from the community water supply, and levels of those bacteria can be amplified depending on the water treatment system, dialysis fluid distribution system, type of dialysis machine, and method of disinfection.

All components of dialysis water treatment and distribution systems, and dialysis fluid preparation and distribution systems, can serve as reservoirs of microbial contamination. Dialysis water distribution systems frequently use pipes that are of larger diameter and longer than are needed to handle the required flow. Oversized piping increases both the total fluid volume and the wetted surface area of the system. Gram-negative bacteria in fluids remaining in pipes overnight multiply rapidly and colonize the wet surfaces, thus producing bacterial populations and endotoxin quantities in proportion to the volume and surface area. Such colonization results in the formation of protective biofilm that is difficult to remove once formed and that provides a barrier between the bacteria and germicide during disinfection.

Biofilm is a community of microorganisms consisting of cells that are irreversibly attached to a surface or interface or to each other.<sup>[117]</sup> Biofilms can occur at solid-liquid, solid-air, and liquid-air interfaces. Most microorganisms can form biofilms and more than 99 % of all microorganisms live in such aggregates.<sup>[132]</sup> A feature of all biofilms is that the organisms are embedded in a matrix of microbial origin, consisting of extracellular polymeric substances (EPS). The EPS comprises mainly polysaccharides and proteins, which form hydrogel matrices.<sup>[133]</sup> The structure of biofilm, and the physiological attributes of biofilm organisms, confer an inherent resistance to antimicrobial agents, whether those agents are antibiotics, disinfectants or germicides.

Mechanisms responsible for resistance can include

- delayed penetration of the antimicrobial agent through the biofilm matrix,
- altered growth rate of biofilm organisms, and
- other physiological changes related to the mode of growth of the biofilm.

A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling. The key to avoiding biofouling is to minimize biofilm development. The extent of biofilm growth is dependent on the availability of nutrients. Classic biocidal approaches usually do not limit nutrient



availability. In fact, some biocides increase nutrient availability by oxidizing recalcitrant organics and making them more bioavailable.<sup>[134]</sup>

Routine disinfection should be performed to control bacterial contamination of distribution systems. The frequency of disinfection will vary with the design of the system and the extent to which biofilm has already formed in existing systems. Sodium hypochlorite and ozone are generally the most effective agents against biofilm, and their use might be more efficacious if the pipes are treated first with a descaling agent. However, in some cases, complete or partial replacement of a distribution system might be the only way to re-establish control over mature biofilm.

It is commonly believed that maintaining flow through piping systems at all times minimizes biofilm formation. However, in many dialysis facilities, there is no flow through distribution systems when the dialysis facility is not in operation, such as at night and on Sundays. Further, it has been demonstrated that microbial growth and biofilm formation in hydraulic systems cannot be controlled by the fluid velocity.<sup>[119]</sup> Data from the semiconductor industry show that a Reynolds number of 3 000 in a piping system is sufficient to prevent bacterial contamination in the water.<sup>[126]</sup> A Reynolds number of approximately 3 000 is obtained with a flow velocity of 0.15 m/s in a 2-cm-diameter pipe (0.5 ft/s in a 3/4" diameter pipe). However, even in systems operating with a Reynolds number of 3 000, biofilm was found on the internal surface of the pipes.<sup>[126]</sup> Even if it were possible to specify a minimum flow velocity that was effective in reducing biofilm formation and bacterial contamination, use of such a minimum flow velocity would not provide a substitute for regular disinfection of the distribution system. Other measures can also help protect pipes from contamination. A mechanism should be incorporated in a distribution system to ensure that disinfectant does not drain from pipes during the disinfection period. Dead-end pipes and unused branches and taps that can trap fluid should be eliminated because they act as reservoirs of bacteria and are capable of continuously inoculating the entire volume of the system. Joints between sections of piping and between piping and fittings should be formed in a manner that minimizes the formation of crevices and other voids that might serve as sites for bacterial colonization. Pipes should not be cut with a hacksaw. Any burrs should be removed before the joint is formed. These measures also minimize the possibility that pockets of residual disinfectant could remain in the piping system after disinfection.

A storage tank in the dialysis water or dialysis fluid distribution system greatly increases the volume of fluid and surface area available and can serve as a niche for water bacteria. Storage tanks are therefore not recommended for use in dialysis water or dialysis fluid distribution systems unless they are frequently drained and adequately disinfected. It could be necessary for the user to scrub the sides of the tank to remove bacterial biofilm if the tank design and maintenance are not adequate to prevent bacterial proliferation. A bacteria- and endotoxin-retentive filter, distal to the storage tank, or some other form of bacterial control device, is recommended.

For most hemodialysis machines, routine disinfection with hot water or with a chemical germicide connected to a disinfection port on the machine does not disinfect the line between the outlet from the dialysis water distribution system and the back of the dialysis machine. Users should establish a procedure for regular disinfection of this line. One approach is to rinse the hemodialysis machines with water containing germicide or hot water when the dialysis water distribution loop is disinfected. If this procedure is used with a chemical germicide, each hemodialysis machine should be rinsed and tested for the absence of residual germicide following disinfection.

Storage times for bicarbonate concentrate should be minimized (normally less than 24 h), as well as the mixing of fresh bicarbonate concentrate with unused portions of concentrate from a previous batch. The manufacturer's instructions should be followed if they are available. Facilities that reuse concentrate containers for bicarbonate concentrate should disinfect the containers at least weekly. Bicarbonate concentrate can support prolific growth of microorganisms. Containers can be disinfected with household sodium hypochlorite solutions (300 mg/l to 600 mg/l free chlorine), with a contact time of about 30 min or according to another nationally approved standard or regulation, or according to the manufacturer's instructions. Following disinfection, the containers should be drained, rinsed, and inverted to dry.

## **D.2 Microbial monitoring methods**

### **D.2.1 General**

The microbial quality of dialysis water should be monitored regularly to validate the effectiveness of the disinfection programme. The frequency of monitoring should be determined during the process of system validation. In the absence of a formal determination of frequency, monitoring is usually performed monthly. Monitoring can be accomplished by direct plate counts, in conjunction with the measurement of bacterial endotoxins.

Samples of dialysis water should be collected from several places to give an indication of the microbial quality of the water throughout the dialysis water distribution system. For routine monitoring, samples should be collected from the last outlet of the dialysis water distribution loop, where dialysis water enters equipment used to reprocess dialyzers, and where dialysis water enters equipment used to prepare bicarbonate concentrate or from the bicarbonate concentrate mixing tank. Additional testing, such as at the end of the water treatment cascade and at the outlet of the storage tank, if one is used, can be necessary during qualification of a newly installed system or when troubleshooting the cause of contamination within the dialysis water distribution loop. For central dialysis fluid distribution systems, samples should be collected from the last outlet of the dialysis fluid distribution loop.

For dialysis machines that are not fitted with validated endotoxin-retentive filters, dialysis fluid samples should be collected from enough machines so that each machine is tested at least once per year. For dialysis machines fitted with validated endotoxin-retentive filters, samples should be collected according to the filter manufacturer's instructions. If testing of any hemodialysis machine reveals a level of contamination above the action level, an investigation should be conducted. The investigation should be based on the presumption that other hemodialysis machines might also be contaminated. It should include a review of compliance with disinfection and sampling procedures and an evaluation of microbiological data for the previous three months to look for trends. The offending machine should be retested and an additional sample of machines tested to determine if the contamination was limited to a single machine or more widespread. The person in charge should also be notified.

Cultures should be repeated when bacterial counts exceed the allowable levels. If culture growth exceeds permissible standards, samples from the dialysis water distribution system or dialysis fluid distribution system and hemodialysis machines should be cultured weekly until acceptable results are obtained. Additional samples should be collected when there is a clinical indication of a pyrogenic reaction or septicemia, and following a specific request by the clinician or the infection control practitioner.

Samples should always be collected before sanitization/disinfection or no sooner than 24 h after disinfection. For systems disinfected daily, samples should be collected before, and as close as practicable to, the next disinfection. Samples from hemodialysis machines should always be collected before disinfection. Culture dialysis water and dialysis fluid weekly for new systems until a pattern has been established. For established systems, culture monthly unless a greater frequency is dictated by historical data at a given institution. If biofouling is suspected, for example due to erratic microbiological test results, it could be necessary to check for the presence of biofilm (see D.2.3).

### **D.2.2 Sample collection**

Samples should be collected directly from sampling ports situated in different parts of the dialysis water or dialysis fluid distribution system. In general, the sampling ports should be opened and the dialysis water or dialysis fluid should be allowed to run for at least 60 s before a sample is collected in a sterile, endotoxin-free container. Containers validated for collection of pyrogen samples should be used to collect samples. A minimum of 50 ml of fluid, or the volume specified by the laboratory performing the test, should be collected. Sampling ports should be disinfected using sterile gauze saturated with alcohol, or another solution validated for this purpose, to wipe the sampling port. The sample should be collected only when no disinfectant residual is present.

Dialysis fluid samples should be collected from a sampling port in the dialysis fluid inlet line to the dialyzer, or from the dialysis fluid outlet port of the dialyzer, or from a sampling port in the dialysis fluid outlet line of the dialyzer. In some newer hemodialysis machines, dialysis fluid flow stops when the dialysis fluid lines are disconnected from the port. In these instances, the machines are equipped with dialysis fluid sampling ports that can be accessed using a syringe. Sampling ports may be disinfected with alcohol and allowed to air dry. A 30 ml sterile syringe should then be used to aspirate dialysis fluid out of and into the sampling port before filling the syringe. The filled syringe should be discarded, and a fresh sample of dialysis fluid should be collected using a new sterile syringe. At least 25 ml of fluid, or the volume specified by the laboratory performing the test, should be collected in sterile endotoxin-free specimen containers.

### D.2.3 Heterotrophic plate count

Samples should be analyzed as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analyzed within 4 h of collection, they should be stored at <10 °C during transit to the laboratory. Sample storage for more than 24 h should be avoided. The reference method for culturing is the membrane filtration technique. With this method, a known volume of sample or diluted sample is filtered through a 0.45 µm membrane filter and the membrane filter is aseptically transferred to the surface of an agar plate. The spread-plate technique may also be used. With this method, an inoculum of at least 0.2 ml of sample is spread equally over the surface of the agar plate. Use of a calibrated loop to apply the sample to the agar plate is not permitted. The pour-plate technique may also be used. A sample volume of 1 ml is usually used with this method. Dip samplers should not be used. The culture medium should be tryptone glucose extract agar (TGEA), Reasoner's agar no. 2 (R2A), or another medium that can be demonstrated to provide equivalent results. Blood and chocolate agars should not be used. Plates should be incubated at 17 °C to 23 °C for 7 d. Other incubation times and temperatures may be used if it can be demonstrated that they provide equivalent results. During incubation, the plates should be sealed or kept in a plastic bag to avoid desiccation of the agar if that is a concern. Colonies should be counted using a magnifying device. If a more accurate count from plates containing fewer than 30 colonies or more than 300 colonies is desired, larger or smaller volumes may be cultured. Smaller volumes can be obtained by making 1:10 serial dilutions in sterile phosphate buffer. If larger volumes are required, the membrane filtration method should generally be used.

It is virtually impossible to keep a dialysis water or dialysis fluid distribution system sterile; microorganisms will always be present on surfaces waiting for nutrients which, in the case of lithotrophic organisms, can even be inorganic.<sup>[118]</sup> Heterotrophic plate counts do not provide a good measure of the presence of biofilm. Fluid samples give no information about the site, extent, or composition of a biofilm. Although biofilms contaminate the fluid in a distribution system, they do so only very irregularly. Erratic colony counts might indicate the presence of biofouling since clusters of cells might be sloughed from the biofilm with release of bacteria into flowing fluid. Currently, few practical methods are available for the routine detection of biofilm. Conventional methods rely on sampling-defined surface areas or on exposure of test surfaces (coupons) with subsequent analysis in the laboratory. A classic example is the so-called "Robbins device",<sup>[135]</sup> which consists of plugs inserted flush with pipe walls, thereby experiencing the same shear stress as the wall itself. After given periods of time, they are removed and analyzed in the laboratory for all biofilm-relevant parameters. The disadvantage of such systems is the time-lag between analysis and result. Jacobs et al. (1996)<sup>[136]</sup> described a simple spectrophotometric monitoring method, using a nucleotide-specific fluorescent stain (4',6-diamidino-2-phenylindole), and automated measurement. Other methods which report biofilm growth online, non-destructively and in real time have been invented. They are all based on physical methods. If careful attention is paid to routine disinfection, routine monitoring for biofilm is not necessary. However, when the level of biofilm leads to a biofouling situation, it might be necessary to determine the level of biofilm in the system using the methods currently available.

#### D.2.4 Bacterial endotoxin test

Bacterial endotoxin testing is done using the *Limulus* amoebocyte lysate (LAL) assay. Two basic types of assay can be performed. The first is a kinetic assay, which is available in a colourimetric or turbidimetric format, and the second is a gel-clot assay.

The kinetic LAL assay uses control standard endotoxins to generate a standard curve to which unknowns are compared and concentrations are determined using linear regression. The kinetic assays employed in laboratories generally use a computer-driven spectrophotometer that automatically calculates the amount of endotoxins on the basis of colour development or onset times for gel formation.

The gel-clot LAL assay is not as sensitive as the kinetic assay and provides only a positive or negative result; that is, it shows if endotoxins are present, or not, at a particular concentration. Single-tube gel-clot tubes are available from several commercial sources, and kits with the following sensitivities are available: 0.015 EU, 0.03 EU, 0.06 EU, 0.125 EU, 0.25 EU, and 0.5 EU. At a minimum, two tubes should be run each time the assay is performed. The first tube contains LAL reagent and the sample to be tested. The second tube contains LAL reagent, a known amount of endotoxins, and the sample to be tested. The second tube acts as a positive control to confirm the absence of any interference that might lead to a false-negative result. Positive control tubes are available from the suppliers of commercial LAL assays.

### D.3 Interpreting the results of microbial monitoring

Ongoing governance of the water system is critical to the safe delivery of dialysis. Culture results reflect the presence of planktonic organisms in a fluid storage and distribution system. However, more than 99 % of all microorganisms in such a system live in biofilms on the surfaces of the system.<sup>[132]</sup> Thus, care should be taken in interpreting culture results since a low bacterial count might be obtained even though a system was contaminated with an established biofilm if the sample was taken at a point in time after disinfection, but before a biofilm shedding event re-established a population of planktonic organisms. More information on the degree of microbial contamination and, as a consequence, the adequacy of the disinfection schedule, can be obtained by considering both the culture results and endotoxin levels and acting based on the worst-case scenario. .

The sampling and disinfection regimes should be in accordance with the system validation plan (see E.2.4). Careful monitoring of the results of the microbiological analyses should be undertaken, together with a review of the trends so that any possible increase noted, not explained by the normally observed variability, is appropriately addressed. Modifications in the disinfection process may be necessary in the presence of such increasing trends.

## **Annex E** **(informative)**

### **Validation**

#### **E.1 General and background**

This annex provides background for Clauses 6 and 8 as well as for Annex C.

The dialysis fluid and the substitution fluid used for online convective therapies are the result of an online process and are used immediately after their production. For this reason, the use of “batch control” techniques based on testing at fixed intervals is not the most effective way to ensure the required quality level is continuously reached. Periodic assessment of the chemical and microbial fluid quality might not identify a potential problem; for example, if that problem arose just after a test sample was collected.

Furthermore, compliance with the requirement that substitution fluid used for online convective therapies be sterile cannot be demonstrated by culturing but has to be ensured by the application of a validated and adequately monitored process.

The monitoring plan of the overall system (i.e. including the steps from the dialysis water production to the generation of the dialysis fluid and substitution fluid) is based on the knowledge acquired with the validation plan for the specific dialysis water or dialysis fluid production system and the monitoring strategies applicable to the dialysis fluid production devices as validated by the manufacturer.

Moreover, when using a validated and monitored process for removal of bacteria and endotoxins at the dialysis machine, sampling of the substitution fluid is not needed. The presence in the system of parts and equipment (e.g. dialysis machine or endotoxin-retentive filters) that have already been validated by the manufacturer is sufficient to ensure fluid quality, provided those parts and equipment are operated in accordance with the manufacturer's instructions. Sampling of the dialysis water or dialysis fluid should be performed if required by the manufacturer of the validated process.

For these reasons, and under the above-mentioned conditions, an effective monitoring strategy should be based on the direct sampling of the dialysis and/or dialysis fluid and on monitoring of the process parameters as recommended by the manufacturer and defined by knowledge of the water treatment or dialysis fluid preparation system acquired during the validation phase.

#### **E.2 Validation programme**

##### **E.2.1 General**

The performance of the dialysis water or dialysis fluid production system should be verified to demonstrate that the system is “fit for purpose”. The validation procedure should provide documentary evidence that the process will consistently produce dialysis water, dialysis fluid, or substitution fluid meeting the quality requirements of ISO 13959 and/or ISO 11663.

##### **E.2.2 Validation steps**

As described in Clause 6, validation consists of the following:

- validation plan;
- installation and operational qualification;
- performance qualification;
- revalidation through the data collected during routine monitoring.

### **E.2.3 Validation plan**

The validation plan is the road map for successful validation and provides a complete picture of the dialysis facility's validation activities.

The validation plan defines and lists all necessary activities and documentation for

- installation and operational qualification,
- performance qualification, and
- revalidation.

The level of detail in the plan should reflect the risk, complexity and novelty of the system. The validation plan should define all responsibilities during validation and subsequent system operation.

### **E.2.4 Performance qualification**

As described in Clause 6, the aim of performance qualification is to establish that the system, as a whole, functions consistently to produce water and dialysis fluid of the required quality when operated in accordance with the defined procedures and with an incoming water supply of defined characteristics.

The prerequisites for performance qualification are as follows:

- a demonstration that the plant has been installed in accordance with the design plans and following the manufacturer's procedures for installation (i.e. installation qualification);
- a demonstration that the system performs all the required actions and can be operated in accordance with relevant technical manuals (i.e. operational qualification).

Performance qualification includes periodic assessment of a set of physical, chemical, and microbiological parameters to demonstrate that a consistent performance pattern can be achieved for the specific system design and performance requirements.

The sampling and testing pattern can be relaxed during the monitoring phase (normal operation) provided it can be demonstrated that the system consistently yields high quality results over an extended period and that continuously monitored parameters provide full surveillance of the system performance.

Under these assumptions, the following pattern for performance qualification can be adopted.

The first phase requires a full chemical and microbiological analysis of the dialysis water or microbiological analysis of the dialysis fluid, followed by regular microbiological analyses to demonstrate consistent quality in the interval between disinfections. During this period, all the information about the system behavior should be collected and fine-tuning of the action levels performed.

In this phase, the testing frequency of the microbiological parameters is kept at a higher level to create a “trend analysis” and to identify any deviations to ensure the patients' safety.

The achievement of at least three consecutive results, consistently below the action level, allows the start of the second phase where the final frequency of testing of microbiological parameters and the final frequency of disinfection are implemented. Sampling should be performed prior to disinfection or, alternatively, not sooner than 24 h after the disinfection process, to avoid false-negative results and to demonstrate adequate system behavior. Samples taken after disinfection are used to demonstrate the effectiveness of the disinfection procedure; they should be taken at least once after the first disinfection and following any significant deviations in the microbiological quality of the dialysis water or dialysis fluid.

Attainment of two consecutive results within the action level allows the successful completion of performance qualification and the start of routine monitoring operations.

### **E.3 Consequences for the monitoring strategy**

As a result of the validation process for the water treatment or dialysis fluid preparation system, adequate maintenance and routine monitoring plans are established. Based on these regimes, system monitoring starts after performance qualification and ensures ongoing conformance to quality criteria regarding dialysis fluid and in-house produced concentrates.

Trend analysis through monitoring should be used as a source of advanced information on system performance, thus enabling a proactive approach to system maintenance with consequential operational and financial benefits.

Monitoring is achieved with online and offline measurements. With current technology, the majority of parameters have to be measured offline.

The online monitoring of suitable parameters (such as conductivity) provides immediate identification of deviations from normal operating conditions, offering the following advantages:

- timely identification of potential problems in their early stage;
- quick and easy diagnosis of the root causes (incoming water quality/technical malfunction);
- implementation of necessary countermeasures;
- triggering of specific offline measurements.

As mentioned above, a purely time-based offline sampling regime has inherent limitations for the monitoring of a continuous production process since deviations might occur during the sampling intervals.

Table C.1 lists possible monitoring parameters and related frequencies of measurement.

## **Annex F** **(informative)**

### **Special considerations for home hemodialysis**

#### **F.1 General**

The quality of dialysis water used to prepare concentrate and dialysis fluid is as important for home hemodialysis as it is for in-centre hemodialysis. This International Standard is written principally to address equipment used for in-centre hemodialysis. While many of the provisions of this International Standard are also applicable to home hemodialysis, the latter treatment might pose some special challenges not encountered with in-centre hemodialysis. Similarly, home hemodialysis might require some departures from the provisions of this guidance regarding dialysis fluid preparation. Because of a renewed interest in home hemodialysis and, in particular, the use of more frequent treatment schedules, this annex was included in this International Standard to address some of the concerns particular to the home hemodialysis setting. The recommendations included in this annex apply to water treatment systems assembled from individual components. Some of the recommendations in this annex might not apply to systems for home hemodialysis containing integrated water treatment equipment designed and validated to produce water and dialysis fluid of the quality required by ISO 13959 and ISO 11663. Validated systems require assurance that the system is being operated under the validated conditions. Also, the recommendations of this annex do not apply to sorbent-based dialysate regeneration systems, which are excluded from the scope of this International Standard.

Home hemodialysis differs from in-centre hemodialysis in that the patient or a helper will be responsible for day-to-day operation and maintenance of the water treatment and other dialysis equipment. In general, these individuals will not have formal technical training in hemodialysis. Therefore, the dialysis centre should provide training in the operation and maintenance of the equipment and require a demonstration of competence in those areas before home treatments are begun.

#### **F.2 Fluid quality**

Dialysis water, concentrate, and dialysis fluid used for home hemodialysis applications should meet the quality requirements set forth in Clause 3 of ISO 13959:2014, Clause 4 of ISO 13958:2014, and Clause 4 of ISO 11663:2014.

#### **F.3 Utilities**

To incorporate a hemodialysis machine in a home, the home will need a water supply, a drain connection, and a dedicated power source. It is recommended that the utility companies providing water and power to the patient's home be notified that home dialysis is being performed at that location and that restoring service after any interruption should be a priority.

##### **F.3.1 Water supply**

If the water is supplied by a municipal water system, it should meet the applicable standards for drinking water. Periodic evaluation of source water should be performed to confirm that it meets this International Standard.

If the water is not supplied by a municipal water system, for example, water obtained from a private well, applicable drinking water standards might not be met. Since the quality of such water might change over time, and since the water source might not be routinely monitored, the source water should be analyzed at least yearly. More frequent analyses can be needed if the water source is subject to seasonal changes or contamination from sources such as



septic tanks, underground fuel storage tanks, or agricultural waste and chemicals. These analyses might not need to include all the contaminants listed in Tables 1 and 2 of ISO 13959:2014 if only certain contaminants are known to be of concern. If there is documented contamination of the water from any of the sources listed above, use of the water for home hemodialysis should be reconsidered. If the home also has a septic system, the source water should be monitored for contamination by fluids from the septic system. Water quality should also be analyzed following a heavy rain or flood.

If a system is used that contains integrated water treatment equipment designed and validated to produce dialysis water and dialysis fluid of the quality required by ISO 13959 and ISO 11663, there should be periodic evaluation of the feed water to demonstrate that the quality of the feed water meets the requirements for that system or, if not, that there is adequate pretreatment.

The water supply should support the maximum demand of the water treatment components. The piping to a single-patient system should be at least 1 cm in diameter. The water pressure should meet the minimum requirements of the water treatment system, typically at least 150 kPa (approximately 20 psi or 1.5 bar). Other components in the home that use water can temporarily reduce the water pressure if activated. These components include showers, toilets, clothes washers and dishwashers. A loss of water pressure could cause the RO system used for dialysis water treatment to shut down, thereby triggering the dialysis machine's low-water-pressure alarm. If fluctuations in water pressure become an issue, a bladder tank may be installed in the line supplying water to the water treatment system to allow the system to continue operation during periods of low water pressure. Homes with an individual well might need to increase the pressure setting of the well pump, increase the size of the pump, or install a booster pump to ensure adequate pressure.

Water temperature might be an issue, particularly during winter. The performance of an RO system is temperature dependent, with the product-water flow rate decreasing as the temperature decreases. Removal of chloramine by activated carbon is also temperature dependent, with the efficiency of removal decreasing as the temperature decreases. Finally, the treated water temperature needs to meet the minimum requirement for the dialysis machine, typically 10 °C. If the water temperature decreases below 10 °C, the heater in the dialysis machine might be unable to increase the temperature to the desired dialysate temperature. A tempering valve could be needed to ensure a consistent supply of water of an adequate temperature. If a tempering valve is installed, it should meet the requirements of 4.2.3 of ISO 26722:2014 and the water heater should be capable of delivering the amount of hot water needed to provide water of the desired temperature for the duration of the dialysis treatment. Alternatively, the demand for treated water may be reduced during periods of reduced water temperature by decreasing the dialysis fluid flow rate.

Backflow protection should be installed before the start of the water treatment system in compliance with any requirements of the local plumbing code. These devices should be inspected at the frequency specified by the local plumbing code.

### **F.3.2 Drain**

The drain should be capable of supporting the maximum flow from the dialysis machine, RO system, and any water pretreatment equipment. Typically, a 2.5 cm or larger diameter drain pipe is needed. The drain should incorporate some means of protecting against back siphon, such as an air break in the wastewater stream, to avoid backflow from the drain system into the hemodialysis machine or any water treatment component with a drain line. If the home has a septic tank, the septic tank should be able to process the volume of water from this drain. It might not be possible to perform nocturnal hemodialysis in a home with a septic tank since this tank might not be able to support the volume of water delivered to it over an extended period (8 h). Another potential limitation is that the septic system will be exposed to disinfectant chemicals (sodium hypochlorite, peracetic acid, hydrogen peroxide, etc.), which could kill the bacteria needed for the septic system to function.

### **F.3.3 Electrical wiring and power supply**

When hemodialysis equipment is used in the home, consideration should be given to the requirements of IEC/TR 62653 with respect to wiring. The power source used for the hemodialysis equipment should comply with the requirements of IEC 60601-2-16.

## **F.4 Environment**

Hemodialysis involves large volumes of water and waste dialysate. Loose tubing connections or equipment malfunction might produce leaks that can cause damage to the home. If water treatment or dialysis equipment is located on an upper floor, leaking fluids might seep through the floor and damage ceilings on lower levels. It is recommended that areas where water is treated for dialysis, and in which dialysis is performed, be designed to contain fluid spills when they occur. The flooring material should be water resistant and capable of being easily cleaned. Carpeting or wooden floors are not recommended. In addition to being difficult to clean, carpet can mask blood spills in the dialysis area.

Home hemodialysis generally requires an area for storage of supplies, including dialysis concentrate. That area should provide a year-round environment that meets the manufacturer's recommendations for storage of the supplies.

## **F.5 Equipment**

### **F.5.1 General**

The equipment selected for home hemodialysis should be simple to operate. The patient/helpers in the home should be formally trained in the proper operation and maintenance of the hemodialysis and supporting water treatment equipment by the dialysis centre or its designee.

The final configuration of the water treatment system will depend on the quality of the feed water. As with in-centre dialysis, the water treatment system should be designed to produce dialysis water of the quality set forth in Clause 3 of ISO 13959:2014, when supplied with water containing contaminants at the highest anticipated level. Water treatment equipment may include sediment filters, softeners, carbon beds, reverse osmosis (RO) system, or deionizers (DI). Depending on the contaminants in the water, additional water treatment equipment may include iron filters, dealkalinizers, and nitrate filters. Unless specified otherwise in ISO 26722 or in this International Standard, water treatment equipment for home hemodialysis should meet the requirements of ISO 26722.

### **F.5.2 Softener**

A water softener might be needed to prevent calcium and magnesium from forming scale on the membranes of a reverse osmosis system. For water with a high level of hardness, removal of calcium and magnesium with a softener can be necessary if the reverse osmosis system is to produce dialysis water that meets the requirements of ISO 13959 for calcium and magnesium. A softener typically is not needed to support a deionization system.

Softeners should be regenerated or exchanged on a regular basis. Only sodium chloride should be used to regenerate a softener. Potassium chloride should not be used for softener regeneration. Also, salt designated as rock salt should not be used for regeneration since it is not refined and typically contains sediments and other impurities that might damage O-rings and pistons and clog orifices in the softener control head. Single tank softeners can be set to regenerate automatically on set days or after they have processed a designated amount of water; alternatively, regeneration can be initiated manually. Softeners used for hemodialysis applications that regenerate automatically are fitted with a mechanism to prevent water from entering the product line during regeneration. Typically, the timer on the softener is not interlocked to stop the reverse osmosis system when regeneration occurs. If the dialysis machine is producing dialysis fluid at that time, a low water pressure alarm will occur. For that reason, attention should be paid to setting the time for softener regeneration, particularly when daily nocturnal hemodialysis is being performed.

### **F.5.3 Carbon media**

At least one carbon bed or filter should be installed even if the water supply is from a well and no chlorine is present. In addition to chlorine, carbon can remove organic contaminants from ground water, including solvents, pesticides, industrial wastes, and substances leaking from underground storage tanks. When water is obtained from a municipal water supply containing 1 mg/l or more of chloramine, two carbon beds connected in series and providing the equivalent of an empty bed contact time of 10 min, or some other process incorporating safety redundancy for chloramine removal, is recommended. A means should be provided to sample the water between the primary chloramine removal process and the secondary removal process. If chlorine is not present in the water, the carbon should be changed on a routine schedule. If a means of chloramine removal, other than two series-connected carbon beds with 10 min of total empty bed contact time, is used then the system should be flushed for a sufficient period of time to ensure that water sampled is representative of the water to be used for treatment. Sufficient flushing is necessary to ensure that sampled water has not been resident in the removal system between treatments, such that it would under-represent the chloramine level that would be delivered during normal operation. In this case, the minimum flush time should be determined by the manufacturer of the equipment.

### **F.5.4 Reverse osmosis**

Since the product flow rate will decrease with decreasing water temperature, a reverse osmosis system installed without a tempering valve to ensure constant feed-water temperature needs to be sized so that it will deliver the quantity of water required by the dialysis machine with the coldest anticipated water temperature.

### **F.5.5 Deionization**

Deionization systems for home hemodialysis should have a means of preventing product water from reaching the point of use if the resistivity of the water is 1 MΩ·cm or less).

### **F.5.6 Dialysis water distribution**

For home hemodialysis, a direct feed system will typically be used to distribute dialysis water to its points of use. The water-contacting surfaces of the distribution system should not be constructed of materials containing aluminium, copper, lead or zinc. Because systems used for home hemodialysis operate intermittently, the distribution system should be designed and maintained to minimize bacterial proliferation. The reverse osmosis system should be disinfected according to the manufacturer's instructions. The dialysis machine should be disinfected following each treatment according to the manufacturer's instructions. Because the line supplying dialysis water to the dialysis machine is not disinfected when the machine is disinfected, this line should be disinfected when the reverse osmosis system is disinfected and consideration should be given to replacing this line on a regular basis, such as yearly. Opaque tubing is preferred for this line to reduce the likelihood of algae growth; however, the tubing is to be approved by the manufacturer of the dialysis machine. Consideration should also be given to installing an endotoxin-retentive filter in the dialysis machine, if the machine allows that option. If installed, this filter should be maintained and replaced according to the manufacturer's instructions.

## **F.6 Concentrate**

### **F.6.1 Bicarbonate concentrate**

Excess bicarbonate concentrate should be discarded after each treatment. Reusable bicarbonate containers should be disinfected, rinsed with treated water, and inverted to dry after each treatment. Pick-up tubes should be rinsed with treated water and allowed to air dry after each treatment. If the bicarbonate solution is prepared from a powder, the patient/helpers should be trained to prepare the solution according to the proper procedure.

### **F.6.2 Acid concentrate**

The patient/helpers should be trained to know that different hemodialysis machines use different proportioning ratios for concentrate and water and that they should ensure use of the correct acid concentrate for their hemodialysis machine. The acid concentrate used should be documented as part of the treatment record.

## **F.7 Monitoring**

### **F.7.1 Dialysis Water and dialysis fluid quality**

The chemical quality of the dialysis water should be analyzed at least once a year to ensure that it meets the requirements of ISO 13959. More frequent analysis could be needed if there are seasonal variations in source water quality or if the source water is supplied from a well. When any repairs are made to water treatment equipment, the impact on dialysis water quality should be evaluated and a chemical analysis performed if indicated. Chemical testing might not be required when replacing consumable components, such as filters or other components defined by the manufacturer as requiring regular replacement under normal use. Chemical testing might not be required when an entire water purification device is replaced with an equivalent device which has been validated by the manufacturer according to an equivalent performance specification as the device being replaced.

The microbiological quality of the dialysis fluid should be analyzed using cultures and endotoxin measurements. If the dialysis fluid meets the recommendations of ISO 11663, then the dialysis water feeding the dialysis machine, and the bicarbonate concentrate, can be assumed to meet the appropriate requirements. Sampling for microbiological testing should be performed before disinfecting the water treatment system and dialysis machine. To avoid disconnecting hoses, and opening the system to possible contamination, the system should be designed with the necessary sampling ports. To obtain meaningful results, a system should be established to ensure proper collection of the samples and their timely submission to the testing laboratory.

As part of their training for home hemodialysis, patients/helpers should be instructed in any sample collection or water and dialysis fluid quality tests that they will be expected to perform in their homes. If the sample is collected by someone other than the patient/helper, that person should also be trained in the correct procedures for sample collection and testing.

### **F.7.2 Equipment**

#### **F.7.2.1 General**

A log sheet should be provided by the dialysis facility and used to record all measures of water treatment system performance required by the equipment manufacturer or the dialysis facility. Measurements should be made at least 15 min after the water treatment system has been set in operation and before dialysis is initiated.

If any measure of water treatment system performance is found to be outside its acceptable range, the dialysis centre should be notified.

#### **F.7.2.2 Cartridge filter**

Monitoring the pressure drop ( $\Delta P$ ) across a sediment filter may be used in the home environment to determine when the sediment filter has increased resistance of flow. Systems for use in the home environment which are capable of detecting reduced flow conditions through a sediment filter by alternative methods (such as with flow monitoring or insufficient feed-water detection) should also be considered acceptable for determination of sediment filter replacement.

#### **F.7.2.3 Softener**

The water hardness should be monitored prior to each treatment, using a sample obtained through a labelled sample port located between the softener and the reverse osmosis membranes or from the reject line from the reverse osmosis system. For hardness tests requiring color differentiation, the person performing the analysis should be able to distinguish between the color outputs of the test criteria. If the person cannot differentiate these colors, an automated meter should be used.

#### **F.7.2.4 Carbon media**

When the source water contains chloramine at a concentration of 1 mg/l, or more, the total chlorine concentration should be checked prior to each treatment. The patient/helper should be trained how to perform the total chlorine analysis, and should be trained regarding what action to take if total chlorine is detected above the specified limit. Depending on the test used, the patient/helper should be capable of distinguishing between different shades of pink or a digital meter should be used to indicate the total chlorine concentration.

#### **F.7.2.5 Reverse osmosis**

Prior to each treatment, the performance of the reverse osmosis system should be monitored by checking the product-water conductivity and per cent rejection.

## **Annex G** (informative)

### **Special considerations for acute hemodialysis**

#### **G.1 General**

The items included within this annex are equipment used to treat water for the preparation of concentrates and dialysis fluid in the acute (hospital) setting. This annex deals with portable water treatment systems intended for use with a dialysis delivery system to deliver dialytic therapies at the bedside. This annex excludes equipment used in central systems that supply three or more points of use in an “acute dialysis” room. These systems are considered “central” water systems and thus are covered by the general guidance of this International Standard. Equipment used for a single patient in a home or nursing home setting is excluded from this annex because it falls within the scope of Annex F.

Single patients are treated in an acute hospital setting where dialysis equipment is taken to the patient's bedside. Acute dialysis patients might have increased susceptibility to adverse reactions due to their co-morbid conditions. The appearance of easy rolling “acute” carts that hold the portable water treatment system and dialysis machine, along with technological advancements, has attenuated many of the reasons given in the past for relaxing safety design standards established for equipment used in central water treatment systems when that equipment is used for acute dialysis. Therefore, the recommendations outlined in this International Standard are generally applicable in the acute setting, with the addition of the guidance provided in this annex. When less rigorous design standards are allowed, however, the onus is on the user to ensure appropriate dialysis water quality through increased monitoring and maintenance of the water treatment system.

#### **G.2 Fluid quality**

Water and concentrate used to prepare dialysis fluid for acute hemodialysis should meet the quality requirements set forth in Clause 3 of ISO 13959:2014 and Clause 4 of ISO 13958:2014, respectively. Dialysis fluid prepared from dialysis water and concentrate for use in acute hemodialysis should meet the quality requirements set forth in Clause 4 of ISO 11663:2014. Monitoring to demonstrate ongoing compliance with the chemical quality requirements of Clause 3 of ISO 13959:2014 should be performed as described in Clause 7 and G.3, with the exception that, in general, monitoring is not necessary on days when the equipment is not in operation. Compliance with the microbiological quality requirements of Clause 3 of ISO 13959:2014 and Clause 4 of ISO 11663:2014 requires regular and frequent disinfection of the equipment coupled with testing to demonstrate compliance with those requirements. If the test results fail to show compliance with the requirements, steps should be taken to change the frequency and/or procedure of disinfection and testing until compliance can be demonstrated. Because patients in the acute setting are likely to be more susceptible to microbiological contaminants in the dialysate, there could be benefit in using ultrapure dialysis fluid. One means of achieving ultrapure dialysis fluid is to pass the standard dialysis fluid through an endotoxin-retentive filter.

#### **G.3 Equipment**

##### **G.3.1 General**

This subclause contains recommendations for water treatment equipment specific to the acute hemodialysis setting. The general requirements and recommendations for equipment used to treat water for hemodialysis applications contained in ISO 13959 and ISO 26722 apply, unless otherwise noted in this annex.

The installer and user of acute hemodialysis water treatment systems are responsible for assuring that the water produced by the system can meet the maximum allowable chemical and microbiological contaminant levels specified in Clause 3 of ISO 13959:2014, or the prescription of the physician at installation. Beyond this qualification, it becomes the responsibility of the physician in charge of acute dialysis or his/her representative to monitor the system to ensure that the treatment device or devices maintain a level of water quality that meets the requirements of Clause 3 of ISO 13959:2014. Consideration should be given to seasonal or worst-case water quality when selecting portable water treatment systems. The use of pretreatment to remove contaminants that might impair the performance of the portable reverse osmosis (RO) or deionization (DI) system is recommended.

Any maintenance procedure related to the water treatment equipment, such as exchange of exhausted components, should be performed when no patient is connected to the dialysis delivery system.

### **G.3.2 Backflow prevention**

Unlike central water systems in free-standing dialysis clinics, acute water systems in most cases connect directly to potable water systems. Though it is very unlikely that a portable (acute) water treatment system would back up and contaminate the potable water system, backflow prevention is considered a necessary and safe precaution for these systems. A backflow prevention device, such as a pressure principle backflow assembly (PPBA) or a vacuum breaker, should be installed at the point of connection to the potable water system. In some instances, a local code could require a “break tank” device in place of a PPBA as the preferred method to prevent backflow. Portable water treatment system designers should consider possible pressure drops and their effects on downstream components when sizing such devices. Backflow prevention devices should be tested and maintained per local plumbing codes.

Spent dialysis fluid and reject water from a reverse osmosis system unit should be discharged to drain in a manner that minimizes the potential for contamination of the patient-care area and the dialysis machine. An appropriate floor drain or standpipe connected to a sink drain should be utilized for this purpose. If such a drain is not available, spent dialysis fluid and reverse osmosis reject water may be discharged into a sink. In that circumstance, the sink should not be used for other purposes during dialysis and care should be taken to properly clean the sink after the treatment. In all cases, there should be an air gap at the point of discharge to prevent backflow into the dialysis machine.

### **G.3.3 Electrical safety**

Consideration should be given to the requirements of IEC/TR 62653 with respect to wiring. The power source used for the hemodialysis equipment should comply with the requirements of IEC 60601-2-16. The power source used for the water treatment equipment should comply with the requirements of IEC 60601-1.

Portable water treatment systems should comply with applicable electrical safety standards regarding electrostatic discharge (ESD), electromagnetic compatibility (EMC), and any other electrical safety standards as outlined in IEC 60601-1. It is critically important that electrical noise and current leakage be minimized in both the critical care and general bedside settings. These environments are likely to have life-sustaining equipment, such as ventilators, for which loss of function because of electrical interference could evoke a medical emergency. An electrical safety check should be performed at least once per year. An electrical safety check should also be performed following repairs that involve the power supply system, including repairs to power cords and cord caps. Portable water treatment system component enclosures should possess a level of water resistance equal to IEC 60529 IPX 1. Continued monitoring of the water system is necessary to maintain treatment methods consistent with safety.

### **G.3.4 Carbon media**

Patients in the acute setting might be less capable of coping with premature chlorine/chloramine breakthrough than stable patients being treated in an outpatient facility because of their co-morbid conditions. Where practical, when the municipal water contains chloramine at a concentration of 1 mg/l, or more, portable water treatment systems should include two carbon beds in series, which together provide a minimum of 10 min empty bed contact time (EBCT).

Historically, the requirement for two carbon beds in series was waived for portable dialysis systems because of the impracticality of providing these features while retaining the portability of the system. However, alternative technologies are now available that allow portability while retaining the redundancy associated with two carbon beds in series. Some portable reverse osmosis systems employ one granular activated carbon (GAC) tank followed by a dense carbon block as a polisher. Alternatively, experience suggests that two carbon block filters in series rated according to the NSF for a minimum chlorine reduction capacity of 150 m<sup>3</sup> (approximately 40 000 gal) at a flow rate of 7.7 l/min (2 gal/min) and an incoming free chlorine concentration of 2 mg/l can be used. When used, carbon block filters should be intended for chloramine removal. Block carbon filters used in this application should not compromise the feed-water requirements specified by the manufacturer of the reverse osmosis system. Testing to demonstrate that the level of total chlorine is less than 0.1 mg/l should be performed before each treatment using a sample obtained from a port located between the two beds or filters. The equipment should be allowed to operate for at least 15 min before the test sample is drawn. For prolonged treatments, such as sustained low-efficiency dialysis (SLED), testing may be performed approximately every 8 h providing the EBCT of the carbon media is based on a dialysate flow rate of at least 500 ml/min and the actual dialysate flow rate is not more than 300 ml/min. Where it is not possible to provide the equivalent of a 10 min EBCT with carbon, practical alternatives include the addition of ascorbic acid to the acid concentrate or more frequent monitoring of the product water during the dialysis treatment.

Acute dialysis programmes should determine if the potable water supplied by the hospital or other water supplier contains secondary disinfectants and request that they be notified in advance of the use of secondary disinfectants, to ensure that their impact on water quality and patient safety can be evaluated. An example of a secondary disinfection would be the installation of a chlorine-dioxide-generating system. In the event that chlorine dioxide is present in the potable water, and in the absence of data regarding the hemolytic potential of chlorine dioxide, it is suggested that, in the interim, chlorine dioxide levels be measured using a commercially available test kit and that the maximum acceptable chlorine dioxide level be set at 0.1 mg/l.

### **G.3.5 Ion exchange**

#### **G.3.5.1 Deionization**

When deionization is the primary method of water treatment, two portable mixed-bed DI tanks in a worker-polisher configuration are recommended. Alternatively, a cation tank and an anion tank, followed by a mixed-bed tank, can be installed. A DI polishing cartridge may also be used following a portable RO when the source water chemistry is such that the portable RO, on its own, will not produce water meeting the quality requirements of Clause 3 of ISO 13959:2014. Deionization systems for acute hemodialysis should have a mechanism to prevent product water from reaching the point of use if the specific resistivity of the water is 1 MΩ·cm or less. DI should be followed by an ultrafilter or other bacteria- and endotoxin-reducing device to remove microbiological contaminants that originate in the deionizer resin bed.

#### **G.3.5.2 Softeners**

Unless otherwise specified by the manufacturer of the reverse osmosis system, water treatment systems presented with incoming water with a hardness of >10 GPG (equivalent to 170 ppm of calcium carbonate or 10 °dH) should have a softener or other means of preventing scale formation. At lower levels of hardness (<10 GPG), the user may forgo the use of a softener by increasing the frequency of membrane descaling (acid cleaning) or by periodically replacing the reverse osmosis membranes in accordance with the instructions of the manufacturer of the reverse osmosis system. The amount of hardness in the source water and the volume of water used will determine the frequency of membrane cleaning and/or membrane replacement. To minimize space and weight requirements, softeners used in portable systems should not be equipped with a brine tank. Instead, a separate regeneration station with a brine tank and water source should be used for regenerating softeners.

Unlike central water treatment systems, regeneration devices, such as softeners, used in portable (acute) water treatment systems do not include a means to prevent product water from reaching the reverse osmosis system during regeneration. A portable water treatment system should not be operated without all its pretreatment devices online. In



hospital settings where there is central softening of the potable water supply, hospital maintenance/plant staff should be made aware of the potential impact of hard water on reverse osmosis performance and the potential hazard to hemodialysis patients of untimely regeneration.

### **G.3.6 Reverse osmosis**

A reverse osmosis system should demonstrate delivery of water meeting the quality requirements of Clause 3 of ISO 13959:2014; otherwise, additional treatment devices should be employed. The user may define monitoring in terms of per cent rejection and product-water conductivity (RO). Compliance with both monitored parameters is required since an increase in feed-water contaminants might result in product water unsuitable for hemodialysis applications, even though the per cent rejection of the membrane modules remains high. In this scenario, an additional water purification device should be installed after the reverse osmosis system to meet the standard. An example of such a device would be a deionizer polishing cartridge. The user should establish alarm limits for rejection and product-water conductivity or total dissolved solids (TDS) specific to the acute site.

Because reverse osmosis membranes tend to fail gradually, the risk is different from exhaustion of a deionizer where very high levels of contaminants, such as fluoride, might occur abruptly in the product water. It is recommended that reverse osmosis systems used in an acute dialysis setting incorporate a means of preventing the product water from reaching the patient in the event of a product-water conductivity or rejection rate alarm. Means of preventing product water from reaching the patient could include an automated divert to drain valve, reverse osmosis shutdown, or an immediate response by the operator to an alarm.

### **G.3.7 Endotoxin-retentive filters**

It has been argued that the use of endotoxin-retentive filters in a water treatment system for acute dialysis using reverse osmosis is redundant, given that such systems are operated in a direct-feed configuration. Endotoxin-retentive filters should be installed after the deionizer tanks in systems using deionization. Even with reverse osmosis, it can be difficult to maintain portable water treatment equipment and the associated dialysis machine free of microbiological contamination because the equipment is often used intermittently and is subject to frequent connection and disconnection. For these reasons, in-line dialysis fluid filters are recommended as a final barrier against contamination of the dialysis fluid.

## **G.4 Microbial control strategies**

Control of microbial contamination is the single most difficult aspect of maintaining portable equipment in compliance with the requirements of ISO 11663. Because of the non-routine nature of acute dialysis, systems used for acute hemodialysis operate intermittently and can be frequently connected and disconnected; they should be designed and maintained to minimize bacterial proliferation. There should be a continuous quality assessment performance improvement programme for monitoring the performance and maintenance of systems used for acute dialysis. The reverse osmosis system should be disinfected according to the manufacturer's instructions, and more frequently if the equipment is not operated for several days or if test results demonstrate that the disinfection schedule is inadequate to ensure compliance with the microbiological quality requirements of 4.1 of ISO 11663:2014. The potential for bacterial proliferation can be diminished by operating the equipment for at least 15 min each day, regardless of whether or not a treatment is being performed. Another approach would be to add a bacteriostatic agent (e.g. sodium bisulfite) to reverse osmosis systems that are to be stored. If a bacteriostatic agent is used, the machine should be clearly labelled to indicate the presence of that agent. Because of the potential for bacterial growth in carbon media, the manufacturer's instructions for scheduled replacement of carbon media should be followed, even though the product water might still meet the requirements for total chlorine. In the absence of a manufacturer's recommendation, carbon media should be replaced at least every six months. Provided that there is a continuous flow of dialysis fluid through the machine, dialysis machines that are used to perform multiple treatments during the day should be cleaned following each treatment and disinfected at the end of the day according to the manufacturer's instructions. If there is no dialysis fluid flow for more than 4 h between treatments, the machine should be disinfected

before a second treatment is performed. If the machine is not disinfected daily, it should be disinfected before it is used. Because the line supplying water to the dialysis machine is not disinfected when the machine is disinfected, this line should be disinfected when the reverse osmosis system is disinfected and consideration should be given to replacing this line on a regular basis, such as yearly. Opaque tubing is preferred for this line to reduce the likelihood of algae growth; however, the tubing is to be approved by the manufacturer of the dialysis machine. If individual containers of bicarbonate concentrate are used, pick-up tubes should be disinfected at the end of each treatment day. If reusable containers are used for bicarbonate concentrate, they should also be disinfected at least weekly as described in 8.2.2.4. Consideration should be given to installing an in-line dialysis fluid filter in the dialysis machine, if the machine manufacturer allows that option. If installed, the dialysis fluid filter should be maintained and replaced according to the manufacturer's instructions.

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# Quality of dialysis fluid for hemodialysis and related therapies

Approved 21 July 2014 by  
**Association for the Advancement of Medical Instrumentation**

Approved 8 August 2014 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies minimum quality requirements for dialysis fluids used in hemodialysis and related therapies. Includes dialysis fluids used for hemodialysis and hemodiafiltration, including substitution fluid for hemodiafiltration and hemofiltration.

**Keywords:** action, chemical, contaminant, endotoxin, microbiological, compliance

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Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-547-7

# Contents

Page

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| Glossary of equivalent standards.....                                                                   | iv  |
| Committee representation.....                                                                           | v   |
| US deviation to ISO 11663:2014.....                                                                     | vi  |
| Introduction .....                                                                                      | vii |
| 1 Scope.....                                                                                            | 1   |
| 2 Normative references .....                                                                            | 1   |
| 3 Terms and definitions.....                                                                            | 1   |
| 4 Requirements.....                                                                                     | 6   |
| 4.1 Microbiological contaminants in dialysis fluid .....                                                | 6   |
| 4.2 Chemical contaminants in dialysis fluid.....                                                        | 7   |
| 5 Tests for compliance with microbiological requirements.....                                           | 7   |
| Annex A (informative) Rationale for the development and provisions of this International Standard ..... | 9   |
| Annex B (informative) Reference tables from ISO 13959 .....                                             | 12  |
| Bibliography .....                                                                                      | 16  |

## **Glossary of equivalent standards**

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

**[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)**



## Committee representation

### Association for the Advancement of Medical Instrumentation

#### AAMI Renal Disease and Detoxification Committee

This American National Standard was developed by the AAMI Renal Disease and Detoxification Committee. Approval of the American National Standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the AAMI Renal Disease and Detoxification Committee had the following members:

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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NOTE—Participation by federal agency representatives in the development of this American National Standard does not constitute endorsement by the federal government or any of its agencies.

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## US deviation to ISO 11663:2014

The International Organization for Standardization (ISO) published ISO 11663:2014, *Quality of dialysis fluid for haemodialysis and related therapies* as a revision of ISO 11663:2009 on 2014-04-01. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for minimum quality requirements for dialysis fluids used in haemodialysis and related therapies. The 2014 ISO revision editorially aligned ISO 11663 with the ISO dialysis fluid standards ISO 13958, ISO 13959, ISO 23500, and ISO 26722 which had been developed serially over several years.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

While considering the US adoption of ISO 11663:2014, the AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) approved a US deviation to the International Standard. ANSI/AAMI 11663:2014 deviates from ISO 11663:2014 in the following aspect:

The fifth paragraph of Clause 5, Tests for compliance with microbiological requirements, which in ISO 11663:2014 reads:

“Culture media shall be tryptone glucose extract agar (TGEA) or Reasoner’s 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d) are recommended. Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods.”

is replaced in ANSI/AAMI 11663:2014 by the following:

“Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner’s 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods.”

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

## Introduction

Hemodialysis patients are directly exposed to large volumes of dialysis fluid, with the dialyzer membrane being the only barrier against transfer of hazardous contaminants from the dialysis fluid to the patient. It has long been known that there could be hazardous contaminants in the water and concentrates used to prepare the dialysis fluid. To minimize this hazard, ISO 13958 and ISO 13959 set forth quality requirements for the water and concentrates used to prepare dialysis fluid. However, if the dialysis fluid is not prepared carefully, it could contain unacceptable levels of contaminants even though it is prepared from water and concentrates, meeting the requirements of ISO 13958 and ISO 13959. Further, the dialysis fluid might be used as the starting material for the online preparation of fluids intended for infusion into the patient, for example, in therapies such as online hemodiafiltration. For these reasons, this International Standard for dialysis fluid quality was developed to complement the existing International Standards for water and concentrates, ISO 13959 and ISO 13958, respectively. Guidelines to aid the user in routinely meeting the requirements of this International Standard and ISO 13959 can be found in ISO 23500.

Within these International Standards, measurement techniques current at the time of preparation have been cited. Other standard methods can be used, provided that such methods have been appropriately validated and compared to the cited methods. This International Standard reflects the conscientious efforts of healthcare professionals, patients, and medical device manufacturers to develop recommendations for the quality of dialysis fluid. This International Standard is directed at the healthcare professionals involved in the management of dialysis facilities and the routine care of patients treated in dialysis facilities, since they are responsible for the final preparation of dialysis fluid. The recommendations contained in this International Standard are not intended for regulatory application.

The requirements of this International Standard aim to help protect hemodialysis patients from adverse effects arising from known chemical and microbiological contaminants that can be found in improperly prepared dialysis fluid. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysis fluid is correctly formulated and meets the requirements of all applicable quality standards.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this International Standard, the auxiliary verb

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard,
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.

The concepts incorporated in this International Standard should not be considered inflexible or static. The recommendations presented here should be reviewed periodically in order to assimilate increased understanding of the role of dialysis fluid purity in patient outcomes and technological developments.



# Quality of dialysis fluid for hemodialysis and related therapies

## 1 Scope

This International Standard specifies minimum quality requirements for dialysis fluids used in hemodialysis and related therapies. This International Standard includes dialysis fluids used for hemodialysis and hemodiafiltration, including substitution fluid for hemodiafiltration and hemofiltration. This International Standard does not address the requirements for the water and concentrates used to prepare dialysis fluid or the equipment used in its preparation. Those areas are covered by other International Standards.

Sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use prepackaged solutions, and systems and solutions for peritoneal dialysis are excluded from this International Standard.

## 2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13958, *Concentrates for hemodialysis and related therapies*

ISO 13959, *Quality of water for hemodialysis and related therapies*

## 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

### 3.1

#### **acid concentrate**

##### **A-concentrate**

acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term “acid” refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate may contain glucose.

Note 3 to entry: Acid concentrate may be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

### 3.2

#### **action level**

concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

### 3.3

#### **bicarbonate concentrate**

##### **B-concentrate**

concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate can be in the form of a liquid or a dry powder.

Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

### 3.4

#### **central dialysis fluid delivery system**

system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

### 3.5

#### **chlorine, combined**

chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it may be measured indirectly by measuring both total and free chlorine and calculating the difference.

### 3.6

#### **chlorine, free**

chlorine present in water as dissolved molecular chlorine ( $\text{Cl}_2$ ), hypochlorous acid ( $\text{HOCl}$ ), and hypochlorite ion ( $\text{OCl}^-$ )

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

### 3.7

#### **chlorine, total**

sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid and/or hypochlorite ion (free chlorine), or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

### 3.8

#### **colony-forming unit**

##### **CFU**

measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

Note 1 to entry: Colonies can also form from groups of organisms when they occur in aggregates.

### **3.9**

#### **concentrate generator**

system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyzer

### **3.10**

#### **device**

individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term “component” as used by the US Food and Drug Administration (see Reference [48]).

### **3.11**

#### **dialysis fluid**

#### **dialysate**

#### **dialysis solution**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis

Note 1 to entry: The term “dialysis fluid” is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyzer by the dialysis fluid delivery system. Such phrases as “dialysate” or “dialysis solution” are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyzer is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyzer is referred to as “spent dialysis fluid”.

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as hemodiafiltration and hemofiltration.

### **3.12**

#### **dialysis fluid delivery system**

device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; circulates the dialysis fluid through the dialyzer; monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow, and blood leaks; and, prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system might be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

### **3.13**

#### **dialysis water**

water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in hemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialyzers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

### 3.14

#### disinfection

destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization, because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

### 3.15

#### endotoxin

major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. [see also *pyrogen* (3.25)].

### 3.16

#### endotoxin units

##### EU

units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

### 3.17

#### hemodiafiltration

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyzer (predilution hemodiafiltration), after the dialyzer (postdilution hemodiafiltration), or a combination of the two (mixed dilution hemodiafiltration).

### 3.18

#### hemodialysis

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

### 3.19

#### hemofiltration

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the hemofilter (predilution hemofiltration), after the hemofilter (postdilution hemofiltration), or a combination of the two (mixed dilution hemofiltration).



Note 2 to entry: There is no dialysis fluid stream in hemofiltration.

### 3.20

#### ***Limulus* amoebocyte lysate test**

##### **LAL test**

assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, can also be used to detect endotoxin.

### 3.21

#### **manufacturer**

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

### 3.22

#### **microbiological contamination**

contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

### 3.23

#### **nonpyrogenic**

not eliciting a pyrogen reaction

Note 1 to entry: Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

Note 2 to entry: The volume of fluid administered should not exceed the volume that would result in a total dose of endotoxin of  $\geq 5$  EU/kg/h.

Note 3 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 4 to entry: The commonly used gel clot method has a sensitivity limit of 0.03 EU/ml.

### 3.24

#### **proportioning system**

apparatus that proportions dialysis water and hemodialysis concentrate to prepare dialysis fluid

### 3.25

#### **pyrogen**

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.15)].

### **3.26**

#### **sterile**

free from viable microorganisms

Note 1 to entry: "Sterile" can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of  $10^{-6}$ , i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, "sterile" can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from viable microorganisms for the validated life of the filter.

### **3.27**

#### **substitution fluid**

fluid used in hemofiltration and hemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

### **3.28**

#### **ultrapure dialysis fluid**

highly purified dialysis fluid that can be used in place of conventional dialysis fluid

Note 1 to entry: A widely accepted specification of ultrapure dialysis fluid is  $<0.1$  CFU/ml and  $<0.03$  EU/ml.

### **3.29**

#### **user**

physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

### **3.30**

#### **water treatment system**

collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce dialysis water meeting the requirements of ISO 13959 for hemodialysis applications and deliver it to the point of use

## **4 Requirements**

### **4.1 Microbiological contaminants in dialysis fluid**

#### **4.1.1 General**

The requirements contained in this clause apply to a sample of the dialysis fluid collected at the inlet to the dialyzer or the reinfusion point.

#### **4.1.2 Microbiological requirements for standard dialysis fluid**

Standard dialysis fluid shall contain a total viable microbial count of less than 100 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration of less than 0.5 EU/ml (when tested in accordance with Clause 5).

Action levels for the total viable microbial count and endotoxin concentration in dialysis fluid should also be set based on knowledge of the microbial dynamics of the system. Typically, the action levels are set at 50 % of the maximum allowable levels for total viable microbial count and endotoxin; other levels may be set.

If microbial counts exceeding the action levels are observed in the dialysis fluid, corrective measures, such as disinfection and retesting, should be taken promptly to reduce the levels.

#### **4.1.3 Microbiological requirements for ultrapure dialysis fluid**

Ultrapure dialysis fluid shall contain a total viable microbial count of less than 0.1 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration less than 0.03 EU/ml (when tested in accordance with Clause 5). If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels to an acceptable range. The user is responsible for monitoring the dialysis fluid bacteriology of the system following installation. It is incumbent on the user to establish a regular monitoring routine.

#### **4.1.4 Microbiological requirements for online prepared substitution fluid**

The requirements contained in this clause apply to online prepared fluid intended to be infused into the patient as it enters the patient's blood.

This fluid shall be sterile and nonpyrogenic.

Substitution fluid for convective therapies, such as hemodiafiltration and hemofiltration, may be produced online by a process of ultrafiltration with bacteria-retentive and endotoxin-retentive filters. This online process shall be validated to produce fluid that is sterile and nonpyrogenic.

Compliance of online produced fluid with the requirements of this International Standard cannot be demonstrated with traditional test procedures. For this reason, compliance with this International Standard shall be ensured by proper operation of a validated system, verified according to the manufacturer's instructions at the time of installation, and confirmed by the user with a regular monitoring and maintenance schedule. The user shall follow the manufacturer's instructions for use of the validated system, and the user's monitoring and maintenance schedule shall be designed to confirm that the water and concentrates used to prepare the substitution fluid continue to meet the specifications of ISO 13958 and ISO 13959.

#### **4.2 Chemical contaminants in dialysis fluid**

Dialysis fluid shall be prepared from water meeting the requirements of ISO 13959 and acid and bicarbonate concentrates meeting the requirements of ISO 13958. The water and concentrates shall be combined using individual dialysis fluid delivery systems or a central dialysis fluid delivery system constructed from materials that do not contribute chemical contaminants to the final dialysis fluid. The maximum levels of chemical contaminants permitted in water used to prepare dialysis fluid and concentrates are given in Tables B.1 and B.2.

### **5 Tests for compliance with microbiological requirements**

Samples shall be collected where the dialysis fluid enters the dialyzer.

**NOTE** In some newer dialysis machines, dialysis fluid flow stops when the effluent line is disconnected from the dialyzer. In these instances, the machines are equipped with dialysis fluid sampling ports that can be accessed using a syringe. Sample ports can be disinfected with alcohol and allowed to air-dry. A sterile syringe can then be used to aspirate dialysis fluid out of and into the port before filling the syringe. The filled syringe is discarded, and a fresh sample of dialysis fluid is collected using a new sterile syringe. For sample ports consisting of a simple septum

penetrated with a needle, the use of a second syringe is not necessary. Alternatively, if the dialysis machine permits, samples can be collected immediately after the dialyzer by disconnecting the effluent connector and aseptically collecting a "free/clean" catch sample after allowing dialysis fluid to run for 30 s to 60 s.

Microbial analysis of water and dialysis fluid samples should be conducted as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analysed within 4 h of collection, follow the laboratory's instructions for sample storage and shipping. Samples intended for colony counts should not be frozen.

Total viable microbial counts (standard plate counts) shall be obtained using conventional microbiological assay procedures (pour plate, spread plate, membrane filter techniques). The calibrated loop technique shall not be used.

Preferred methods and sample volumes:

Dialysis fluid, routine test:

- spread plate, 0.1 ml to 0.3 ml;
- pour plate, typically 1 ml.

Ultrapure dialysis fluid, routine test:

- membrane filtration, 10 ml to 1,000 ml.

Substitution fluid:

- sterility cannot be proven by sampling.

Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods.

Compliance with the microbial standards for ultrapure dialysis fluid and substitution fluid prepared online with a validated system can be met by following the requirements and instructions of the manufacturer of the dialysis fluid delivery system.

The presence of pyrogens shall be determined by the *Limulus* amoebocyte lysate test for endotoxins.

## **Annex A**

(informative)

### **Rationale for the development and provisions of this International Standard**

#### **A.1 Microbiological contaminants in dialysis fluid**

**NOTE** The information in this clause is intended to give the reader a historical perspective of how the microbial limits were developed for this International Standard.

Pyrogenic reactions are caused by lipopolysaccharides or endotoxins that are associated with gram-negative bacteria. Furthermore, gram-negative water bacteria have been shown to have the capability of multiplying rapidly in a variety of hospital-associated fluids, including distilled, deionized, reverse osmosis, and softened water, all of which have been used in the past as supply water for hemodialysis systems. The dialysis fluid, which is a balanced salt solution made with this water, likewise provides a very good growth medium for these types of bacterium. Several studies have demonstrated that the incidence of pyrogenic reactions can be related directly to the number of bacteria in dialysis fluid.<sup>[10][14][15]</sup> Even at low levels of bacterial contamination, pyrogenic reactions have been reported when the source of endotoxin was exogenous to the dialysis system (i.e. present in the community water supply).<sup>[18]</sup>

Several investigators<sup>[22][23]</sup> have shown that bacteria growing in dialysis fluid can produce products that cross dialysis membranes. It has also been shown<sup>[17][37]</sup> that gram-negative bacteria growing in dialysis fluid produced endotoxins, that in turn stimulated the production of anti-endotoxin antibodies in hemodialysis patients. These data suggest that bacterial endotoxins, although relatively large molecules, do indeed cross dialysis membranes, either intact or as fragments. The use of the very permeable membranes known as high-flux membranes has raised the possibility of a greater likelihood of passage of endotoxins into the blood path. Several studies support this contention. Vanholder et al.<sup>[52]</sup> observed an increase in plasma endotoxin concentrations during dialysis against dialysis fluid containing 103 CFU/ml to 104 CFU/ml *Pseudomonas* species. In vitro studies using both radiolabelled lipopolysaccharide and biological assays have demonstrated that biologically active substances derived from bacteria found in dialysis fluid can cross a variety of dialysis membranes.<sup>[26][13][29][50][9][43][53][44]</sup> Also, patients treated with high-flux membranes are reported to have higher levels of anti-endotoxin antibodies than normal subjects or patients treated with conventional low-flux membranes.<sup>[54]</sup> Finally, it was reported that the use of high-flux dialyzers is a significant risk factor for pyrogenic reactions.<sup>[46]</sup> Although other investigators have not been able to demonstrate endotoxin transfer across dialysis membranes,<sup>[6][8]</sup> the preponderance of reports now supports the ability of endotoxin to transfer across at least some high-flux membranes under some operating conditions. Furthermore, in a Japanese Society for Dialysis Therapy (JSDT) survey, the 1-year mortality rate was significantly higher at facilities with a dialysis fluid endotoxin concentration of >0.100 EU/ml.<sup>[55]</sup> Consequently, it seems prudent to impose an upper limit on the endotoxin content of dialysis water and dialysis fluid. A level of 2 EU/ml was chosen by AAMI in 2001 as the upper limit for endotoxin, since these levels were easily achieved with contemporary water treatment systems using reverse osmosis, ultrafiltration, or both. At the same time, the European Community chose to use 0.25 EU/ml as the maximum allowable level of endotoxin in dialysis water. When ISO 13959 was revised in 2009, the 0.25 EU/ml limit for dialysis water was included. In developing this International Standard for dialysis fluid quality, the maximum allowable level of endotoxin was set at 0.5 EU/ml by the Limulus amoebocyte lysate test.

The level is set higher than that for dialysis water in recognition that both the water and concentrates used in the preparation of dialysis fluid can contribute endotoxin.

In addition to the acute risk of pyrogenic reactions, there is increasing indirect evidence that chronic exposure to low amounts of endotoxin might play a role in some of the long-term complications of hemodialysis therapy. Patients treated with ultrafiltered dialysis fluid have demonstrated a decrease in serum  $\beta_2$ -microglobulin concentrations,<sup>[35][33]</sup> a decrease in markers of an inflammatory response and oxidant stress,<sup>[42][45][40][36][19][4][20][16]</sup> and an increased responsiveness to erythropoietin.<sup>[45][31][19][36]</sup> In longer term studies, use of ultrafiltered dialysis fluid has been associated with a decreased incidence of  $\beta_2$ -microglobulin-associated amyloidosis,<sup>[5][25][39]</sup> better preservation of residual renal function,<sup>[32][41]</sup> and improved nutritional status.<sup>[40][4][33]</sup> These observations have led to the recommendation that dialysis fluid of a higher microbiological quality, so-called “ultrapure” dialysis fluid, should be used for routine hemodialysis (see Reference [12]). Ultrapure dialysis fluid is defined as one having a bacterial content of less than 0.1 CFU/ml and an endotoxin content of less than 0.03 EU/ml using sensitive assays.<sup>[27]</sup> This definition is now widely accepted, particularly in Europe, as the standard for dialysis fluid used to prepare substitution solution for online convective therapies. In developing this International Standard, the desirability of using ultrapure dialysis fluid was recognized, but it was accepted that obtaining this level of purity on a routine basis might not yet be feasible in all dialysis settings.

Because 7 d can elapse between sampling dialysis fluid for the determination of microbiological contamination and receiving results, and because bacterial proliferation can be rapid, action levels for microbial counts were introduced into this International Standard. These action levels allow the user to initiate corrective action before levels exceed the maximum levels established by this International Standard.

In hemodialysis, the net movement of water is from the blood to the dialysis fluid, although within the dialyzer there can be movement of dialysis fluid to the blood due to the phenomenon of back-filtration, particularly in dialyzers with highly permeable membranes.<sup>[28]</sup> In contrast, hemofiltration and hemodiafiltration feature infusions of large volumes of electrolyte solution (20 l to more than 100 l) into the blood. Increasingly, this electrolyte solution is being prepared online from water and concentrate. The large volumes of fluid infused in hemofiltration and hemodiafiltration, and general concerns about the transfer of endotoxin and endotoxin fragments across high-flux membranes, necessitate the use of ultrapure dialysis fluid in the online preparation of substitution fluid for hemofiltration and hemodiafiltration.

## A.2 Chemical contaminants in dialysis fluid

When this International Standard was being developed, the need to include maximum levels for chemical contaminants in dialysis fluid was discussed. It was proposed that the maximum allowable levels of chemical contaminants in dialysis fluid should be the same as those in the water used to prepare the dialysis fluid since there were no data supporting the need for lower levels. Dialysis fluid is prepared from water and concentrates, meeting the requirements of ISO 13959 and ISO 13958, including the same requirements for maximum levels of chemical contaminants that were proposed for inclusion in this International Standard. Because the water and concentrates are combined using individual dialysis machines or central dialysis fluid delivery systems that are required to be constructed of materials that do not contribute chemical contaminants to the dialysis fluid, it was concluded that including maximum allowable levels of chemical contaminants in the dialysis fluid would be redundant and impose an unnecessary burden on dialysis facilities.

## A.3 Tests for compliance with microbiological requirements

The original clinical observations showing a relationship between bacterial levels in dialysis fluid and pyrogenic reactions were based on cultures performed with standard methods agar (SMA), a medium containing relatively few nutrients.<sup>[14]</sup> Later, the use of tryptic soy agar (TSA), a general-purpose medium for isolating and cultivating fastidious organisms was recommended because it was thought more appropriate for culturing bicarbonate-containing dialysis fluid. However, several studies have shown that the use of tryptone glucose extract agar (TGEA) or R2A results in an increased recovery of bacteria from water and dialysis fluid.<sup>[27][51][34][38]</sup> Extending the culturing time up to 168 h and using a lower incubation temperature have also been shown to increase the recovery of bacteria compared to

incubation for 48 h at 35 °C as recommended in ANSI/AAMI RD52.<sup>[2][27][34][38]</sup> The membrane filtration technique is applied when higher sensitivity is required or desired. The use of larger volumes (up to 1 000 ml) will provide greater sensitivity, but the improved sensitivity needs to be balanced against the increased risk of contamination in collecting and handling the sample. Even with the most sensitive techniques, compliance with the stringent requirements for online prepared substitution fluid cannot be demonstrated by culturing; it has to be ensured by use of a validated process.

The culturing conditions recommended in this International Standard could fail to identify the presence of some organisms. Specifically, the recommended method might not detect the presence of various non-tuberculous mycobacteria that have been associated with several outbreaks of infection in dialysis units,<sup>[7][30]</sup> or fungi, and yeast, which have been shown to contaminate dialysis fluid.<sup>[24]</sup>

## Annex B (informative)

### Reference tables from ISO 13959

**Table B.1 — Maximum allowable levels of  
toxic chemicals and dialysis fluid electrolytes in dialysis water<sup>a</sup>**

| Contaminant                                                                                                                                                                                                                                      | Maximum concentraion<br>(mg/l) <sup>b</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| <b>Contaminants with documented toxicity in hemodialysis</b>                                                                                                                                                                                     |                                             |
| Aluminum                                                                                                                                                                                                                                         | 0.01                                        |
| Total chlorine                                                                                                                                                                                                                                   | 0.1                                         |
| Copper                                                                                                                                                                                                                                           | 0.1                                         |
| Fluoride                                                                                                                                                                                                                                         | 0.2                                         |
| Lead                                                                                                                                                                                                                                             | 0.005                                       |
| Nitrate (as N)                                                                                                                                                                                                                                   | 2                                           |
| Sulfate                                                                                                                                                                                                                                          | 100                                         |
| Zinc                                                                                                                                                                                                                                             | 0.1                                         |
| <b>Electrolytes normally included in dialysis fluid</b>                                                                                                                                                                                          |                                             |
| Calcium                                                                                                                                                                                                                                          | 2 (0.05 mmol/l)                             |
| Magnesium                                                                                                                                                                                                                                        | 4 (0.15 mmol/l)                             |
| Potassium                                                                                                                                                                                                                                        | 8 (0.2 mmol/l)                              |
| Sodium                                                                                                                                                                                                                                           | 70 (3.0 mmol/l)                             |
| <p>NOTE This table is reproduced from ISO 13959.</p> <p><sup>a</sup> A dialysis facility's medical director has the ultimate responsibility for ensuring the quality of water used for dialysis.</p> <p><sup>b</sup> Unless otherwise noted.</p> |                                             |



**Table B.2 — Maximum allowable levels of other trace elements in dialysis water**

| Contaminant                                   | Maximum concentration (mg/l) |
|-----------------------------------------------|------------------------------|
| Antimony                                      | 0.006                        |
| Arsenic                                       | 0.005                        |
| Barium                                        | 0.1                          |
| Beryllium                                     | 0.0004                       |
| Cadmium                                       | 0.001                        |
| Chromium                                      | 0.014                        |
| Mercury                                       | 0.0002                       |
| Selenium                                      | 0.09                         |
| Silver                                        | 0.005                        |
| Thallium                                      | 0.002                        |
| NOTE This table is reproduced from ISO 13959. |                              |

Chemical analyses of the substances listed in Tables B.1 and B.2 can be obtained by using methods referenced by ISO, the American Public Health Association,<sup>[3]</sup> or the US Environmental Protection Agency,<sup>[47]</sup> or other equivalent analytical methods. Where testing for the individual trace elements listed in Table B.2 is not available, an analysis for total heavy metals can be used with a maximum allowable level of at 0.1 mg/l.

NOTE The maximum allowable levels of contaminants listed in Tables B.1 and B.2 include the anticipated uncertainty associated with the analytical methodologies listed in Table B.3.

**Table B.3 — Analytical test methods for chemical contaminants**

| Contaminant | Analytical technique                                                                | Reference, method number           |
|-------------|-------------------------------------------------------------------------------------|------------------------------------|
| Aluminium   | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)  | ISO 17294-2:2003                   |
|             |                                                                                     | American Public Health Assn, #3113 |
| Antimony    | Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)        | ISO 17294-2:2003                   |
|             |                                                                                     | US EPA, #200.9                     |
| Arsenic     | Inductively coupled plasma mass spectrometry or Atomic Absorption (gaseous hydride) | ISO 17294-2:2003                   |
|             |                                                                                     | American Public Health Assn, #3114 |
| Barium      | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)  | ISO 17294-2:2003                   |
|             |                                                                                     | American Public Health Assn, #3113 |
| Beryllium   | Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)        | ISO 17294-2:2003                   |
|             |                                                                                     | US EPA, #200.9                     |

| <b>Contaminant</b> | <b>Analytical technique</b>                                                                                                                     | <b>Reference, method number</b>                                                                                            |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Cadmium            | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)                                                              | ISO 17294-2:2003<br>American Public Health Assn, #3113                                                                     |
| Calcium            | Inductively coupled plasma mass spectrometry or EDTA Titrimetric Method, or Atomic Absorption (direct aspiration), or Ion Specific Electrode    | ISO 17294-2:2003<br>American Public Health Assn, #3500-Ca D<br>American Public Health Assn, #3111B                         |
| Total chlorine     | DPD Ferrous Titrimetric Method, or DPD Colorimetric Method<br>TMK/MTK colorimetric method                                                       | American Public Health Assn, #4500-CI F<br>American Public Health Assn, #4500-CI G                                         |
| Chromium           | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)                                                              | ISO 17294-2:2003<br>American Public Health Assn, #3113                                                                     |
| Copper             | Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Neocuproine Method                                    | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Cu D                          |
| Fluoride           | Ion chromatography or Ion Selective Electrode Method, or sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalenedisulfonate (SPADNS) Method | ISO 17294-2:2003<br>ISO 10359-1:1992<br>American Public Health Assn, #4500-F- C<br>American Public Health Assn, #4500-F- D |
| Lead               | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)                                                              | ISO 17294-2:2003<br>American Public Health Assn, #3113                                                                     |
| Magnesium          | Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration)<br>Ion chromatography                                     | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>EPA 300.7:1986                                                   |
| Mercury            | Flameless Cold Vapor Technique (Atomic Absorption)                                                                                              | American Public Health Assn, #3112                                                                                         |
| Nitrate            | Ion chromatography or Spectrophotometric method using sulfosalicylic acid or Cadmium Reduction Method                                           | ISO 10304-1:2007<br>ISO 78901-3:1988<br>American Public Health Assn, #4500-NO3 E                                           |

| Contaminant                                   | Analytical technique                                                                                                                          | Reference, method number                                                                                                                   |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Potassium                                     | Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-K D<br>American Public Health Assn, #3500-K E |
| Selenium                                      | Inductively coupled plasma mass spectrometry or Atomic Absorption (gaseous hydride), or Atomic Absorption (electrothermal)                    | ISO 17294-2:2003<br>American Public Health Assn, #3114<br>American Public Health Assn, #3113                                               |
| Silver                                        | Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)                                                            | ISO 17294-2:2003<br>American Public Health Assn, #3113                                                                                     |
| Sodium                                        | Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Na D                                          |
| Sulfate                                       | Ion chromatography or Turbidimetric Method                                                                                                    | ISO 10304-1:2007<br>American Public Health Assn, #4500-SO42- E                                                                             |
| Thallium                                      | Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)                                                                  | ISO 17294-2:2003<br>US EPA, 200.9                                                                                                          |
| Total heavy metals                            | Colorimetric                                                                                                                                  | European Pharmacopoeia, 2.4.8<br>US Pharmacopoeia, < 231 >                                                                                 |
| Zinc                                          | Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Dithizone Method                                    | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Zn D                                          |
| NOTE This table is reproduced from ISO 13959. |                                                                                                                                               |                                                                                                                                            |

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# Concentrates for hemodialysis and related therapies

Approved 21 July 2014 by  
**Association for the Advancement of Medical Instrumentation**

Approved 15 August 2014 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies minimum requirements for concentrates used for hemodialysis and related therapies. Addressed to the manufacturer of concentrates. Includes concentrates in both liquid and powder forms. Also included are additives, also called spikes, which are chemicals that may be added to the concentrate to increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid. Gives requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

**Keywords:** action, acid, bicarbonate, biofilm, fluid, endotoxin, pyrogen, sterile

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-548-5



# Contents

Page

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| Glossary of equivalent standards.....                                                                   | iv  |
| Committee representation.....                                                                           | v   |
| US deviation to ISO 13958:2014.....                                                                     | vi  |
| Introduction .....                                                                                      | vii |
| 1 Scope.....                                                                                            | 1   |
| 2 Normative references .....                                                                            | 1   |
| 3 Terms and definitions.....                                                                            | 2   |
| 4 Requirements.....                                                                                     | 7   |
| 4.1 Concentrates.....                                                                                   | 7   |
| 4.2 Manufacturing equipment.....                                                                        | 10  |
| 4.3 Systems for mixing concentrate at a dialysis facility .....                                         | 10  |
| 5 Tests .....                                                                                           | 12  |
| 5.1 General .....                                                                                       | 12  |
| 5.2 Concentrates.....                                                                                   | 12  |
| 5.3 Manufacturing equipment.....                                                                        | 14  |
| 5.4 Systems for mixing concentrate at a dialysis facility .....                                         | 15  |
| 6 Labelling.....                                                                                        | 16  |
| 6.1 General .....                                                                                       | 16  |
| 6.2 General labelling requirements for concentrates .....                                               | 16  |
| 6.3 Labelling requirements for liquid concentrate .....                                                 | 17  |
| 6.4 Labelling requirements for powder concentrate.....                                                  | 18  |
| 6.5 Additives.....                                                                                      | 18  |
| 6.6 Labelling requirements for concentrate generators.....                                              | 18  |
| 6.7 Labelling for concentrate mixer systems .....                                                       | 19  |
| Annex A (informative) Rationale for the development and provisions of this International Standard ..... | 21  |
| Bibliography .....                                                                                      | 27  |

## **Glossary of equivalent standards**

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

**[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)**

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### AAMI Renal Disease and Detoxification Committee

This American National Standard was developed by the AAMI Renal Disease and Detoxification Committee. Approval of the American National Standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the AAMI Renal Disease and Detoxification Committee had the following members:

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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NOTE—Participation by federal agency representatives in the development of this American National Standard does not constitute endorsement by the federal government or any of its agencies.

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## US deviation to ISO 13958:2014

The International Organization for Standardization (ISO) published ISO 13958:2014, *Concentrates for hemodialysis and related therapies* as a revision of ISO 13958:2009 on 2014-04-01. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for minimum requirements for concentrates used for hemodialysis and related therapies. The 2014 ISO revision editorially aligned ISO 13958 with the ISO dialysis fluid standards ISO 11663, ISO 13959, ISO 23500, and ISO 26722 which had been developed serially over several years.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

While considering the US adoption of ISO 13958:2014, the AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) approved a US deviation to the International Standard. ANSI/AAMI 13958:2014 deviates from ISO 13958:2014 in the following aspect:

The second paragraph of Subclause 5.2.4, Bacteriology of bicarbonate concentrates, which in ISO 13958:2014 reads:

“Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d) are recommended. Other test methods may also be used, provided such methods have been appropriately validated, and compared to the cited methods.”

is replaced in ANSI/AAMI 13958:2014 by the following:

“Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods.”

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

## Introduction

The requirements and goals established by this American National Standard will help ensure the effective, safe performance of hemodialysis concentrates and related materials. This American National Standard reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians and dialysis patients, in consultation with device manufacturers and government representatives, to develop a standard for performance levels that could be reasonably achieved at the time of publication. The term “consensus” as applied to the development of voluntary medical device standards does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests must be merged.

Throughout this American National Standard, recommendations are made to use ISO-quality water. Therefore, it is recommended to review ISO 13959 along with this American National Standard.

This American National Standard does not cover the dialysis fluid that is used to clinically dialyze patients. Dialysis fluid is covered in ISO 11663. The making of dialysis fluid involves the proportioning of concentrate and water at the bedside or in a central dialysis fluid delivery system. Although the label requirements for dialysis fluid are placed on the labelling of the concentrate, it is the user's responsibility to ensure proper use.

In addition, this American National Standard does not cover hemodialysis equipment, which is addressed in the new edition of IEC 60601-2-16.

The verbal forms used in this American National Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this American National Standard, the auxiliary verb

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard,
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.



# Concentrates for hemodialysis and related therapies

## 1 Scope

This International Standard specifies minimum requirements for concentrates used for hemodialysis and related therapies. For the purpose of this International Standard, “concentrates” are a mixture of chemicals and water, or chemicals in the form of dry powder or other highly concentrated media, that are delivered to the end user to make dialysis fluid used to perform hemodialysis and related therapies. This International Standard is addressed to the manufacturer of such concentrates. In several instances in this International Standard, it became necessary to address the dialysis fluid, which is made by the end user, to help clarify the requirements for manufacturing concentrates. Because the manufacturer of the concentrate does not have control over the final dialysis fluid, any reference to dialysis fluid is for clarification and is not a requirement of the manufacturer.

This International Standard includes concentrates in both liquid and powder forms. Also included are additives, also called spikes, which are chemicals that may be added to the concentrate to increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid. This International Standard also gives requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

Concentrates prepared from prepackaged salts and water at a dialysis facility for use in that facility are excluded from the scope of this International Standard. Although references to dialysis fluid appear herein, this International Standard does not address dialysis fluid as made by the end user. Also excluded from the scope of this International Standard are requirements for the monitoring frequency of water purity used for the making of dialysis fluid by the dialysis facility. Recommendations from the technical committee responsible for this International Standard for monitoring water quality are contained in ISO 23500. This International Standard does not address bags of sterile dialysis fluid or sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid.

## 2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11663, *Quality of dialysis fluid for hemodialysis and related therapies*

ISO 13959:2014, *Water for hemodialysis and related therapies*

ISO 14971, *Medical devices — Application of risk management to medical devices*

IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 61010-1, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

### 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

#### 3.1

##### **acetate concentrate**

concentrated solution of salts containing acetate, which, when diluted with dialysis water, yields bicarbonate-free dialysis fluid for use in dialysis

Note 1 to entry: Acetate concentrate may contain glucose.

Note 2 to entry: Sodium acetate is used to provide a buffer in place of sodium bicarbonate.

Note 3 to entry: Acetate concentrate is used as a single concentrate.

#### 3.2

##### **acid concentrate**

##### **A-concentrate**

acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term “acid” refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate may contain glucose.

Note 3 to entry: Acid concentrate may be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

#### 3.3

##### **action level**

concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

#### 3.4

##### **additive**

##### **spike**

small amount of a single chemical that, when added to the concentrate, will increase the concentration of a single existing chemical by a value labelled on the additive packaging

#### 3.5

##### **batch system**

apparatus in which the dialysis fluid is prepared in bulk before each dialysis session

#### 3.6

##### **bicarbonate concentrate**

##### **B-concentrate**

concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate may be in the form of a liquid or a dry powder.



Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

### 3.7

#### **bicarbonate dialysis fluid**

dialysis fluid containing physiological or higher concentrations of bicarbonate

Note 1 to entry: Bicarbonate dialysis fluid is generally produced from two concentrates: one containing bicarbonate and the other containing acid and other electrolytes. See *acid concentrate* (3.2)) and *bicarbonate concentrate* (3.6).

### 3.8

#### **biofilm**

microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

Note 1 to entry: The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

### 3.9

#### **bulk delivery**

delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery includes containers such as drums, which can be pumped into a storage tank maintained at the user's facility. Alternatively, the drums can be left at the facility and used to fill transfer containers to transfer the concentrate to the dialysis machines. Bulk delivery can also include large containers for direct connection to a central concentrate supply system.

Note 2 to entry: Bulk delivery also includes dry powder concentrates intended to be used with an appropriate concentrate mixer.

### 3.10

#### **central concentrate system**

system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

### 3.11

#### **central dialysis fluid delivery system**

system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

### 3.12

#### **concentrate generator**

system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyzer.

### 3.13

**concentrate mixer**

mixer for preparation of dialysis concentrate or dialysis fluid at a dialysis facility

**3.14****device**

individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term “component” as used by the US Food and Drug Administration (see Reference [15]).

**3.15****dialysis fluid****dialysate****dialysis solution**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis

Note 1 to entry: The term “dialysis fluid” is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyzer by the dialysis fluid delivery system. Such phrases as “dialysate” or “dialysis solution” are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyzer is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyzer is referred to as “spent dialysis fluid.”

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as hemodiafiltration and hemofiltration.

**3.16****dialysis fluid delivery system**

device that: prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; circulates the dialysis fluid through the dialyzer; monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks; and, prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system can be an integral part of a single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

**3.17****dialysis water**

water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in hemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialyzers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

**3.18****disinfection**

destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

### 3.19

#### **endotoxin**

major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. [See also *pyrogen* (3.30).]

### 3.20

#### **endotoxin units**

##### **EU**

units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

### 3.21

#### **germicide**

agent that kills microorganisms

### 3.22

#### **hemodiafiltration**

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing replacement solution into the blood either before the dialyzer (predilution hemodiafiltration) after the dialyzer (postdilution hemodiafiltration), or a combination of the two (mixed dilution hemodiafiltration).

### 3.23

#### **hemodialysis**

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

### 3.24

#### **hemofiltration**

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the hemofilter (predilution hemofiltration), after the hemofilter (postdilution hemofiltration) or a combination of the two (mixed dilution hemofiltration).

Note 2 to entry: There is no dialysis fluid stream in hemofiltration.

### 3.25

#### ***Limulus* amoebocyte lysate test**

**LAL test**

assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, may also be used to detect endotoxin.

**3.26****manufacturer**

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

**3.27****microbiological contamination**

contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

**3.28****nonpyrogenic**

not eliciting a pyrogen reaction

Note 1 to entry: Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

Note 2 to entry: The volume of fluid administered should not exceed the volume that would result in a total dose of endotoxin of  $\geq 5$  EU/kg/h.

Note 3 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 4 to entry: The commonly used gel clot method has a sensitivity limit of 0.03 EU/ml.

**3.29****proportioning system**

apparatus that proportions dialysis water and hemodialysis concentrate to prepare dialysis fluid

**3.30****pyrogen**

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.19)].

**3.31****sodium hypochlorite**

chemical used for disinfection of hemodialysis systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and javel. These solutions are used for disinfection at concentrations recommended by equipment manufacturers.

### **3.32**

#### **sterile**

free from viable microorganisms

Note 1 to entry: "Sterile" can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of  $10^{-6}$ , i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, "sterile" can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

### **3.33**

#### **storage tank**

tank at the user's facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

### **3.34**

#### **substitution fluid**

fluid used in hemofiltration and hemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid may also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

### **3.35**

#### **user**

physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

## **4 Requirements**

### **4.1 Concentrates**

#### **4.1.1 Physical state**

The concentrate for hemodialysis may be supplied in dry or aqueous form. Packaging may be for direct use with a single dialysis machine or for use in systems supplying multiple dialysis machines (bulk use).

#### **4.1.2 Solute concentrations**

##### **4.1.2.1 Liquid solute concentrations**

All electrolytes identified on the label shall be present within  $\pm 5\%$  or  $\pm 0.1$  mEq/l (expressed as dialysis fluid concentrations), whichever is greater, of the stated concentration, with the exception of sodium, which shall be present within  $\pm 2.5\%$  of the labelled concentration, or shall be present according to approved specifications by the

local regulations. If used, glucose shall be present within  $\pm 5\%$  or  $\pm 0.05$  g/l (when measured as properly diluted dialysis fluid), whichever is greater, of the labelled concentration, or shall be present according to approved specifications by the local regulations. Where concentrates include non-traditional constituents, such as antioxidants and iron compounds, these constituents shall be present at nominal concentrations with  $\pm 5\%$  tolerances, or shall be present according to approved specifications by the local regulations. If alternate, locally approved tolerances are used, the tolerances shall be similarly stated and the rationale for their use documented.

Most concentrates are manufactured with standard traditional chemicals such as sodium chloride, potassium chloride, magnesium chloride, calcium chloride, acetic acid, glucose, etc. New concentrates are available in which certain chemicals have been substituted by others; for example, citric acid has been substituted for acetic acid. Where this occurs, the labelling shall correctly reflect this and the substitute chemicals shall be present at nominal concentrations with  $\pm 5\%$  tolerances, or shall be present according to approved specifications by the local regulations. If alternate, locally approved tolerances are used, the tolerances shall be similarly stated and the rationale for their use documented.

#### **4.1.2.2 Solute concentrations from powder**

When concentrate is packaged in dry form or a combination of dry and liquid and is mixed according to the manufacturer's instruction for use, the final concentrate shall meet the requirements of 4.1.2.1.

#### **4.1.3 Water**

The quality of water used in the manufacture of the concentrate shall be in accordance with ISO 13959.

#### **4.1.4 Bacteriology of concentrates**

##### **4.1.4.1 Bacteriology of bicarbonate concentrates**

Concentrate containing bicarbonate supplied as a liquid shall be provided in a sealed container and manufactured by a process validated to produce dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions. Bicarbonate powder intended for the preparation of concentrate at a dialysis facility shall be capable of producing dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions.

##### **4.1.4.2 Bacteriology of acid concentrates**

There are no published reports of acid concentrate supporting bacterial growth and as such, acid concentrate need not be tested for bacterial growth.

#### **4.1.5 Endotoxin levels**

The concentrate shall be formulated and packaged using a process validated to produce dialysis fluid meeting the endotoxin requirements of ISO 11663 or the applicable pharmacopoeia when used according to the manufacturer's instructions.

#### **4.1.6 Fill quantity**

The excess fill volume of liquid containers and the excess fill weight of powder containers used with batch systems for a single dialysis treatment shall be within  $2\%$  of the labelled volume or weight. The fill weight of bulk delivered powdered concentrate shall be such that, when mixed according to the manufacturer's instructions, it produces liquid concentrate that meets the requirements of 4.1.2.1. The fill weight of a concentrate generator shall be such that the

device performs as intended. For all other applications, the fill volume or weight shall be  $\geq 100\%$  of the stated volume or weight.

#### **4.1.7 Chemical grade**

All chemicals shall meet the requirements of the applicable pharmacopoeia, including all applicable portions of the general notices and of the general requirements for tests and assay. If all other requirements are met, monograph limits for sodium, potassium, calcium, magnesium, and/or pH may be exceeded provided that correction is made, if necessary, for the presence of those ions in the final formulation. Also, any pharmacopoeia requirements that the chemicals be labelled for use in hemodialysis need not be complied with if the manufacturer is performing its own testing to meet the requirements of the applicable pharmacopoeia.

#### **4.1.8 Particulates**

The aqueous dialysis concentrate shall be filtered through a nominal 1  $\mu\text{m}$  or finer particulate filter. The particulate filter used shall have a non-fibre-releasing membrane that does not contain material of known potential for human injury.

#### **4.1.9 Additives — “Spikes”**

If additives are supplied, the concentration, when properly diluted with water or concentrate, shall yield values within  $\pm 5\%$  by weight of the labelled value.

#### **4.1.10 Containers**

Containers, including the closures, shall not interact chemically or physically with the contents to alter the strength, purity, or quality of the concentrate during handling, storage, and shipment. The containers shall have closures that prevent contamination or loss of content. Each container shall be marked to indicate its contents. One means of indicating the contents is to use an appropriate symbol (see Table 2).

#### **4.1.11 Bulk-delivered concentrate**

When concentrate is delivered in bulk form, the responsibility for ensuring compliance with this International Standard shall pass from the manufacturer to the user at the legal point of transfer of the shipment. Once the concentrate is transferred from the manufacturer to the user, it becomes the user's responsibility to maintain the product in a usable state with appropriate labels and non-tamper procedures.

#### **4.1.12 Concentrate generators**

Concentrate generator systems include systems that mix powder, or powder and a highly concentrated liquid, into a concentrate by forming a slurry or concentrated solution in a container designed to function with specific dialysis machines. Mixing is accomplished by an automated dynamic proportioning system within the dialysis fluid delivery system. Because these concentrates are delivered to the user as a powder or a highly concentrated liquid in containers designed for specific machines, it is the concentrate generator manufacturer's responsibility to ensure that

- all applicable clauses of this document dealing with powder are met,
- the container will function with the machines as defined by the manufacturers of the machines, and
- undissolved powder is prevented from entering the dialysis fluid stream.

## **4.2 Manufacturing equipment**

Any material components of the manufacturing equipment (e.g. piping, storage, and distribution systems) that have contact with the final concentrate or any component of the concentrate shall not interact physically or chemically with the product so as to significantly alter the strength, purity, or quality of the concentrate delivered to the user. Examples of materials that should not be used in manufacturing equipment include copper, brass, zinc, galvanized material, or aluminium.

## **4.3 Systems for mixing concentrate at a dialysis facility**

### **4.3.1 General**

The following requirements apply to systems, such as a central concentrate system, used to prepare acid or bicarbonate concentrates from dialysis water and powder or other highly concentrated media at a dialysis facility.

### **4.3.2 Materials compatibility**

The materials of any components of concentrate mixing devices/systems (including storage and distribution systems) that contact the concentrate solutions shall not interact chemically or physically so as to adversely affect their purity or quality. Such components shall be fabricated from non-reactive materials (e.g. plastics) or appropriate stainless steel. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, zinc, galvanized material, or aluminium, are specifically prohibited.

### **4.3.3 Disinfection protection**

#### **4.3.3.1 General**

When the manufacturer of the mixing system recommends chemical disinfectants [see 6.7.2 k)], means shall be provided to restore the system to a safe condition relative to residual disinfectant prior to the system being used to prepare a batch of concentrate. When formaldehyde is used, the residual level shall be less than 3 mg/l; when sodium hypochlorite is used, the residual level shall be less than 0.1 mg/l; when ozone is used, the residual level shall be less than 0.1 mg/l; when a commercially available chemical germicide other than formaldehyde, sodium hypochlorite, or ozone is used, the residual level shall be less than that recommended by the manufacturer of the specific germicide. When recommending chemical disinfectants, the manufacturer shall also recommend methods for testing for residual levels of the disinfectants.

When the manufacturer of the mixing system recommends high-temperature disinfection, a means shall be provided to restore the system to a safe temperature prior to being used to prepare a batch of concentrate.

#### **4.3.3.2 System lock out**

When disinfection is accomplished automatically by chemical disinfectant, ozone, or by high temperature procedures, activation of the disinfection system shall result in activation of a warning system and measures should be taken to isolate hemodialysis machines from the concentrate preparation and distribution system.

### **4.3.4 Safety requirements**

Each concentrate mixing device/system shall exhibit the following minimum safety features:

- a) operating controls shall be positioned so as to minimize inadvertent operation and resetting of functions;
- b) distribution controls shall be clearly labelled to minimize the possibility of error in the transfer of concentrate.



#### 4.3.5 Bulk storage tanks

When used for bicarbonate concentrate, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Bicarbonate storage tanks should have a tight fitting lid to prevent ingress of contaminants and be vented through a hydrophobic 0.45 µm air filter.

Rigid, non-flexing acid concentrate storage tanks may have a flat bottom and should be vented in a way to prevent dirt contamination of the concentrate.

Storage tanks should not have sight tubes, which can grow algae and fungi. Means shall be provided to effectively disinfect any storage tank in a concentrate distribution system that is subject to microbiological contamination.

The disinfection of acid concentrate tanks is normally not necessary. However, bicarbonate tanks should be disinfected frequently. For acid concentrate storage alternative bulk storage containers, such as bladders, may be used.

#### 4.3.6 Ultraviolet irradiators

When concentrate storage and distribution systems are provided with an ultraviolet irradiator for bacterial control, the following shall be complied with:

- a) the ultraviolet irradiator shall emit radiation at a wave frequency of 254 nm;
- b) the ultraviolet irradiator shall provide a dose of radiant energy of 16 mW·s/cm<sup>2</sup> if it is fitted with a calibrated ultraviolet intensity meter, otherwise it shall provide a dose of radiant energy of 30 mW s/cm<sup>2</sup>;
- c) the ultraviolet irradiator shall be sized appropriately for the maximum flow rate;
- d) the ultraviolet irradiator shall be equipped with an online monitor of radiant energy output or a recommended frequency of lamp replacement shall be stated;
- e) the ultraviolet irradiator shall be followed by an endotoxin-retentive filter.

#### 4.3.7 Piping systems

Concentrate distribution systems shall not contribute microbiological contaminants to the concentrate. Concentrate distribution systems shall be designed and operated in a manner that minimizes bacterial proliferation and biofilm formation that can contaminate susceptible concentrates. Frequent disinfection of bicarbonate concentrate distribution systems is one way to minimize bacterial proliferation and biofilm. The disinfection of piping systems for acid concentrate is normally not necessary because acid concentrates are typically bacteriostatic.

#### 4.3.8 Electrical safety requirements

Where there is a possibility of a sustainable fluid pathway to the patient which is capable of conducting electrical current, the device shall meet the requirements of IEC 60601-1 with respect to electrical safety. Where the electrical system is isolated from the patient the device shall meet the requirements of IEC 61010-1, with respect to electrical safety.

**NOTE** There is a possibility of a sustainable fluid pathway to the patient which is capable of conducting electrical current. Its existence would depend on the distribution system and the manufacturer's instructions for use of the concentrate mixing system. To maximize electrical safety two cases are presented: a) where there is a possibility of a sustainable electrical pathway and b) where the electrical system is isolated from the patient.

## **5 Tests**

### **5.1 General**

Clause 5 defines test methods by which compliance with the requirements of Clause 4 can be verified. The test methods listed do not represent the only acceptable test methods available, but are intended to provide examples of acceptable methods. Other test methods may be used provided such methods have been appropriately validated, and compared to the cited methods.

### **5.2 Concentrates**

#### **5.2.1 Physical state**

Compliance with the requirements of 4.1.1 can be determined by visual inspection.

#### **5.2.2 Solute concentrations**

##### **5.2.2.1 Liquid solute concentrations**

Compliance with the requirements of 4.1.2.1 for calcium, potassium, magnesium and sodium can be determined by using methods described by the American Public Health Association,<sup>[7]</sup> methods referenced by the US. Environmental Protection Agency,<sup>[12]</sup> methods referenced in applicable pharmacopoeia, or other equivalent validated analytical methods. Samples shall be collected in sealed containers. Appropriate sample preparation, including using suitable mixing vessels and adjusting for pH if necessary, shall be used to ensure accurate determinations.

Compliance with the requirements of 4.1.2.1 for new and non-traditional concentrate constituents can be determined by using appropriate and validated analytical methods.

The maximum contaminant levels referred to in ISO 13959 shall be used as a reference for dialysis water.

Compliance with the requirements for the contents of the dialysis fluid can be determined as described in Table 1. Other test methods may also be used, provided such methods have been appropriately validated, and compared to the cited methods.

**Table 1 — Analytical tests for chemical components**

| Component   | Test methods                                                                                                                                                                |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acetate     | Gas chromatography, liquid chromatography, enzymatic, or potentiometric methods                                                                                             |
| Bicarbonate | Acid titration and calculation, ion chromatography, or other method for total CO <sub>2</sub>                                                                               |
| Calcium     | EDTA titrimetric method, or atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration) or ion chromatography                        |
| Glucose     | Polarimetry, enzymatic, liquid chromatography, or chemical methods                                                                                                          |
| Magnesium   | Atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration), or ion chromatography                                                   |
| Potassium   | Flame photometry method, atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration) or ion chromatography                           |
| Sodium      | Atomic absorption (direct aspiration), flame photometric method, inductively coupled plasma spectrometry (direct aspiration), ion-specific electrode, or ion chromatography |

#### 5.2.2.2 Solute concentrations from powder

To test for the solute concentration from dry powders the contents of a package should be mixed according to the manufacturer's instructions and tested according to 5.2.2.1.

#### 5.2.3 Water

Compliance with the water quality requirements of 4.1.3 can be determined by using methods referenced in this International Standard.

#### 5.2.4 Bacteriology of bicarbonate concentrates

To ensure compliance with 4.1.4 the following procedure can be used. Total viable counts (standard plate counts) shall be obtained using the membrane filter technique or other validated standard bacteriology test methods. The calibrated loop technique shall not be used. Culture media shall be tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent.

Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods.

#### 5.2.5 Endotoxin levels

Compliance with the requirements of 4.1.5 can be determined by the LAL test for endotoxins.

### **5.2.6 Fill quantity**

Compliance with the requirements of 4.1.6 can be determined by the use of appropriate volumetric or gravimetric techniques.

### **5.2.7 Chemical grade**

Purity of chemicals as specified in 4.1.7 can be determined by test methods outlined in the appropriate pharmacopoeia.

### **5.2.8 Particulates**

Compliance with the requirements of 4.1.8 can be determined by inspection of the manufacturing records of the product to ensure that the concentrate was filtered through a nominal 1  $\mu\text{m}$  filter.

### **5.2.9 Additives — “Spikes”**

Compliance with 4.1.9 may be determined by dissolving the additive in the appropriate concentrate and then measuring the concentration of the added chemical to determine if the presence of the additive altered the concentration of that chemical to within  $\pm 5\%$  of the amount specified on the additive label. Alternately, the additive may be diluted into the appropriate quantity of water and tested to determine if the additive provides the stated increase in concentration within  $\pm 5\%$  of the labelled value. Testing should be done according to 5.2.2.1 once the additive is mixed.

### **5.2.10 Containers**

Compliance with the requirements of 4.1.10 can be determined by visual inspection and by appropriate biocompatibility testing. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

### **5.2.11 Bulk delivered concentrate**

Compliance with the requirements of 4.1.11 can be determined by review of the delivery procedures.

### **5.2.12 Concentrate generators**

Compliance with 4.1.12 can be confirmed by review of the design records of the container that holds the powder, functional testing with the intended hemodialysis machine and inspection of the product label.

**NOTE** It is recognized that a dialysis machine manufacturer could modify his equipment to use another manufacturer's concentrate generator system. When this occurs it becomes the machine manufacturer's responsibility to ensure that the concentrate generator system is compatible with the dialysis machine.

## **5.3 Manufacturing equipment**

The biocompatibility of material components used in the manufacturing equipment should be determined by verifying that the components in contact with the concentrate or water are non-reactive materials (e.g. plastics or appropriate stainless steel) that are not known to cause toxicity in dialysis fluid systems. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

## **5.4 Systems for mixing concentrate at a dialysis facility**

### **5.4.1 General**

The following test methods apply to 4.3.2 to 4.3.8, as indicated.

### **5.4.2 Materials compatibility**

Compliance with the requirements of 4.3.2 can be verified by visual inspection and by appropriate biocompatibility testing. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

### **5.4.3 Disinfection protection**

#### **5.4.3.1 General**

Compliance with the requirements of 4.3.3.1 can be determined by testing for the disinfectant in the rinse water at the end of the disinfection loop. When the disinfectant is formaldehyde, residual levels can be determined by the Hantzsch reaction, Schiff's reagent or an equivalent test. When the disinfectant is sodium hypochlorite, residual levels can be determined using the DPD ferrous titrimetric methods or an equivalent test. When the disinfectant is ozone, residual levels can be determined using an online monitor for dissolved ozone or analysis of water samples using test kits based on indigo trisulfonate or DPD chemistry. If a commercially available chemical germicide other than formaldehyde, sodium hypochlorite, or ozone is used, the test established by the manufacturer of the germicide for residual germicide shall be used according to the test manufacturer's instructions.

Compliance with the requirements of 4.3.3.1 for high-temperature disinfection can be shown by demonstrating that the rinse water has returned to a safe temperature.

#### **5.4.3.2 System lock out**

Compliance with the requirements of 4.3.3.2 can be determined by physical test and/or visual inspection.

### **5.4.4 Safety requirements**

Compliance with 4.3.4 can be determined by inspection.

### **5.4.5 Bulk storage tanks**

Compliance with the requirements of 4.3.5 can be determined by visual inspection.

### **5.4.6 Ultraviolet irradiators**

Compliance with 4.3.6 can be determined by inspection.

### **5.4.7 Piping systems**

The absence of aluminium, copper, lead, zinc, and galvanized components and the configuration of a concentrate mixing system/device can be determined by visual inspection. Non-contribution of bacteria and specific chemical contaminants to the solution by the distribution system can be verified by using the tests described in 5.2.4 and 5.3.

#### 5.4.8 Electrical safety requirements

Compliance with the requirements of 4.3.8 can be determined using the tests found in IEC 60601-1 or IEC 61010-1 as appropriate.

## 6 Labelling

### 6.1 General

The term “labelling” in this International Standard includes any written material accompanying the hemodialysis concentrates and concentrate mixing system or any written instructions provided by the manufacturer.

The label on the concentrate container shall, at a minimum, provide the applicable information contained in 6.2 to 6.6. Symbols may be used where appropriate.

NOTE 1 See ISO 15223.

NOTE 2 With some machines the mixing of concentrate is automated and not performed by the user. In these cases the instructions for use can be modified to fit the appropriate situation. For example, if the machine takes powder and liquid concentrate and mixes them internally, it would not be necessary to state that the “concentrate be mixed well before use.” The design of the machine should take this into account and mix the concentrate appropriately.

### 6.2 General labelling requirements for concentrates

General labelling requirements for concentrates shall include the following.

- a) Name and address of the manufacturer/distributor.
- b) Expiry date, if applicable.

NOTE Normally, the expiry date and not the manufacturing date will be on the product.

- c) Manufacturing date, only if expiry date is not applicable.
- d) Identifying lot number.
- e) A list of all ingredients in the final concentrate and the following.
- f) Composition, including the concentration, in grams per litre (g/l), of each ingredient for liquid concentrate or the weight per container of each ingredient for powder.
- g) Composition of the dialysis fluid, including the nominal concentration of each electrolyte in millequivalents per litre (mEq/l) or millimoles per litre (mmol/l) and the concentration of non-electrolytes in the dialysis fluid in grams per litre (g/l) or mmol/l; the chemical concentration of the final dialysis fluid shall be placed on the acid concentrate label.

NOTE Where there is insufficient space on the label to properly present the information required, it is acceptable to provide this information in an alternative format such as a package insert.

- h) For batch systems, the volumes or weight of dialysis concentrate(s) and the amount and quality of the water that shall be mixed; if mixing is automated an instruction to follow the manufacturer's instructions for use.

- i) For proportioning systems, the ratio of dialysis concentrate and water that shall be mixed.
- j) Trade name of the product, if appropriate.
- k) A statement regarding storage requirements such as, if appropriate: “Store at or below room temperature”; “Do not freeze”; and/or “Short-term exposure to warm conditions (40 °C) will not harm acid concentrate”.
- l) Any special requirements that is necessary because of the specificity of the product (i.e. the use of concentrate generators with a specific dialysis fluid delivery system).
- m) A warning stating that bacterial growth can occur when using bicarbonate concentrate (bicarbonate concentrate only) and any other precautions that shall be taken in the mixing of the concentrate.
- n) When appropriate, a statement to test the final dialysis fluid for one of the following parameters: conductivity, pH, osmotic pressure, sodium concentration, or chloride concentration.
- o) A statement that ISO-quality water meeting the requirements of ISO 13959 shall be used to dilute the concentrate to make dialysis fluid.
- p) A statement to not overmix bicarbonate concentrate.
- q) A statement regarding any special buffering concerns (including the impact of varying the dialysis fluid sodium and bicarbonate concentration during dialysis) on the labelled composition of the final dialysis fluid, if appropriate (see A.2.1.1)”.

### **6.3 Labelling requirements for liquid concentrate**

Labelling for liquid concentrate shall include the following.

- a) Instructions for use.
  - 1) The label shall include instructions to mix thoroughly prior to use and instructions not to use damaged containers. When bicarbonate is used, a warning shall be included noting that bacterial growth can occur in concentrated or diluted bicarbonate solutions.
  - 2) The labelling shall state that once opened, the bicarbonate concentrate shall be used within the time limit specified by the manufacturer, or within 24 h, unless measures to extend that limit are documented. The time limit for use (determined by the manufacturer) shall be the period during which the concentrate consistently produces a dialysis fluid that meets the chemical and microbiological recommendations of ISO 11663 when used in a properly maintained system.
  - 3) Liquid concentrate labelling may include geometric symbols (see Table 2) to differentiate different proportioning ratios. If such symbols are used, the numbers representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol. The label should incorporate a means to differentiate between acid and bicarbonate. If a concentrate contains no potassium or no calcium, that shall be prominently displayed on the label. If colour coding is used, red should be used for acid, blue for bicarbonate, and white for acetate.
- b) Fill volume of the container.
- c) Nominal conductivity of the final dialysis fluid when mixed according to the manufacturer's instructions or a statement that such information is available from the manufacturer.

## 6.4 Labelling requirements for powder concentrate

Labelling for powder concentrate shall include the following.

- a) Instructions for use.
  - 1) The label shall include recommended storage conditions and mixing precautions. When bicarbonate is used, microbial limits for water used and other microbial concerns (e.g. disinfection of mixing and storage apparatus) shall be stated. The maximum storage time (shelf life) before dissolution and following dissolution shall be stated for specified storage conditions. Where necessary, to ensure quality of the product by the end user, directions shall instruct the user on the proper use of the product. Such directions shall include, but not be limited to, the quality of water to be used to dissolve the dry powder, the correct testing method (e.g. conductivity or pH) to ensure proper dilution of the final dialysis fluid, and any specific precautions that shall be followed to ensure proper use of the product.
  - 2) Powder concentrate labelling may include geometric symbols (see Table 2) to differentiate different proportioning ratios. If such symbols are used, the numbers representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol. The label should incorporate a means of differentiating between acid and bicarbonate. If a concentrate contains no potassium or no calcium, that shall be prominently displayed on the label. If colour coding is used, red should be used for acid and blue for bicarbonate.
- b) Instructions for mixing the dry powders into a liquid concentrate.
- c) The amount of water that shall be used to reconstitute the concentrate.
- d) If applicable, the mixing equipment for which the powder is to be used.
- e) For bicarbonate concentrate, the time limit for use in order to prevent possible bacterial contamination. Also, appropriate warnings that residual bicarbonate concentrate, uncleaned mixing tanks, and mixing systems will support bacterial growth.
- f) The water quality that should be used to mix the concentrate (i.e. the maximum bacterial and endotoxin levels).

## 6.5 Additives

Labelling for additives shall include the following.

- a) A list of the product(s) for which the additive can be used. The effective changes in the concentrate formula and the subsequent change to the dialysis fluid, which result from the addition of the additive.
- b) Dilutional effects on the final dialysis fluid of any liquid additives (labelling on liquid additives only).

## 6.6 Labelling requirements for concentrate generators

Labelling for concentrate generators shall include the following.

- a) Proportioning system or dialysis machine with which they are to be used.

**NOTE** It is possible that a manufacturer could modify his machine to accept another manufacturer's concentrate generator system. In this case the machine manufacturer has the responsibility to label the machine with the correct concentrate generator system model and manufacturer.



- b) The amount of time that the concentrate generator can reasonably be expected to provide solution, based on a manufacturer's specified flow rate to the dialyser (e.g. 6 h at a flow rate of 500 ml/min.); alternatively, the capacity of the concentrate generator can be expressed as the volume of concentrate which can be produced by the concentrate generator.
- c) Any additional information that shall be known by the user to ensure that the product will be used correctly (e.g. water quality, shelf life after mixing, etc.).

**Table 2 — Symbols for concentrate container system: concentrate types**

| Designation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |  | Other <sup>a</sup><br>(new) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|
| Mix ratio <sup>bc</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1:1.23:32.77                                                                      | 1:1.83:34                                                                         | 1:1.72:42.28                                                                       | 1:1,1:34                                                                            | TBD <sup>a</sup>            |
| Acid mix ratio <sup>de</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1:34                                                                              | 1:35.83                                                                           | 1:44                                                                               | 1:35.1                                                                              | TBD <sup>a</sup>            |
| Bicarbonate mix ratio <sup>fg</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1:27.46                                                                           | 1:19.13                                                                           | 1:25.16                                                                            | 1:31.8                                                                              | TBD <sup>a</sup>            |
| Symbol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Square □                                                                          | Circle ○                                                                          | Triangle △                                                                         | Diamond ◇                                                                           | TBD <sup>a</sup>            |
| <sup>a</sup> Any new ratio that does not fit the above matrix should be designated with a unique geometric symbol with the ratio contained in the symbol (to be determined).<br><sup>b</sup> Acid:bicarbonate:water.<br><sup>c</sup> There can be minor differences in mix ratios within each concentrate type; e.g. 1:1.18:32.82 and 1:1.26:32.74 can be used instead of 1:1.23:32.77, and 1:1.58:42.42 can be used instead of 1:1.72:42.28.<br><sup>d</sup> Acid:water + bicarbonate concentrate.<br><sup>e</sup> The acid mix ratio may also be expressed as acid + (water + bicarbonate concentrate); e.g. 1 + 34, and 1 + 44, can be used instead of 1:34 and 1:44, respectively.<br><sup>f</sup> Bicarbonate: acid + water.<br><sup>g</sup> Bicarbonate mix ratios are based on 8.4 % sodium bicarbonate solution (1 000 mmol/l). Other solutions may be used clinically and their use will result in a different mixing ratio. |                                                                                   |                                                                                   |                                                                                    |                                                                                     |                             |

## 6.7 Labelling for concentrate mixer systems

### 6.7.1 General

Labelling for concentrate mixing devices shall include the following:

- name and address of manufacturer (affixed to the device);
- trade name and type of device (affixed to the device);
- model and serial number (affixed to the device);
- warning that product literature should be read before use of the concentrate mixing system;
- prominent warnings about substances (e.g. germicides) that need to be removed from the device before using the device;

- f) identification of fitting type or specification when necessary to prevent improper connections (preferably attached to the device, but otherwise included in the instructions for use).

#### **6.7.2 Product literature for concentrate mixers**

The manufacturer shall provide literature to each user, which contains, but is not limited to the following information:

- a) a warning that each batch of concentrate should be tested according to the manufacturer's instructions before use;
- b) a warning that selection of concentrate mixing equipment for dialysis is the responsibility of the dialysis physician;
- c) a description of the device or system, including a list of monitors, alarms, and component devices provided as standard equipment;
- d) a schematic diagram of the device or system showing the location of any valves, online monitors, or sampling ports;
- e) operating specifications, such as water pressure and flow rate;
- f) detailed instructions for use, including initial start-up, testing and calibration, operation and meaning of alarms, operational adjustments to monitors, alarms, and controls, and connections;
- g) safety features and warnings concerning the consequences if these features are circumvented;
- h) information pertaining to online monitors of water or concentrate quality, including operational factors that could affect monitor performance (e.g. temperature);
- i) construction materials, identified generically, that are in contact with solutions;
- j) information about germicides and cleaning agents known to be compatible with materials used in the device, as well as information about known chemicals with which materials used in the construction of the device are incompatible;
- k) if applicable, a method of cleaning and disinfecting the equipment, the time interval between cleanings and disinfections of the system, and a method of removing the residual germicide;
- l) other maintenance and service instructions, including recommended preventive maintenance procedures, and schedules, recommended monitoring schedules, trouble-shooting guidelines intended for the user, service information, a recommended spare parts list, a warning of the consequences if maintenance instructions are not followed;
- m) a warning that if, after installation and subsequent use, any component of the concentrate mixing system is changed or replaced, the user should conduct appropriate tests and calibrations;
- n) where ultraviolet irradiators are used, the necessary maintenance steps, such as bulb replacement and cleaning, to maintain the system.

## **Annex A**

### **(informative)**

# **Rationale for the development and provisions of this International Standard**

## **A.1 Scope**

The items included within the scope of this International Standard are the reagents and devices required to manufacture hemodialysis concentrate. This International Standard addresses both liquid and dry concentrates. It is addressed primarily to manufacturers but has useful information for the user.

Systems that regenerate dialysis fluid by passing the dialysis fluid through systems to restore the dialysis fluid's original content have been specifically excluded from the scope of this International Standard.

Concentrate solutions for use in preparing dialysis fluid for hemodialysis, whether liquid or dry, whether general or specific, are put into use by a professional user; this critical final step is not under the control of the manufacturer. This two-stage responsibility could produce confusion as to the duties and liabilities of the parties involved.

The concentrate, properly manufactured and labelled, could be used in erroneous combinations; the correct option might not be used for a given patient; improper handling could lead to contamination of the final dialysis fluid. No equipment or system can prevent or avoid these errors. Only an informed and reliable clinical professional can control these final steps in the process. The potential for human error requires human oversight.

These circumstances necessitate that the manufacturer labels the concentrate clearly, completely, and explicitly, and documents the delivery of the product and transfer of responsibility for its application to the user facility and its professional staff.

Clinical experience has made it clear that prescribing physicians might not be fully aware of the amounts of buffer that are added as the result of acetate (when present in liquid concentrate) and acetate and acetic acid (sodium hydrogen diacetate) (when present in dry concentrate). These add  $\geq 6$  mEq/l of anion, which is capable of being metabolized to generate bicarbonate. This being in addition to whatever bicarbonate concentration is prescribed and make the final buffer concentration unexpectedly high.

While the principal concern is for adequate, safe treatment of the patient, other considerations have influenced the content of this International Standard such as theoretical hazards, or remote short- or long-term risks. Hemodialysis is a complicated procedure. Therefore, an attempt has been made to set standards that are consistent with operating constraints and operator convenience whenever possible. Stringent standards have been reserved for serious threats to the patient or for specifications that are readily achievable at low burden with a minimum of inconvenience to the operator. More liberal standards have been chosen when the risk to the patient is low or when a large safety factor approaches the limits of available instruments, requires expensive modifications or poses significant problems for the operator.

## A.2 Requirements

### A.2.1 General

#### A.2.1.1 Overview

The display of identification data and basic content information provides necessary information for use and reference and ensures traceability. The use of bicarbonate dialysis fluid requires two concentrates to be used in preparing dialysis fluid because concentrated calcium and bicarbonate will precipitate when combined. Technology for dual proportioning is widely available. Different systems proportion at different ratios (e.g. 35X, 36,83X, 45X), and other systems directly use dry powder made into a concentrated solution by the dialysis fluid delivery system. Some of these concentrates contain sodium chloride in the bicarbonate solution, requiring a corresponding adjustment in the parallel counterpart acid concentrate. This complicated assortment can lead to confusion. Adequate monitoring does not currently exist to ensure that mismatched concentrates do not produce a final dialysis fluid of proper total conductivity but of improper composition. The user is cautioned not to rely solely on conductivity measurements to ensure safety, but to consider all relevant factors, including pH. Recognition and application of appropriate concentrates to produce the desired dialysis fluid is the responsibility of the end user. When calculating the total amount of base in the final dialysis fluid, the contribution of acetate (or any other organic anion that produces bicarbonate as it is metabolized) from the acid concentrate should be taken into account, since this contribution is additive to the bicarbonate contained in the bicarbonate concentrate.

Some acid concentrates, such as those formulated with sodium hydrogen diacetate (a compound comprised of acetic acid and sodium acetate), contain more organic anions than traditional concentrates. When using one of these concentrates, consideration should be given to the significant increase in base derived from the acid concentrate when selecting a dialysis fluid bicarbonate concentration.

Standards for bicarbonate dialysis fluid delivery systems thus should address both proportioning and monitoring systems, as well as concentrate packaging and labelling.

In view of the potential for improper use of concentrate, a decision has been made to emphasize the importance of user education and training and to specify labelling.

Bicarbonate dialysis fluid can increase precipitation and scaling within the dialysis fluid path, including monitoring electrodes. Regular, effective dialysis fluid path cleaning is critical to machine performance. Haloduric bacteria can multiply in bicarbonate concentrates, although no bacteria are known to multiply in acid or acetate concentrates. Specifications for handling, shelf life and microbiologic monitoring should be established by each user in accordance with manufacturer's recommendations. Manufacturers should provide full information and rational guidance for health professionals to produce safe, appropriate dialysis fluid.

With present technology, the final safeguard is a responsible operator of the equipment. To achieve this final safeguard, staff members should be trained and supervised. Such measures are the responsibility of the medical director of the dialysis programme.

Acetate concentrate is a single component concentrate that uses sodium acetate as the buffer rather than bicarbonate. As technology has advanced, the use of acetate concentrate has diminished.

#### A.2.1.2 Physical state

Concentrate may be in either aqueous or dry form, depending on the application. In some cases, a portion of the concentrate is aqueous and the remainder is in dry form; in other cases, two aqueous concentrates are used.

#### A.2.1.3 Solute concentrations

It is essential that the actual concentrations of the solutes contained in the concentrate be as close as possible to the labelled amount. Although excessive variations could be hazardous to the patient, tolerances of less than 5 % for glucose and the minor cations can consistently be achieved. Further, when those components are present at low levels, a variation of 0.1 mEq/l for the minor cations or of 5 mg/dl for glucose is acceptable. This variance is necessary to account for minor amounts of such solutes present in the other raw materials and limitations of manufacturing and testing.

#### **A.2.1.4 Water**

It was decided that there should be some assurance that the water used to prepare the concentrate would not significantly contribute to the chemical contaminant levels present in the concentrate itself. Accordingly, the requirements for water in ISO 13959 were referenced.

#### **A.2.1.5 Bacteriology of bicarbonate concentrates**

Bicarbonate concentrates have been shown to support bacterial growth and to provide another source of initial bioburden capable of rapid increase after dilution.<sup>[9][8]</sup> Recognition of this hazard requires additional precautions in preparation, containers, storage and prompt use to avoid excess growth of haloduric organisms. Practices to ensure safety shall be recommended by manufacturers and established and followed by users.

There has been considerable discussion regarding the use of appropriate media and incubation conditions to culture bicarbonate concentrate. This International Standard gives one acceptable method described in 5.2.4. Other methods may be used, provided that such methods have been appropriately validated and compared to the cited methods.

Most microorganisms do not grow well in acid concentrates and thus, there is no requirement for testing for release levels of bacteria in acid concentrate.

#### **A.2.1.6 Fill quantity**

The supplier should ensure that the volume or weight is consistent with the label and thus, with expectations of the user.

#### **A.2.1.7 Chemical grade**

It is recommended that all chemicals meet the requirements of the applicable pharmacopoeia. The limits of sodium, potassium, calcium, magnesium, and pH may be exceeded, provided that the exceptions are compensated for in the final formula. Since these ions were being added to the final formula, it would be possible to make the necessary corrections to compensate for these ions without incurring the burden of meeting these limits.

It was also considered whether or not chemicals to be used in hemodialysis should be so labelled. Since the labelling requirement did not reflect any change in pharmacopoeia specifications, it was decided that such a requirement would not increase product quality.

#### **A.2.1.8 Additives — “Spikes”**

All substances in the final concentrate should be specified on the label so that the user will be able to determine the exact composition of the product, because any component of the concentrate could diffuse into the bloodstream. Preservatives or indicators present in the concentrate should be indicated on the label.

#### **A.2.1.9 Containers**

Substances from the containers that contaminate the concentrate could diffuse into the patient during dialysis and could cause harm to the patient. Therefore, relatively non-reactive containers that would not affect strength or purity of the concentrate should be used.

#### **A.2.1.10 Endotoxin levels**

Control of endotoxin in the concentrate is necessary to prevent pyrogenic reactions in the patient during dialysis. An endotoxin limit was deemed to be appropriate for the water and dialysis fluid because evidence was presented that it was possible for pyrogens in the dialysis fluid to enter the patient. This limit was set in ISO 11663 because the final dialysis fluid has the greatest effect on the patient and the dialysis fluid is a combination of many factors such as the bacterial status of the concentrate, water, and the cleanliness of the dialysis machines and any appropriate distribution system.

#### **A.2.1.11 Bulk delivery concentrate**

The delivery of concentrate in bulk containers has become commonplace in some countries. This practice carries with it responsibilities for both the user and the manufacturer. When bulk deliveries of liquid concentrate are made, the product is dispensed in a large holding tank and the original labelling is lost. The maintenance of the holding tank is normally the responsibility of the user. The tank and its associated piping should be periodically cleaned and disinfected according to standard procedures. Care should be taken to ensure that the correct formula is placed into the correct holding tank.

Many different ways of accomplishing bulk delivery of concentrate are used. It was decided that the point of transfer of the concentrate solution is the point at which the responsibility for its labelling and integrity transfers to the user. Written procedures should define this exchange.

When liquid concentrate is delivered to the end user in bulk form, the user should take precautions to ensure the correct formulation is delivered to the correct storage tank. Written documentation of the correct deliveries and the point of transfer of responsibility should be made.

#### **A.2.1.12 Concentrate generator systems**

As technology progresses, some manufacturers produce concentrate preparation systems that prepare a solution for use by the dialysis machine. It was decided that such systems should be added to this International Standard. Those systems create concentrated slurry that is dynamically proportioned with the acid concentrate in the dialysis machine. Because the proportioning is dynamic, these canisters can be used with several different proportioning ratio acids (36,1X and 45X). Symbols on those labels were deemed to be unnecessary and possibly confusing because of their multiple use. Because the connectors could vary, it was considered necessary to state with which machines the canisters could be used.

Concentrate generator systems cannot be used with some proportioning systems, such as 36,83 systems where the sodium bicarbonate is combined with sodium chloride, since there is no way of knowing that the dissolution rates of sodium bicarbonate and sodium chloride will be the same.

It is the machine manufacturer's responsibility to design and manufacture the dialysis machine, including all necessary safety checks, to ensure that the system will deliver a safe and effective dialysis fluid to the dialyzer. Where necessary, filtering should be provided to prevent undissolved powder from entering the dialysis fluid stream.

## **A.2.2 Manufacturing equipment**

### **A.2.2.1 General**

Non-toxicity of construction materials for manufacturing equipment is of major importance to prevent contamination of the concentrate. Data are now available that demonstrate that materials once regarded as inert can be toxic in this application (e.g. copper leaches from copper conduits, especially in the presence of low pH, which can arise when a deionizer is exhausted). Other materials have been documented as being hazardous to the patient (e.g. copper, brass, zinc, galvanized material, and aluminium), and they should also be avoided. Some well-recognized non-toxic materials include certain stainless steel formulations, silicone rubber, borosilicate glass, polypropylene, polyvinylchloride, high-density polyethylene, and polytetrafluorethylene. The hazard in construction materials derives from long-term cumulative toxicity. A risk analysis according to ISO 14971 should be used to assess the suitability and biocompatibility of materials based on existing data. If that analysis suggests the need for additional testing, that testing should be based on the approaches outlined in the ISO 10993 series of standards. Users of this International Standard should be aware of the requirements of those standards.

### **A.2.2.2 Endotoxin levels**

The endotoxin concentration in bicarbonate concentrate is required to be such that, when it is mixed with water in the appropriate proportions, the resulting dialysis fluid meets the quality requirements of ISO 11663. Because endotoxin in the final dialysis fluid could be derived from both the concentrate and the water, the water used to dilute the concentrate for endotoxin testing should contain the maximum allowable level of endotoxin allowed under ISO 13959, to allow the final dialysis fluid to meet the requirements of ISO 11663 under worst case conditions. That implies that the water used to mix the powder for testing could contain 0.25 EU/ml of endotoxin. It is not practical to prepare water containing exactly that level of endotoxin, also, the assayed endotoxin concentration could change with the addition of ions from the concentrate (aggregate formation).

## **A.3 Labelling**

### **A.3.1 General**

Existing regulations establish general requirements for the labelling of all medical devices, including information, such as name and address of manufacturer and lot number. It was decided, however, that redundancy of these requirements was preferable to omission and the requirement that some of the same information already mandated by other regulations be included.

### **A.3.2 Labelling requirements for liquid concentrate**

This specialized information provides for the proper use of concentrate for hemodialysis supplied in an aqueous form. Requiring a precaution against excessive cold, as well as requiring a precaution against excessive heat was considered but it was pointed out that the stipulation for thoroughly mixing before use would protect against using concentrate that had been subjected to extreme cold. Furthermore, preventing inadvertent use of the wrong solution caused by similarities in containers was considered especially important.

There are no known instances of pyrogenic reactions caused by pyrogens in the acid part of the concentrate. There is also the possibility that acid concentrate will deactivate pyrogens because of its low pH.

### **A.3.3 Labelling requirements for powder concentrate**

Bicarbonate concentrate is known to support bacterial growth. Other data support the fact that if containers are not properly cleaned and disinfected, residual bicarbonate concentrate will support bacterial growth. Usually a time limit is

recommended by the manufacturer to minimize the occurrence of bacterial growth. This limit should be closely followed by the user.

The label should include instructions to avoid exposure to excessive temperature and to keep the container tightly sealed until use. When bicarbonate is used, a warning should be included noting that water containing an otherwise acceptable number of bacteria will be entering an environment which can support bacterial growth and, therefore, procedures should be taken to ensure microbiologic safety. The instructions may suggest practices such as improved water quality or short holding time, and they should recommend that containers be clean and recently disinfected. The bicarbonate mixing apparatus should also be disinfected at appropriate intervals, according to the manufacturer's instructions.



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## Water for hemodialysis and related therapies

Approved 21 July 2014 by  
**Association for the Advancement of Medical Instrumentation**

Approved 15 August 2014 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies minimum requirements for water to be used in hemodialysis and related therapies. Includes water to be used in the preparation of concentrates, dialysis fluids for hemodialysis, hemodiafiltration and hemofiltration, and for the reprocessing of hemodialyzers

**Keywords:** chemical, compliance, colony, endotoxin, fluid, microbiological, pyrogen

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-549-3

# Contents

Page

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| Glossary of equivalent standards.....                                                                   | iv  |
| Committee representation.....                                                                           | v   |
| US deviation to ISO 13959:2014.....                                                                     | vi  |
| Introduction .....                                                                                      | vii |
| 1 Scope.....                                                                                            | 1   |
| 2 Terms and definitions.....                                                                            | 1   |
| 3 Dialysis water requirements .....                                                                     | 5   |
| 3.1 Dialysis water verification and monitoring.....                                                     | 5   |
| 3.2 Microbiological requirements.....                                                                   | 5   |
| 3.3 Chemical contaminants.....                                                                          | 6   |
| 4 Tests for compliance with microbiological and chemical requirements .....                             | 7   |
| 4.1 Microbiology of dialysis water.....                                                                 | 7   |
| 4.2 Chemical contaminants test methods .....                                                            | 8   |
| Annex A (informative) Rationale for the development and provisions of this International Standard ..... | 11  |
| Bibliography .....                                                                                      | 15  |

## **Glossary of equivalent standards**

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

**[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)**

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### AAMI Renal Disease and Detoxification Committee

This American National Standard was developed by the AAMI Renal Disease and Detoxification Committee. Approval of the American National Standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the AAMI Renal Disease and Detoxification Committee had the following members:

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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NOTE—Participation by federal agency representatives in the development of this technical information report does not constitute endorsement by the federal government or any of its agencies.

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## US deviation to ISO 13959:2014

The International Organization for Standardization (ISO) published ISO 13959:2014, Water for hemodialysis and related therapies as a revision of ISO 13959:2009 on 2014-04-01. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, Cardiovascular implants and extracorporeal systems, to fill a need for minimum requirements for water used for hemodialysis and related therapies. The 2014 ISO revision editorially aligned ISO 13959 with the ISO dialysis fluid standards ISO 11663, ISO 13958, ISO 23500, and ISO 26722 which had been developed serially over several years.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

While considering the US adoption of ISO 13959:2014, the AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) approved a US deviation to the International Standard. ANSI/AAMI 13959:2014 deviates from ISO 13959:2014 in the following aspect:

The fourth paragraph of Subclause 4.1, Microbiology of dialysis water, which in ISO 13959:2014 reads:

“Culture media shall be tryptone glucose extract agar (TGEA), Reasoner’s 2A (R2A), or other media that can be demonstrated to provide equivalent results. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C and an incubation time of 168 h (7 d) are recommended. Other incubation times and temperatures may be used if it can be demonstrated that they provide equivalent results. No method will give a total microbial count.”

is replaced in ANSI/AAMI 13959:2014 by the following:

“Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner’s 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods. No method will give a total microbial count.”

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.



## Introduction

Assurance of adequate water quality is one of the most important aspects of ensuring a safe and effective delivery of hemodialysis, hemodiafiltration, or hemofiltration.

This International Standard contains minimum requirements, chemical and microbiological, for the water to be used for preparation of dialysis fluids, concentrates, and for the reprocessing of hemodialyzers and the necessary steps to ensure compliance with those requirements.

Hemodialysis and hemodiafiltration can expose the patient to more than 500 l of water per week across the semi-permeable membrane of the hemodialyzer or hemodiafilter. Healthy individuals seldom have a weekly oral intake above 12 l. This over 40-fold increase in exposure requires control and monitoring of water quality to avoid excesses of known or suspected harmful substances. Since knowledge of potential injury from trace elements and contaminants of microbiological origin over long periods is still growing and techniques for treating drinking water are continuously developed, this International Standard will evolve and be refined accordingly. The physiological effects attributable to the presence of organic contaminants in dialysis water are important areas for research. At the time this International Standard was published it was not possible to specify threshold values for organic contaminants permitted in water used for the preparation of dialysis fluids, concentrates, and reprocessing of hemodialyzers. The issue of organic contaminants will be reassessed on the next revision of this International Standard.

Within this International Standard, measurement techniques current at the time of publication have been cited. Other standard methods may be used, provided that such methods have been appropriately validated and compared to the cited methods.

The final dialysis fluid is produced from concentrates or salts manufactured, packaged, and labelled according to ISO 13958 mixed with water meeting the requirements of this International Standard. Operation of water treatment equipment and hemodialysis systems, including ongoing monitoring of the quality of water used to prepare dialysis fluids, and handling of concentrates and salts are the responsibility of the hemodialysis facility and are addressed in ISO 23500. Hemodialysis professionals make choices about the various applications (hemodialysis, hemodiafiltration, hemofiltration) and should understand the risks of each and the requirements for safety for fluids used for each.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this International Standard, the auxiliary verb

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard,
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.

This International Standard is directed towards manufacturers and providers of water treatment systems and also to hemodialysis facilities.



# Water for hemodialysis and related therapies

## 1 Scope

This International Standard specifies minimum requirements for water to be used in hemodialysis and related therapies.

This International Standard includes water to be used in the preparation of concentrates, dialysis fluids for hemodialysis, hemodiafiltration and hemofiltration, and for the reprocessing of hemodialyzers.

The operation of water treatment equipment and the final mixing of treated water with concentrates to produce dialysis fluid are excluded from this International Standard. Those operations are the sole responsibility of dialysis professionals. This International Standard does not apply to dialysis fluid regenerating systems.

## 2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

### 2.1

#### **action level**

concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

### 2.2

#### **chlorine, combined**

chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

### 2.3

#### **chlorine, free**

chlorine present in water as dissolved molecular chlorine ( $\text{Cl}_2$ ), hypochlorous acid ( $\text{HOCl}$ ), and hypochlorite ion ( $\text{OCl}^-$ )

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

### 2.4

#### **chlorine, total**

sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

## **2.5**

### **colony-forming unit**

#### **CFU**

measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

Note 1 to entry: Colonies can also form from groups of organisms when they occur in aggregates.

## **2.6**

### **device**

individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term “component” as used by the US Food and Drug Administration (see Reference [49]).

## **2.7**

### **dialysis fluid**

#### **dialysate**

#### **dialysis solution**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis

Note 1 to entry: The term “dialysis fluid” is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyzer by the dialysis fluid delivery system. Such phrases as “dialysate” or “dialysis solution” are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyzer is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyzer is referred to as “spent dialysis fluid.”

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as hemodiafiltration and hemofiltration.

## **2.8**

### **dialysis fluid delivery system**

device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid, circulates the dialysis fluid through the dialyzer, monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks, and prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system can be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

## **2.9**

### **dialysis water**

water that has been treated to meet the requirements of this International Standard and which is suitable for use in hemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialyzers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

## **2.10**

### **disinfection**

destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

## **2.11**

### **endotoxin**

major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose [see also pyrogen (2.20)].

## **2.12**

### **endotoxin units**

#### **EU**

units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to as a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

## **2.13**

### **feed water**

water supplied to a water treatment system or an individual component of a water treatment system

## **2.14**

### **hemodiafiltration**

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyzer (predilution hemodiafiltration), after the dialyzer (postdilution hemodiafiltration), or a combination of the two (mixed dilution hemodiafiltration).

## **2.15**

### **hemodialysis**

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

## **2.16**

### **hemofiltration**

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the hemofilter (predilution hemofiltration), after the hemofilter (postdilution hemofiltration), or a combination of the two (mixed dilution hemofiltration).

Note 2 to entry: There is no dialysis fluid stream in hemofiltration.

## **2.17**

### ***Limulus* amoebocyte lysate test**

#### **LAL test**

assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, can also be used to detect endotoxin.

## **2.18**

### **manufacturer**

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

## **2.19**

### **microbiological contamination**

contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

## **2.20**

### **pyrogen**

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also endotoxin (2.11)].

## **2.21**

### **source water**

water entering a dialysis facility from an external supplier, such as a municipal water supply

Note 1 to entry: Source water is sometimes referred to as feed water.

## **2.22**

### **sterile**

free from viable microorganisms

Note 1 to entry: “Sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of  $10^{-6}$ , i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

## **2.23**

### **substitution fluid**

fluid used in hemofiltration and hemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

## **2.24**

### **total dissolved solids**

#### **TDS**

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of  $\text{CaCO}_3$ , NaCl, KCl, or 442 equivalents, in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

## **2.25**

### **user**

physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

## **2.26**

### **water treatment system**

collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water meeting the requirements of this International Standard for hemodialysis applications and deliver it to the point of use

## **3 Dialysis water requirements**

### **3.1 Dialysis water verification and monitoring**

The quality of the dialysis water, as specified in 3.2 and 3.3, shall be verified upon installation of a water treatment system. Monitoring of the dialysis water quality shall be carried out thereafter.

### **3.2 Microbiological requirements**

Total viable microbial counts in dialysis water shall be less than 100 CFU/ml, or lower if required by national legislation or regulations. An action level shall be set based on knowledge of the microbial dynamics of the system. Typically, the action level will be 50 % of the maximum allowable level.

Endotoxin content in dialysis water shall be less than 0.25 EU/ml, or lower if required by national legislation or regulations. An action level shall be set, typically at 50 % of the maximum allowable level.

NOTE See A.1 for a history of these requirements.

### 3.3 Chemical contaminants

Dialysis water shall not contain chemicals at concentrations in excess of those listed in Tables 1 and 2, or as required by national legislation or regulations.

NOTE 1 See A.2 for an explanation of values supplied.

NOTE 2 The maximum allowable levels of contaminants listed in Tables 1 and 2 include the anticipated uncertainty associated with the analytical methodologies listed in Table 3.

Where the dialysis water is used for the reprocessing of hemodialyzers (cleaning, testing, and mixing of disinfectants), the user is cautioned that the dialysis water shall meet the requirements of this International Standard. The dialysis water should be measured at the input to the dialyzer reprocessing equipment.

**Table 1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water<sup>a</sup>**

| Contaminant                                                                                                                              | Maximum concentration<br>mg/l <sup>b</sup> |
|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| <b>Contaminants with documented toxicity in hemodialysis</b>                                                                             |                                            |
| Aluminium                                                                                                                                | 0.01                                       |
| Total chlorine                                                                                                                           | 0.1                                        |
| Copper                                                                                                                                   | 0.1                                        |
| Fluoride                                                                                                                                 | 0.2                                        |
| Lead                                                                                                                                     | 0.005                                      |
| Nitrate (as N)                                                                                                                           | 2                                          |
| Sulfate                                                                                                                                  | 100                                        |
| Zinc                                                                                                                                     | 0.1                                        |
| <b>Electrolytes normally included in dialysis fluid</b>                                                                                  |                                            |
| Calcium                                                                                                                                  | 2 (0.05 mmol/l)                            |
| Magnesium                                                                                                                                | 4 (0.15 mmol/l)                            |
| Potassium                                                                                                                                | 8 (0.2 mmol/l)                             |
| Sodium                                                                                                                                   | 70 (3.0 mmol/l)                            |
| <sup>a</sup> A dialysis facility's Medical Director has the ultimate responsibility for ensuring the quality of water used for dialysis. |                                            |
| <sup>b</sup> Unless otherwise noted.                                                                                                     |                                            |



**Table 2 — Maximum allowable levels of other trace elements in dialysis water**

| <b>Contaminant</b> | <b>Maximum concentration<br/>mg/l</b> |
|--------------------|---------------------------------------|
| Antimony           | 0.006                                 |
| Arsenic            | 0.005                                 |
| Barium             | 0.1                                   |
| Beryllium          | 0.0004                                |
| Cadmium            | 0.001                                 |
| Chromium           | 0.014                                 |
| Mercury            | 0.0002                                |
| Selenium           | 0.09                                  |
| Silver             | 0.005                                 |
| Thallium           | 0.002                                 |

## **4 Tests for compliance with microbiological and chemical requirements**

### **4.1 Microbiology of dialysis water**

Samples shall be collected where a dialysis machine connects to the water distribution loop, from a sample point in the distal segment of the loop or where such water enters a mixing tank.

Microbial analysis of water should be conducted as soon as possible after sample collection to avoid unpredictable changes in the microbial population. If samples cannot be assayed within 4 h of collection, follow the laboratory's instructions for sample storage and shipping. Samples intended for colony counts should not be frozen.

Total viable counts (standard plate counts) shall be obtained using conventional microbiological assay procedures (pour plate, spread plate, membrane filter techniques). Membrane filtration is the preferred method for this test. Other methods may be used, provided that such methods have been appropriately validated and compared to the cited methods. The calibrated loop technique is not accepted.

Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods. No method will give a total microbial count.

The presence of endotoxins shall be determined by the Limulus amoebocyte lysate (LAL) test. Other test methods may be used if it can be demonstrated that they provide equivalent results.

## 4.2 Chemical contaminants test methods

Compliance with the requirements listed in Table 1 can be shown by using chemical analysis methods referenced by the ISO, the American Public Health Association<sup>[3]</sup> or the US Environmental Protection Agency<sup>[47]</sup> methods referenced in applicable pharmacopoeia, or by any other equivalent validated analytical method.

Compliance with the requirements listed in Table 2 can be shown in one of three ways.

- Where such testing is available, the individual contaminants in Table 2 can be determined using chemical analysis methods referenced by ISO, the American Public Health Association<sup>[3]</sup> or the US Environmental Protection Agency,<sup>[47]</sup> or other equivalent analytical methods.
- Where testing for the individual trace elements listed in Table 2 is not available, and the source water can be demonstrated to meet the standards for potable water as defined by the WHO or local regulations, an analysis for total heavy metals can be used with a maximum allowable level of 0.1 mg/l.
- If neither of these options is available, compliance with the requirements of Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO (see Reference [53]) or local regulations and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity, or TDS. Samples shall be collected at the end of the water purification cascade or at the most distal point in each water distribution loop.

Table 3 lists suitable test methods for each contaminant, along with an appropriate reference.

**Table 3 — Analytical test methods for chemical contaminants**

| Contaminant | Analytical technique                                                                   | Reference, method number                                   |
|-------------|----------------------------------------------------------------------------------------|------------------------------------------------------------|
| Aluminium   | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)  | ISO 17294-2:2003<br><br>American Public Health Assn, #3113 |
| Antimony    | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (platform)        | ISO 17294-2:2003<br><br>US EPA, #200.9                     |
| Arsenic     | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (gaseous hydride) | ISO 17294-2:2003<br><br>American Public Health Assn, #3114 |
| Barium      | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)  | ISO 17294-2:2003<br><br>American Public Health Assn, #3113 |
| Beryllium   | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (platform)        | ISO 17294-2:2003<br><br>US EPA, #200.9                     |
| Cadmium     | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)  | ISO 17294-2:2003<br><br>American Public Health Assn, #3113 |

| Contaminant    | Analytical technique                                                                                                                                        | Reference, method number                                                                                                           |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Calcium        | Inductively coupled plasma mass spectrometry or<br>EDTA titrimetric method or<br>atomic absorption (direct aspiration) or<br>ion specific electrode         | ISO 17294-2:2003<br><br>American Public Health Assn, #3500-Ca D<br>American Public Health Assn, #3111B                             |
| Total chlorine | DPD ferrous titrimetric method or<br>DPD colourimetric method<br><br>TMK/MTK colourimetric method                                                           | American Public Health Assn, #4500-Cl F<br>American Public Health Assn, #4500-Cl G                                                 |
| Chromium       | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                                       | ISO 17294-2:2003<br><br>American Public Health Assn, #3113                                                                         |
| Copper         | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration) or<br>neocuproine method                                           | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Cu D                              |
| Fluoride       | Ion chromatography or<br>Ion selective electrode method or<br>sodium 2-(parasulfophenylazo)-1,8-dihydroxy-<br>3,6-naphthalenedisulfonate<br>(SPADNS) method | ISO 10304-1:2007<br><br>ISO 10359-1:1992<br><br>American Public Health Assn, #4500-F- C<br>American Public Health Assn, #4500-F- D |
| Lead           | Inductively coupled plasma mass spectrometry<br>Atomic absorption (electrothermal)                                                                          | ISO 17294-2:2003<br><br>American Public Health Assn, #3113                                                                         |
| Magnesium      | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration)<br><br>Ion chromatography                                          | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br><br>EPA 300.7:1986                                                   |
| Mercury        | Flameless cold vapour technique<br>(atomic absorption)                                                                                                      | American Public Health Assn, #3112                                                                                                 |
| Nitrate        | Ion chromatography or<br>Spectrophotometric method using sulfosalicylic acid<br>or Cadmium reduction method                                                 | ISO 10304-1:2007<br><br>ISO 7890-3:1988<br><br>American Public Health Assn, #4500-NO3 E                                            |

| <b>Contaminant</b> | <b>Analytical technique</b>                                                                                                                          | <b>Reference, method number</b>                                                                                                                        |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Potassium          | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration) or<br>flame photometric method or<br>ion specific electrode | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br><br>American Public Health Assn, #3500-K D<br><br>American Public Health Assn, #3500-K E |
| Selenium           | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (gaseous hydride) or<br>atomic absorption (electrothermal)                      | ISO 17294-2:2003<br><br>American Public Health Assn, #3114<br>American Public Health Assn, #3113                                                       |
| Silver             | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                                | ISO 17294-2:2003<br><br>American Public Health Assn, #3113                                                                                             |
| Sodium             | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration) or<br>flame photometric method or<br>ion specific electrode | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Na D                                                  |
| Sulfate            | Ion chromatography or<br>Turbidimetric method                                                                                                        | ISO 10304-1:2007<br><br>American Public Health Assn, #4500-SO42-E                                                                                      |
| Thallium           | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (platform)                                                                      | ISO 17294-2:2003<br><br>US EPA, 200.9                                                                                                                  |
| Total heavy metals | Colourimetric                                                                                                                                        | European Pharmacopoeia, 2.4.8<br>US Pharmacopoeia, < 231 >                                                                                             |
| Zinc               | Inductively coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration) or<br>dithizone method                                      | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br><br>American Public Health Assn, #3500-Zn D                                              |

## **Annex A**

### **(informative)**

## **Rationale for the development and provisions of this International Standard**

### **A.1 Microbiology of dialysis water**

**NOTE** The information in this clause is intended to give the reader a historical perspective of how the microbial limits were developed for this International Standard.

Originally, it was considered that the water used to prepare dialysis fluid need not be sterile. However, several studies had demonstrated that the attack rates of pyrogenic reactions were related directly to the number of bacteria in dialysis fluid.<sup>[14][18][19]</sup> These studies provided the rationale for setting the maximum level of bacteria in dialysis water at 200 CFU/ml in the original AAMI standard for water quality published in 1982. Later, the European community chose to use a slightly lower level of 100 CFU/ml as their bacterial limit for dialysis water and that value has been adopted in this International Standard. Because 7 d can elapse between sampling water for the determination of microbiological contamination and receiving results, and because bacterial proliferation can be rapid, action levels for microbial counts and endotoxin were introduced into this International Standard. These action levels allow the user to initiate corrective action before levels exceed the maximum levels established by this International Standard.

Several groups of investigators have shown convincingly that pyrogenic reactions are caused by lipopolysaccharides or endotoxins that are associated with gram-negative bacteria. Furthermore, gram-negative water bacteria have been shown to be capable of multiplying rapidly in dialysis water prepared by distillation, deionization, reverse osmosis, and softening. Dialysis fluid made with this water likewise provides a very good growth medium for these types of bacteria. Even at low levels of bacterial contamination, pyrogenic reactions have been reported when the source of endotoxin was exogenous to the dialysis system (i.e. present in the community water supply).<sup>[21]</sup> Consequently, it was thought prudent to impose an upper limit on the endotoxin content of dialysis water. A level of 2 EU/ml was chosen by AAMI in 2001 as the upper limit for endotoxin, since compliance with that level could be easily achieved with contemporary water treatment systems using reverse osmosis, ultrafiltration, or both. At the same time, the European community chose to use an upper limit of 0.25 EU/ml for endotoxin. During the revision for the second edition of this International Standard in 2008, the 0.25 EU/ml limit was included as the upper limit for endotoxin in dialysis water.

### **A.2 Chemical contaminants in dialysis water**

**NOTE** This historical review is provided to help the reader understand the considerations given to the chemical contamination of water used for dialysis treatments.

Contaminants identified as needing restrictions on the allowable level that can be present in water for dialysis are divided into three groups for the purposes of this International Standard. The first group includes chemicals shown to cause toxicity in dialysis patients. These chemicals include fluoride, aluminium, chloramine, sulfate, nitrate, copper, zinc, and lead. Chlorine is included here because of its potential toxicity.

Toxicity of fluoride in dialysis patients at the levels usually associated with fluoridated water, 1 mg/l, is questionable. In the absence of a consensus on fluoride's role in uremic bone disease, it was initially thought prudent to restrict the fluoride level of dialysis fluid.<sup>[40]</sup> Subsequently, illness in all of eight dialysis patients, with the death of one patient, was reported as a result of accidental overfluoridation of a municipal water supply.<sup>[12]</sup> Fluoride levels of up to 50 mg/l

were found in water used for dialysis that was treated only with a water softener. Probably, these illnesses would have been less severe, if not prevented, if the dialysis water had been treated with deionization or reverse osmosis. In one case, where deionizers were allowed to exhaust, 12 of 15 patients became acutely ill from fluoride intoxication.<sup>[5]</sup> Three of the patients died from ventricular fibrillation. Fluoride concentrations in the water used to prepare the dialysis fluid were as high as 22.5 mg/l.

The suggested maximum aluminium level has been specified to prevent accumulation of this toxic metal in the patient.<sup>[30][33]</sup> Aluminium is particularly likely to increase suddenly to high levels caused by changes in the method of water treatment to include aluminium-containing compounds. As with fluoride, water treatment would provide a measure of safety even if the aluminium levels should increase dramatically between chemical tests of the dialysis water.

The toxicity of chloramine is undisputed.<sup>[15]</sup> Although the role of free chlorine in oxidative blood damage is unclear, its high oxidation potential and ability to form chloramines suggests the avoidance of highly chlorinated water in preparation of dialysis fluid. Chlorine can be present in water as both free chlorine and chlorine in chemically combined forms. Chloramine is a form of chemically combined chlorine. Determining the level of chloramine typically involves measuring both total chlorine and free chlorine and assigning the difference in concentrations to chloramine. During the edition for the second revision of this International Standard in 2008, the working group chose to simplify this situation by setting a maximum allowable level for total chlorine at the same value used previously for chloramine (0.1 mg/l), thus permitting a single test to be used.

Sulfate at levels above 200 mg/l has been related to nausea, vomiting, and metabolic acidosis. The symptoms disappear when the level remains below 100 mg/l.<sup>[13]</sup> Nitrates are a marker for bacterial contamination and fertilizer runoff and have caused methemoglobinemia.<sup>[11]</sup> They should, therefore, be permitted only at very low levels. Both copper and zinc toxicity have been demonstrated when these substances are present in dialysis fluid at levels below those permitted by the US Environmental Protection Agency (EPA) standard.<sup>[22][36]</sup> Hence, a lower level has been chosen.

Dialysis fluid lead levels of 52 µg/l to 65 µg/l have been associated with abdominal pain and muscle weakness.<sup>[25]</sup> There is no evidence of lead toxicity when lead levels in water or dialysis fluid are below 5 µg/l.

The second group of substances addressed in 3.3 and Table 1 consists of physiological substances that can adversely affect the patient if present in the dialysis fluid in excessive amounts. Calcium, magnesium, potassium, and sodium are examples of these substances.

Of the physiological substances that can be harmful when present in excessive amounts, calcium has been reduced from the 10 mg/l originally selected to 2 mg/l on the basis of the critical role of calcium in bone disorders associated with renal disease. A level of 10 mg/l would have allowed a potential 20 % error in dialysis fluid calcium, whereas a level of 2 mg/l reduces that error risk to less than 5 %.

The third group of chemical contaminants addressed in 3.3 is based on the US EPA maximum allowable levels for drinking water.<sup>[48]</sup> When the AAMI standard ANSI/AAMI RD5<sup>[55]</sup> was initially developed, the US EPA Safe Drinking Water Act<sup>[48]</sup> included maximum allowable levels for barium, selenium, chromium, silver, cadmium, mercury, and arsenic. Selenium and chromium levels in dialysis water were set at the “no-transfer” level.<sup>[28]</sup> The “no-transfer” level was chosen even though it is above the US EPA limit for selenium and 28 % of the US EPA limit for chromium, because a restriction is not needed below the level at which there is no passage from the dialysis fluid to the blood. The International Standard specified the maximum allowable limits for the other contaminants in this group to be one tenth of the US EPA maximum allowable limits because the volume of water used for dialysis far exceeds that used for drinking water, because protein binding of these solutes could occur in the blood, and because there is reduced renal excretion of these substances. These reduced limits were selected using the following assumptions: 1) feed water entering dialysis systems typically meets the US EPA Safe Drinking Water Act; 2) typically, reverse osmosis treatment removes 90 % to 99 % of dissolved inorganic solids; and 3) reverse osmosis-treated water is a suitable standard for safety of water used in dialysis. These assumptions are based on the recommendations of Keshaviah et

al.<sup>[26]</sup> Although these assumptions can be questioned, it was reasoned that setting standards in this way would cause little or no economic impact, even though some feed water exceeds the US EPA maximum allowable levels. It should be noted that the level for arsenic, 0.05 mg/l in the Keshaviah report, is a typographical error. The correct value is 0.005 mg/l as given in Table 2 of this International Standard (E. Klein, personal communication). It should also be noted that the EPA maximum allowable level for arsenic in drinking water was reduced to 0.01 mg/l, effective from January 26th, 2006.

Several changes occurred in the *Safe Drinking Water Act* after these levels were established. Specifically, antimony, beryllium, free cyanide, and thallium were added to the list of contaminants covered by the Act and the maximum allowable level for cadmium had been decreased. For consistency, antimony, beryllium, and thallium were added to the list of contaminants in the United States. The maximum allowable levels of antimony and thallium were set at values above one-tenth of the US EPA maximum allowable level because of limitations in the sensitivity of commonly available analytical methods for these two contaminants. After considerable discussion, it was decided not to add free cyanide to the list of contaminants. There was concern that special requirements for sample collection and shipment, together with the need to pre-treat the sample before analysis to eliminate interfering substances, would impose a burden on dialysis facilities that could not be justified in the absence of specific toxicity data. It was also decided not to decrease the maximum allowable level of cadmium in the list of contaminants. This decision was based on the absence of toxicity data in dialysis patients treated with water that meets this International Standard and the minimum detection levels of currently used analytical methods.

Little, if any, data exist to indicate that hemodialysis patients are at particular risk from any of the third group of contaminants, which are included in the AAMI standard solely by virtue of their inclusion in the *Safe Drinking Water Act*. In the United States, there was discussion about eliminating the third group of contaminants from Table 2 and moving discussion of them to this Annex. This discussion was prompted by the ongoing addition of contaminants to the US *Safe Drinking Water Act*. As was the case with antimony, beryllium, and thallium, in general no data exist to indicate that these new contaminants are of particular concern in the setting of hemodialysis. On the other hand, adding new contaminants to Table 2 has the potential to increase the operating constraints to dialysis facilities for testing water samples for compliance. There was enough discomfort about removing the third category of contaminants from Table 2 that it was decided to leave the list of contaminants unchanged but to reorganize the table into three clear sections and not to add new contaminants to the table unless there was accompanying evidence of toxicity in the setting of hemodialysis. During the revision for the second edition of this International Standard in 2008, a decision was made to separate the third group of contaminants into a separate table. One reason for this change was to allow alternative approaches to monitoring these contaminants to facilitate use of this International Standard in areas lacking the appropriate analytical tools for measuring trace elements at the levels listed in Table 2. Three options are provided. The preferred option is to measure concentrations of the individual trace elements. If this option is not available, two other approaches may be used. The first, and preferred alternative, is to measure total heavy metals. The second, and least preferred alternative, is to use reverse osmosis with a demonstrated rejection of at least 90 %. Both these alternative approaches are based on the use of feed water meeting applicable potable water standards and it is the responsibility of the dialysis facility to ensure that its water supply routinely meets potable water standards. Finally, it should be evident from the discussion in this Annex that the maximum allowable levels for the contaminants listed in Tables 1 and 2 are not precisely determined values but represent reasonable estimates based on sparse clinical data. As a result, any uncertainty in the analytical methods listed in Table 3 is likely to be small compared to the uncertainty involved in establishing the maximum allowable level and, for that reason, analytical uncertainty is considered to be included in the values listed in Tables 1 and 2.

Tables 1 and 2 of this International Standard should not be taken as a definitive list of harmful substances but as a partial listing of those that might reasonably be expected to be present and have clinical implications. Iron is not included because it does not enter the patient's blood in sufficient quantities to cause toxicity. Iron can, however, cause fouling of water purification devices or dialysis fluid supply systems. While no specific limit has been set, water treatment equipment suppliers are encouraged to consider the iron content of the feed water when recommending suitable equipment. A concern was raised regarding the injection of formulated phosphates (known as polyphosphates) primarily to bind iron and manganese to avoid the staining of fixtures and clothing. The concern was raised that this practice could cause significant problems in water purification. Some municipal water suppliers were

considering the use of chlorine dioxide as a disinfectant for potable water supplies. Chlorine dioxide breaks down in water to yield chlorite, chlorate, and chloride ions. Little information could be found about the potential for chlorine dioxide and its daughter products to be toxic to hemodialysis patients. A limited study of 17 patients unknowingly treated with dialysis water prepared by carbon and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects.<sup>[4]</sup> In that study, the dialysis water used to prepare dialysis fluid contained 0.02 mg/l to 0.08 mg/l of chlorite ions and no detectable chlorate ions. However, the patient population was small, and potentially important hematological parameters were not measured. Further, there were only sparse data included on the removal of chlorine dioxide, chlorite ions, and chlorate ions by carbon and reverse osmosis, and it was not clear that sufficiently sensitive methods were available for their analysis in a dialysis facility. Therefore, there was no basis for setting maximum allowable levels of chlorine dioxide, chlorite ions, or chlorate ions in water to be used for dialysis applications, or for making recommendations on methods for their removal at that time. However, in specifying water purification systems, manufacturers of such systems should be aware of the possibility that municipal water suppliers may add chlorine dioxide to the water.

Limits could not be determined for toxic organic substances or for radioactive materials.<sup>[26]</sup> However, the US EPA drinking water standard<sup>[48]</sup> lists maximum contaminant levels (MCL) for more than 50 toxic organic substances. Following the rationale used in establishing levels for other potentially toxic contaminants that have not been shown to be harmful to dialysis patients (see previous paragraph), it is reasonable that these levels should be reduced tenfold if they are monitored. These data are provided for information purposes only, because these substances are only representative of a vast number of contaminants that occur in tap water, all of whose toxic effects are largely unknown.<sup>[26]</sup> In agreement with the Keshaviah report, it is thought that systems including reverse osmosis and carbon filtration would adequately remove most organics. In support of this position, reverse osmosis has been demonstrated to remove 92 % to 98 % of 14 different pesticides during water treatment for dialysis.<sup>[7]</sup>



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# Water treatment equipment for hemodialysis and related therapies

Approved 21 July 2014 by  
Association for the Advancement of Medical Instrumentation

Approved 8 August 2014 by  
American National Standards Institute, Inc.

**Abstract:** Covers devices used to treat water intended for use in the delivery of hemodialysis and related therapies, including water used for: (1) the preparation of concentrates from powder or other highly concentrated media at a dialysis facility; (2) the preparation of dialysis fluid, including dialysis fluid that can be used for the preparation of substitution fluid; (3) the reprocessing of dialyzers for multiple uses. Included within the scope are all devices, piping and fittings between the point at which potable water is delivered to the water treatment system, and the point of use of the dialysis water. Addressed to the manufacturer and/or supplier of water treatment systems and/or devices used for the express purpose of providing water for hemodialysis or related therapies.

**Keywords:** action, acid, biofilm, chlorine, compliance, endotoxin, labeling, pyrogen

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

1-57020-551-5

# Contents

Page

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| Glossary of equivalent standards.....                                                                   | iv  |
| Committee representation.....                                                                           | v   |
| US deviation to ISO 26722:2014.....                                                                     | vi  |
| Introduction .....                                                                                      | vii |
| 1 Scope.....                                                                                            | 1   |
| 2 Normative references .....                                                                            | 1   |
| 3 Terms and definitions.....                                                                            | 2   |
| 4 Requirements .....                                                                                    | 7   |
| 4.1 Dialysis water quality requirements.....                                                            | 7   |
| 4.2 Water treatment equipment requirements.....                                                         | 8   |
| 5 Tests .....                                                                                           | 14  |
| 5.1 Compliance with dialysis water quality requirements.....                                            | 14  |
| 5.2 Compliance with water treatment equipment requirements .....                                        | 15  |
| 6 Labelling .....                                                                                       | 18  |
| 6.1 General .....                                                                                       | 18  |
| 6.2 Device markings .....                                                                               | 18  |
| 6.3 Product literature.....                                                                             | 19  |
| Annex A (informative) Rationale for the development and provisions of this International Standard ..... | 21  |
| Annex B (informative) Reference tables from ISO 13959 .....                                             | 31  |
| Bibliography .....                                                                                      | 35  |

## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

**[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)**



## Committee representation

### Association for the Advancement of Medical Instrumentation

#### AAMI Renal Disease and Detoxification Committee

This American National Standard was developed by the AAMI Renal Disease and Detoxification Committee. Approval of the American National Standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the AAMI Renal Disease and Detoxification Committee had the following members:

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NOTE—Participation by federal agency representatives in the development of this American National Standard does not constitute endorsement by the federal government or any of its agencies.

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## US deviation to ISO 26722:2014

The International Organization for Standardization (ISO) published ISO 26722:2014, *Water treatment equipment for hemodialysis and related therapies* as a revision of ISO 26722:2009 on 2014-04-01. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for minimum requirements for devices used to treat water intended for use in the delivery of hemodialysis and related therapies. The 2014 ISO revision editorially aligned ISO 26722 with the ISO dialysis fluid standards ISO 11663, ISO 13958, ISO 13959, and ISO 23500 which had been developed serially over several years.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the guidance provided in this document.

While considering the US adoption of ISO 26722:2014, the AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) approved a US deviation to the International Standard. ANSI/AAMI 26722:2014 deviates from ISO 26722:2014 in the following aspect:

The third paragraph of Subclause 5.1.2, Microbiology of dialysis water, which in ISO 26722:2014 reads:

“Total viable counts (standard plate counts) shall be obtained using the membrane filter technique, spread plates, or pour plates. The calibrated loop technique shall not be used. Culture media shall be tryptone glucose extract agar (TGEA), Reasoner’s 2A (R2A) or equivalent. Blood agar and chocolate agar shall not be used. Incubation is at 17 °C to 23 °C and colonies shall be counted after 168 h (7 d) of incubation. Alternative incubation conditions and colony counting times can be used if validated and proven to be equivalent or better than the stated conditions. Endotoxin concentrations shall be determined by the LAL assay or kinetic method validated to yield results that are equivalent to LAL.”

is replaced in ANSI/AAMI 26722:2014 by the following:

“Total viable counts (standard plate counts) shall be obtained using the membrane filter technique, spread plates, or pour plates. The calibrated loop technique shall not be used.

Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner’s 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods. Endotoxin concentrations shall be determined by the LAL assay or kinetic method validated to yield results that are equivalent to LAL.”

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

## Introduction

This International Standard reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians, and dialysis patients, in consultation with device manufacturers and government representatives, to develop an International Standard for performance levels that could be reasonably achieved at the time of publication. The term “consensus,” as applied to the development of voluntary medical device International Standards, does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests should be merged.

The provisions of this International Standard apply to individual water treatment devices and to water treatment systems assembled from one or more of these devices. In the first instance, this International Standard is directed at the individual or company that specifies the complete water treatment system and, second, at the supplier who assembles and installs the system. Since systems can be assembled from a number of individual water treatment devices, the provisions of this International Standard are also directed at the manufacturers of these devices, provided that the manufacturer indicates that the device is intended for use in hemodialysis applications. This International Standard is written principally to address water treatment systems for dialysis facilities treating multiple patients. However, many of its provisions equally apply to water treatment systems used in applications where a single patient is treated, such as in a home dialysis or acute hospital dialysis setting. Specifically, requirements for the chemical and microbiological quality of water are considered to apply in all settings, regardless of whether a single patient or many patients are being treated.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this International Standard, the auxiliary verb

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard,
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.

The requirements established by this International Standard should help protect hemodialysis patients from adverse effects arising from known chemical and microbial contaminants found in water supplies. However, proper dialysis and patient safety is ultimately dependent on the quality of the dialysis fluid. Since the manufacturer or supplier of water treatment equipment does not have control over the dialysis fluid, any reference to dialysis fluid in this International Standard is for clarification only and not a requirement of the manufacturer. The responsibility for assuring that the dialysis fluid is not contaminated, mismatched, or otherwise damaging to the patient rests with the clinical professionals caring for the patient under the supervision of the medical director. Recommendations on the preparation and handling of water and dialysis fluid in a dialysis facility are provided in ISO 23500.



# Water treatment equipment for hemodialysis applications and related therapies

## 1 Scope

### 1.1 General

This International Standard is addressed to the manufacturer and/or supplier of water treatment systems and/or devices used for the express purpose of providing water for hemodialysis or related therapies.

### 1.2 Inclusions

This International Standard covers devices used to treat water intended for use in the delivery of hemodialysis and related therapies, including water used for: (1) the preparation of concentrates from powder or other highly concentrated media at a dialysis facility; (2) the preparation of dialysis fluid, including dialysis fluid that can be used for the preparation of substitution fluid; (3) the reprocessing of dialyzers for multiple uses.

Included within the scope of this International Standard are all devices, piping and fittings between the point at which potable water is delivered to the water treatment system, and the point of use of the dialysis water. Examples of devices included within the scope of this International Standard are water purification devices, online water quality monitors (such as conductivity monitors), and piping systems for the distribution of dialysis water.

### 1.3 Exclusions

Excluded from the scope of this International Standard are dialysis fluid supply systems that proportion water and concentrates to produce dialysis fluid, sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid, dialysis concentrates, hemodiafiltration systems, hemofiltration systems, systems that process dialyzers for multiple uses, and peritoneal dialysis systems. Some of these devices, such as dialysis fluid delivery systems and concentrates, are addressed in other International Standards. Also excluded from the scope of this International Standard are requirements for the ongoing monitoring of the purity of water used for dialysis fluid, concentrate preparation, or dialyzer reprocessing.

## 2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13959:2014, *Water for hemodialysis and related therapies*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

IEC 60601-1-8, *Medical electrical equipment – Part 1-8: General requirements for basic safety and essential performance – Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*

### 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

#### 3.1

##### **acid concentrate**

##### **A-concentrate**

acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term “acid” refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate can contain glucose.

Note 3 to entry: Acid concentrate can be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

#### 3.2

##### **action level**

concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

#### 3.3

##### **bicarbonate concentrate**

##### **B-concentrate**

concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate can be in the form of a liquid or a dry powder.

Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

#### 3.4

##### **biofilm**

microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

Note 1 to entry: The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

#### 3.5

##### **chlorine, combined**

chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

### **3.6**

#### **chlorine, free**

chlorine present in water as dissolved molecular chlorine ( $\text{Cl}_2$ ), hypochlorous acid ( $\text{HOCl}$ ), and hypochlorite ion ( $\text{OCl}^-$ )

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

### **3.7**

#### **chlorine, total**

sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

### **3.8**

#### **concentrate generator**

system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyzer.

### **3.9**

#### **device**

individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term “component” as used by the US. Food and Drug Administration.<sup>[26]</sup>

### **3.10**

#### **dialysis fluid**

#### **dialysate**

#### **dialysis solution**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis

Note 1 to entry: The term “dialysis fluid” is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyzer by the dialysis fluid delivery system. Such phrases as “dialysate” or “dialysis solution” are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyzer is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyzer is referred to as “spent dialysis fluid.”

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies such as hemodiafiltration and hemofiltration.

### 3.11

#### **dialysis fluid delivery system**

device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid, circulates the dialysis fluid through the dialyzer, monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow, and blood leaks, and prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid supply system might be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

### 3.12

#### **dialysis water**

water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in hemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialyzers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

### 3.13

#### **disinfection**

destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

### 3.14

#### **empty bed contact time**

##### **EBCT**

time taken by a fluid to pass through an empty volume equal to the volume of a particle bed

Note 1 to entry: EBCT (min) is calculated using the following equation:

$$\text{EBCT} = V/Q$$

where

$V$  is the volume of the particle bed in cubic metres ( $\text{m}^3$ );

$Q$  is the flow rate of water through the bed in cubic metres per minute ( $\text{m}^3/\text{min}$ ).

Note 2 to entry: EBCT is used as an indirect measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of particles.

### 3.15

#### **endotoxin**

major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. [See also **pyrogen** (3.26).]



### **3.16**

#### **endotoxin-retentive filter**

##### **ETRF**

membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

Note 1 to entry: The performance of an endotoxin-retentive filter is usually expressed as the logarithmic reduction value (LRV), defined as  $\log_{10}(\text{inlet concentration})/(\text{outlet concentration})$ .

Note 2 to entry: Endotoxin-retentive filters can be configured in a cross-flow or dead-end mode. Some endotoxin-retentive filters also remove endotoxins by adsorption.

### **3.17**

#### **feed water**

water supplied to a water treatment system or an individual component of a water treatment system

### **3.18**

#### **germicide**

agent that kills microorganisms

### **3.19**

#### **hemodiafiltration**

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing replacement solution into the blood either before the dialyzer (predilution hemodiafiltration), after the dialyzer (postdilution hemodiafiltration), or a combination of the two (mixed dilution hemodiafiltration).

### **3.20**

#### **hemodialysis**

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

### **3.21**

#### **hemofiltration**

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the hemofilter (predilution hemofiltration), after the hemofilter (postdilution hemofiltration), or a combination of the two (mixed dilution hemofiltration).

Note 2 to entry: There is no dialysis fluid stream in hemofiltration.

### **3.22**

#### **manufacturer**

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development and initial distributions of foreign

entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

### **3.23**

#### **microfilter**

filter designed to remove particles down to 0.1 µm in size

Note 1 to entry: Microfilters have an absolute size cut-off and are available in both dead-end and cross-flow configurations. Some microfilters can reduce the concentration of endotoxins by adsorption.

### **3.24**

#### **product water**

water produced by a water treatment system or by an individual device thereof

### **3.25**

#### **proportioning system**

apparatus that proportions dialysis water and hemodialysis concentrate to prepare dialysis fluid

### **3.26**

#### **pyrogen**

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also **endotoxin** (3.15)].

### **3.27**

#### **sodium hypochlorite**

chemical used for disinfection of hemodialysis systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and javel. These solutions are used for disinfection at concentrations recommended by equipment manufacturers.

### **3.28**

#### **source water**

water entering a dialysis facility from an external supplier, i.e. water from a municipal water supply or equivalent

Note 1 to entry: Source water is sometimes referred to as feed water and is assumed to be potable water

### **3.29**

#### **storage tank**

tank at the user's facility for storage of source water, dialysis water, or concentrate from bulk deliveries or for concentrate prepared in bulk at the user's facility from powder and dialysis water

### **3.30**

#### **substitution fluid**

fluid used in hemofiltration and hemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

### **3.31**

#### **total dissolved solids**

##### **TDS**

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of  $\text{CaCO}_3$ , NaCl, KCl, or 442 equivalents in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

### **3.32**

#### **user**

physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

### **3.33**

#### **water treatment system**

collection of water treatment devices and associated piping, pumps, valves, gauges, etc. that together produce water meeting the requirements of ISO 13959 for hemodialysis applications and deliver it to the point of use

## **4 Requirements**

### **4.1 Dialysis water quality requirements**

#### **4.1.1 General**

The requirements contained in this International Standard apply to the dialysis water as it enters the equipment used to prepare concentrates from powder or other concentrated media at a dialysis facility, to prepare dialysis fluid, or to reprocess dialyzers for multiple uses. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively, the individual devices shall produce dialysis water that, at a minimum, meets the requirements of the clause.

#### **4.1.2 Microbiology of dialysis water**

Dialysis water used to prepare dialysis fluid or concentrates from powder at a dialysis facility, or to reprocess dialyzers for multiple uses, shall contain a total viable microbial count and endotoxin levels as specified in ISO 13959.

The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system meets the requirements of this International Standard, including those related to action levels at the time of installation.

**NOTE 1** If the manufacturer or supplier does not install the water storage and distribution system, then the responsibility of the manufacturer or supplier is limited to demonstrating that the water treatment system, excluding the water storage and distribution system, meets the requirements of this International Standard. If individual devices of the water treatment system are provided by different manufacturers or suppliers, the person or organization specifying the devices is responsible for demonstrating that the complete system meets the requirements of this International Standard at the time of installation.

For disposable water treatment systems validated by the manufacturer to produce dialysis water meeting the quality requirements of this International Standard for a specified time, monitoring of the incoming feed water is required to ensure that the input to the treatment system is in the range for which the system has been validated. The manufacturer's recommendations for monitoring the final dialysis water can be followed when the system is operated according to the manufacturer's instructions. Alternatively, the quality of the dialysis water can be monitored as outlined for non-validated systems.

NOTE 2 Following installation of a water treatment, storage, and distribution system, the user is responsible for continued monitoring of the water bacteriology of the system and for complying with the requirements of this International Standard, including those requirements related to action levels.

#### **4.1.3 Maximum level of chemical contaminants**

Dialysis water used to prepare dialysis fluid or concentrates from powder at a dialysis facility, or to reprocess dialyzers for multiple uses, shall not contain chemical contaminants at concentrations in excess of those in Tables 1 and 2 of ISO 13959 (reproduced as Tables B.1 and B.2). The manufacturer or supplier of a complete water treatment system shall recommend a system capable of meeting the requirements of this clause based on the analysis of the feed water. The system design should reflect possible seasonal variations in feed water quality. The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of this International Standard at the time of installation.

NOTE 1 If the manufacturer or supplier does not install the water storage and distribution system, then the responsibility of the manufacturer or supplier is limited to demonstrating that the water treatment system, excluding the water storage and distribution system, meets the requirements of this International Standard. If individual devices of the water treatment system are provided by different manufacturers or suppliers, the person or organization specifying the devices is responsible for demonstrating that the complete system meets the requirements of this International Standard at the time of installation.

For disposable water treatment and distribution systems that have been validated to produce dialysis water meeting the quality requirements of this International Standard for a specified time, monitoring of the incoming potable water is required to ensure that the input to the treatment system is in the range for which the system has been validated. The manufacturer's recommendation for monitoring the final dialysis water can be followed when the system is operated according to the manufacturer's instructions. Alternatively, the quality of the dialysis water can be monitored as outlined for non-validated systems.

NOTE 2 Following the installation of a water treatment, storage, and distribution system, the user is responsible for continued monitoring of the levels of chemical contaminants in the water and for complying with the requirements of this International Standard.

### **4.2 Water treatment equipment requirements**

#### **4.2.1 General**

##### **4.2.1.1 Water treatment system**

The supplier of the feed water or the supplier of the water treatment system or a laboratory specified by the user shall perform chemical analyses on feed water to determine the compatibility of the system with the feed water and the suitability of the system for providing dialysis water meeting the requirements of 4.1.3. The result of the chemical analyses shall be available to the user in charge of dialysis. In the case of an individual device, the person incorporating the device into the water treatment system is responsible for ensuring that incorporation of the device does not compromise the ability of the overall system to deliver dialysis water capable of meeting the requirements of 4.1.2 and 4.1.3.

The water treatment and distribution system should include appropriate pressure gauges, flow meters, sample ports, and other ancillary equipment necessary to allow monitoring of the performance of individual system devices and the system as a whole.

Valves can be included in the water treatment system to allow individual devices to be bypassed when there is device failure or to facilitate replacement of a device. If it is possible to bypass a device of the water treatment system, then the manufacturer or installer of that component shall inform the user of the risks associated with bypassing that

device and the need for clearly defining the responsibility for operating the bypass. Where such valves are installed, however, a means should be included to minimize the likelihood that the device will be inadvertently bypassed during normal operation of the system.

Operating controls shall be positioned so as to minimize inadvertent resetting.

Electrical circuits shall be separate from hydraulic circuits and adequately protected from fluid leaks.

#### **4.2.1.2 Materials compatibility**

Materials that contact dialysis water (including materials used in piping, storage, and distribution systems) shall not interact chemically or physically with that water so as to adversely affect its purity or quality. Water-contacting surfaces shall be fabricated from non-reactive materials (e.g. plastics) or appropriate stainless steel. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, galvanized material, or aluminium, is specifically prohibited at any point beyond the water treatment device used to remove contaminating metal ions, most commonly a reverse osmosis system or a deionizer. The materials of any water treatment devices (including piping, storage, and distribution systems) shall be compatible with the means used to disinfect those devices. Chemicals infused into the water in the pre-treatment section, such as chlorine, acid, flocculants, and complexing agents, shall be adequately removed from dialysis water before they reach any point of use. Monitors or specific test procedures to verify removal of additives shall be provided.

#### **4.2.1.3 Regenerated or reconstituted devices**

All devices that are regenerated or reconstituted at a site remote from the dialysis facility, such as deionizers, shall be disinfected at the time of regeneration or reconstitution so that contaminated water is not reintroduced into the system after regeneration or reconstitution. Separate processes shall be used to ensure no intermixing of devices or their component parts between devices returned from medical or potable water users and devices returned from non-potable water users.

#### **4.2.1.4 Disinfection protection**

When the manufacturer recommends chemical disinfectants [see 6.3 item y)], means shall be provided to restore the equipment and the system in which it is installed, to a safe condition relative to residual disinfectant prior to the dialysis water being used for dialysis applications. When recommending chemical disinfectants, the manufacturer shall also recommend methods for testing for residual levels of the disinfectants. When disinfection is accomplished automatically by chemical disinfectant, including ozone, or by high temperature procedures, activation of the disinfection system shall result in activation of a warning system and measures to prevent patient exposure to an unsafe condition.

#### **4.2.2 Backflow prevention device**

All water treatment systems should be preceded by a backflow prevention device to isolate the system from the potable water supply according to local plumbing codes.

#### **4.2.3 Tempering valves**

Tempering valves, if used, shall be sized to accommodate the anticipated range of flow rates of hot and cold water. They shall be fitted with a mechanism to prevent backflow of water into the hot and cold water lines and with a means to monitor the outlet water temperature.

#### **4.2.4 Sediment filters**

Sediment filters should have an opaque housing or other means to inhibit proliferation of algae. Filters should be fitted with pressure gauges on the inlet and outlet water lines to monitor the pressure drop,  $\Delta P$ , across the filter.

NOTE Sediment filters are also known as multimedia or sand filters.

#### 4.2.5 Cartridge filters

Cartridge filters should have an opaque housing or other means to inhibit proliferation of algae. Filters should be fitted with pressure gauges on the inlet and outlet water lines to monitor the pressure drop,  $\Delta P$ , across the filter.

#### 4.2.6 Softeners

Water softeners should be fitted with a mechanism to prevent water containing the high concentrations of sodium chloride used during regeneration from entering the product water line during regeneration. Automatic regeneration can be performed on a volume schedule or on a time schedule. For softeners that are regenerated automatically on a time schedule, the face of the timers used to control the regeneration cycle should be visible to the user. Operating controls shall be positioned so as to minimize inadvertent resetting.

#### 4.2.7 Anion exchange resin tank

Anion exchange resin, sometimes referred to as an organic scavenger, can remove organic matter and other contaminants from the source water and protect carbon media from fouling, which can shorten its effective life for chlorine/chloramine removal. If an organic scavenger is installed to protect the carbon media, the scavenger should be installed upstream of the carbon beds. Anion exchange resins can also be used to remove contaminants that might otherwise foul the reverse osmosis membrane.

#### 4.2.8 Carbon media

Carbon is used to remove small organic compounds, chlorine, and chloramine. When carbon is used for the removal of chloramine, it shall be adapted specifically to the maximum anticipated water flow rate of the system and the level of chloramine in the feed water.

Where chloramine is used to disinfect the potable water supply at a level of 1 mg/l or more, two carbon beds shall be installed in series. Each of the carbon beds shall have an EBCT of at least 5 min at the maximum product water flow rate (a total EBCT of at least 10 min). To avoid overly large beds, carbon beds are sometimes arranged as parallel sets, each set consisting of two beds in series. The beds are equally sized and water flows in parallel through each set. In this situation, each bed shall have a minimum EBCT of 5 min at the maximum flow rate through the bed. When parallel sets of beds are used, the piping should be designed to minimize differences in the resistance to flow from inlet and outlet between each parallel set of beds in order to ensure that water flows equally through all beds. A means shall be provided to sample the product water from the first bed in each series-connected pair and a sample port should be installed following the carbon beds for use in the event of total chlorine breaking through the first bed in a series-connected pair.

NOTE Carbon systems used to prepare water for portable dialysis systems are exempt from the requirement for the second carbon and a 10 min EBCT, provided there is a redundant means of chloramine removal and that a total chlorine concentration of less than 0.1 mg/l is verified in a sample collected after the primary device before each treatment. Possible alternatives include a granular activated carbon bed followed by a dense carbon block and two carbon block filters in series.

In situations where chloramine is not used to disinfect the water, and the ammonium level in the water is low, one carbon bed or a carbon cartridge filter with a shorter EBCT might be sufficient.

Exhausted carbon media shall be discarded and replaced with new media according to a replacement schedule determined by regular monitoring. For example, with two beds, when testing between the beds shows that the first bed is exhausted, the second bed should be moved into the first position, the second bed replaced with a new bed, and the exhausted bed discarded.

Granular activated carbon with an iodine number greater than 900 is considered optimal for chlorine/chloramine removal. However, some source waters, such as those with a high organic content could require alternate types of carbon that are more resistant to organic fouling. These types of carbon can have iodine numbers less than 900. When other forms of carbon or granular activated carbon with an iodine number of less than 900 are used, the manufacturer shall provide performance data to demonstrate that each adsorption bed has the capacity to reduce the total chlorine concentration in the feed water to less than 0.1 mg/l when operating at the maximum anticipated flowrate for the maximum time interval between scheduled testing of the product water for total chlorine. Regenerated carbon shall not be used.

Automatically backwashed carbon beds should be fitted with a mechanism to prevent water containing chlorine or chloramine from entering the feed water line of downstream purification devices, such as reverse osmosis, while the carbon beds are being backwashed. For carbon beds that are backwashed automatically on a time schedule, the face of the timers used to control the backwash cycle should be visible to the user and the timer should be set so that backwashing occurs when dialysis is not being performed.

If carbon beds fitted with an online monitor for measuring total chlorine in the product water are used, there should be a means of preventing patient exposure to unsafe product water, such as the diversion of the product water to drain or a system shutdown, should the total chlorine level in the product water exceed 0.1 mg/l. Accompanying visual and/or audible alarms shall meet the relevant requirements of IEC 60601-1-8 for low-priority alarms if product water is diverted to drain or the system is shut down; otherwise, the alarms shall meet the relevant requirements of IEC 60601-1-8 for high-priority alarms.

In addition, the sound emitted by the audible alarm shall be at least 65 decibels ("A" scale) at 3 m and it shall not be possible to silence the alarm for more than 180 s. Alarms shall be situated so that they ensure a prompt response by personnel in the patient care area.

If the online monitor is placed between two carbon filters in series, a low-priority alarm can be accepted as long as manual monitoring is performed after the last filter or bed in the event of an alarm.

#### **4.2.9 Chemical injection systems**

Sodium bisulphite injected into the source water can be an effective means of reducing chlorine and chloramine concentrations. Ascorbic acid has also been used for this purpose. In addition, reducing the pH of alkaline feed water by the injection of mineral acids can enhance the efficiency of granular activated carbon. Chemical injection systems shall include a means of regulating the metering pump to control the addition of chemical. This control system shall be designed to tightly control the addition of chemical. The control system shall ensure that chemical is added only when water is flowing through the pre-treatment cascade and that it is added in fixed proportion to the water flow or based on some continuously monitored parameter, such as pH, using an automated control system. If an automated control system is used to inject the chemical, there shall be an independent monitor of the controlling parameter. Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention.

#### **4.2.10 Reverse osmosis**

When used to prepare water for hemodialysis applications, either alone or as the last stage in a purification cascade, reverse osmosis systems shall be shown to be capable, at installation, of meeting the requirements of 4.1, when tested with the typical feed water of the user, in accordance with the methods described in 5.1.

Reverse osmosis devices shall be equipped with online monitors that allow determination of product water conductivity and should be equipped with monitors that determine rejection rate based on conductivity. Monitors that display resistivity or total dissolved solids (TDS) could be used in place of conductivity monitors. Resistivity, conductivity, or TDS monitors shall be temperature-compensated, generally to 25 °C. Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention.

When a reverse osmosis system is the last chemical purification process in the water treatment system, it should include a means of preventing patient exposure to unsafe product water, such as diversion of the product water to drain or system shutdown, in the event that the product water conductivity exceeds a preset limit. Accompanying alarms shall meet the relevant requirements of IEC 60601-1-8 for low-priority alarms. If the reverse osmosis system does not have a means of preventing unsafe product water from entering the dialysis machines, the product water conductivity monitor shall activate audible and/or visual alarms when the product water conductivity exceeds the preset limit. Those alarms shall meet the relevant requirements of IEC 60601-1-8 for medium priority alarms. In addition, for medium priority alarms, the sound emitted by the audible alarm shall be at least 65 decibels ("A" scale) at 3 m and it shall not be possible to silence the alarm for more than 180 s. Alarms shall be situated so that they ensure a prompt response by personnel in the patient care area.

#### **4.2.11 Deionization**

Deionization systems, when used to prepare water for hemodialysis applications, shall be monitored continuously with monitors generally temperature-compensated to 25 °C, to produce water of 1 MΩ·cm or greater specific resistivity (or conductivity of 1 μS/cm (0.1 mS/m) or less). Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention. An audible and visual alarm shall be activated when the product water resistivity falls below 1 MΩ·cm and the product water stream shall be prevented from reaching any point of use, by being diverted to a drain. Such alarms shall meet the relevant requirements of IEC 60601-1-8 for low-priority alarms if the product water is diverted to drain, or if the system is shutdown; otherwise, the alarms shall meet the relevant requirements of IEC 60601-1-8 for high-priority alarms. In addition, the sound emitted by the audible alarm shall be at least 65 decibels ("A" scale) at 3 m and shall be audible in the patient care area. It shall not be possible to silence these alarms for more than 180 s. Feed water for deionization systems shall be pretreated with activated carbon, or a comparable alternative, to prevent nitrosamine formation. If a deionization system is the last process in a water treatment system, it shall be followed by an endotoxin-retentive filter or other bacteria- and endotoxin-reducing device.

**NOTE** The requirements given above for deionization might not apply to electrodeionization (EDI) technology, which can be used as an alternative to deionization following reverse osmosis in hemodialysis applications.

#### **4.2.12 Endotoxin-retentive filters**

When an endotoxin-retentive filter is used in a water treatment system for hemodialysis applications, the manufacturer of the filter shall disclose the performance of the filter and the conditions under which that performance can be obtained. It is recommended that filters be configured in a cross-flow mode. However, dead-end filters that have validated endotoxin and bacterial removal characteristics can also be used.

Endotoxin-retentive filters should have an opaque housing or other means to inhibit proliferation of algae. Endotoxin-retentive filters should be fitted with a means of assessing filter integrity and fouling. One suitable means is to monitor the pressure drop,  $\Delta P$ , across the filter using pressure gauges on the inlet and outlet water lines.

#### **4.2.13 Storage and distribution of dialysis water**

##### **4.2.13.1 Piping systems**

The dialysis water distribution system shall not contribute chemicals (such as aluminium, copper, lead and zinc) or bacterial contamination to the product water. Dialysis water distribution systems should be designed to minimize bacterial proliferation and biofilm formation, such as by using a continuous recirculation loop with flow in the return line. Areas of stagnant flow (dead zones) in the loop system shall be avoided. Direct feed systems shall include a means of verifiably preventing retrograde flow of water into the distribution loop from the feed side of the reverse osmosis unit.



#### 4.2.13.2 Storage tanks

When used, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Bladder tanks and pressurized surge tanks should not be used in the dialysis water distribution system. Storage tanks should have a tight-fitting lid and be vented through a hydrophobic 0.45 µm air filter. Sight tubes should be avoided due to the possible growth of algae and fungi. If an overflow pipe is used, it shall be fitted with a means of preventing contamination. Means shall be provided to effectively disinfect any storage tank installed in a dialysis water distribution system. An endotoxin-retentive filter, or some other form of microbial control device, should be installed distal to the storage tank.

#### 4.2.13.3 Ultraviolet irradiators

When used to control bacterial proliferation in dialysis water storage and distribution systems, UV irradiation devices shall emit light at a wavelength of 254 nm and provide a dose of radiant energy of 30 mW sec/cm<sup>2</sup>. If the irradiator includes a calibrated ultraviolet intensity meter, the minimum dose of radiant energy should be at least 16 mW sec/cm<sup>2</sup>. The device shall be sized for the maximum anticipated flow rate according to the manufacturer's instructions. UV irradiators should be followed by an endotoxin-retentive filter.

Ultraviolet irradiation can also be used to control bacteria in the pretreatment section of a water treatment system, such as following carbon beds to reduce the bacterial burden presented to a reverse osmosis unit.

To prevent the use of sublethal doses of radiation that could lead to the development of resistant strains of bacteria, UV irradiators shall be equipped with a calibrated ultraviolet intensity meter, as described above, or with an online monitor of radiant energy output that activates a visible alarm, which indicates that the irradiation source should be replaced. Alternatively, the irradiation source should be replaced on a predetermined schedule according to the manufacturer's instructions to maintain the recommended radiant energy output.

When ultraviolet irradiators are dipped in a storage tank, to control bacteria, they should be designed to keep the required energy at the farthest position in the tank considering the flow situation during operation. The required energy depends on whether sterilization or bacteriostasis is aimed for.

**NOTE** The recommendations provided in this clause concern UV irradiators used specifically for bacterial control. UV irradiators also can be used for other applications in a water treatment and distribution system. If an ultraviolet irradiator is utilized for reduction of chlorine or chloramine as an adjunct to carbon media, the manufacturer should verify the performance of the device and supply instructions regarding minimum radiant energy and wavelength for continuing performance.

#### 4.2.13.4 Hot water disinfection systems

When used to control bacterial proliferation in water treatment, storage, and distribution systems, the water heater of a hot water disinfection system shall be capable of delivering hot water at the temperature and for the exposure time specified by the manufacturer. Hot water disinfection systems should be equipped with a monitoring system that indicates if the temperature at the point farthest from the water heater drops below the manufacturer's recommended minimum temperature during the disinfection cycle. When disinfection is accomplished automatically by high temperature procedures, activation of the disinfection system shall result in activation of a system indicating that disinfection is in process. Operating controls should be positioned so as to minimize inadvertent resetting.

**NOTE** For dialysis water distribution loops, the point farthest from the water heater is where the water re-enters the storage tank (indirect feed systems) or where the water returns to the reverse osmosis system (direct feed systems).

#### **4.2.13.5 Ozone disinfection systems**

When used to control bacterial proliferation in dialysis water storage and distribution systems, an ozone disinfection system shall be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. An ozone concentration of 0.2 mg/l to 0.5 mg/l, combined with a contact time of 10 min, measured at the end of the distribution loop, is capable of killing bacteria, bacterial spores, and viruses in water. Following sanitation, the residual ozone level should be reduced to less than 0.1 mg/l.

When ozone disinfection systems are used, monitoring of the ambient air ozone levels in the area of the ozone generator shall be performed to ensure compliance with exposure limits established by the appropriate health and safety organization.

Activation of an ozone disinfection system shall result in activation of a system to indicate that disinfection is in process and activation of measures to prevent patient exposure to an unsafe condition. Operating controls shall be positioned so as to minimize inadvertent resetting.

## **5 Tests**

### **5.1 Compliance with dialysis water quality requirements**

#### **5.1.1 General**

This clause defines test methods by which compliance with the requirements of Clause 4 can be verified.

**NOTE** The test methods listed do not represent the only acceptable test methods available but are intended to provide examples of acceptable methods. Methods other than those stated can be used provided that they have been appropriately validated and compared to established test methods.

The requirements of ISO 13959 apply to the dialysis water as it enters the equipment used to prepare concentrates from powder at a dialysis facility, to prepare dialysis fluid, or to reprocess dialyzers. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively, the individual devices shall produce water that meets the requirements of ISO 13959 when provided with potable water as received at the facility or dialysis clinic. Tests for compliance with water quality requirements should be performed when the system is operating under stable conditions representing normal operation.

#### **5.1.2 Microbiology of dialysis water**

Samples shall be collected immediately prior to where the water re-enters the storage tank in an indirect feed system or immediately prior to where the water returns to the reverse osmosis system in a direct feed system. Additional samples shall be collected at, or immediately prior to, the point where water enters the equipment used to prepare concentrates or reprocess dialyzers if the line supplying that equipment with water is separate from the distribution loop supplying the dialysis machines.

Microbial analysis of water should be conducted as soon as possible after sample collection to avoid unpredictable changes in the microbial population. If samples cannot be analyzed within 4 h of collection, follow the laboratory's instructions for sample storage and shipping. Samples intended for colony counts should not be frozen.

Total viable counts (standard plate counts) shall be obtained using the membrane filter technique, spread plates, or pour plates. The calibrated loop technique shall not be used.

Approved culture methods shall include one of the following:

- 1) tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d); or
- 2) Trypticase soy agar (TSA, a soybean casein digest agar) or standards method agar and plate count agar (also known as TGYE), incubated at 35 °C for 48 hours.

Other test methods may also be used, provided such methods have been appropriately validated and compared to the cited methods. See USP <1231> for guidance on adoption of alternative methods. Endotoxin concentrations shall be determined by the LAL assay or kinetic method validated to yield results that are equivalent to LAL.

### 5.1.3 Maximum level of chemical contaminants

Chemical analyses of the water contaminants listed in ISO 13959, Table 1 (reproduced as Table B.1) can be obtained by using methods referenced by the American Public Health Association,<sup>[3]</sup> methods referenced by the US. Environmental Protection Agency,<sup>[24]</sup> methods referenced in applicable pharmacopoeia, or other equivalent validated analytical methods.

Compliance with the requirements listed in ISO 13959, Table 2 (reproduced as Table B.2) can be shown in one of three ways.

- Where such testing is available, the individual contaminants in Table 2 can be determined using chemical analysis methods referenced by the American Public Health Association,<sup>[3]</sup> methods referenced by the US. Environmental Protection Agency,<sup>[24]</sup> methods referenced in applicable pharmacopoeia, or other equivalent validated analytical methods.
- Where testing for the individual trace elements listed in Table 2 is not available and the source water can be demonstrated to meet the standards for potable water as defined by the WHO<sup>[28]</sup> or local regulations, an analysis for total heavy metals can be used with a maximum allowable level of 0.1 mg/l.
- If neither of these options is available, compliance with the requirements of Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO<sup>[28]</sup> or local regulations and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity or TDS.

Samples shall be collected at the end of the water treatment cascade or at the most distal point in each water distribution loop.

## 5.2 Compliance with water treatment equipment requirements

### 5.2.1 General

#### 5.2.1.1 Water treatment system

The need for tests to determine the quality of water used to feed water treatment equipment is dependent upon specific features of the devices. Suppliers of water treatment devices should select and perform such tests (e.g. iron, pH, silica, total dissolved solids, alkalinity, and total hardness) as are necessary to ensure the reliable performance of their devices.

#### 5.2.1.2 Materials compatibility

Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis, a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

#### **5.2.1.3 Regenerated or reconstituted devices**

The adequacy of disinfection procedures can be demonstrated by culturing a sample of the device's product water following the disinfection procedure. Where regenerated or reconstituted devices are provided by a vendor as medical devices, the disinfection and intermixing requirements of 4.2.1.3 can be demonstrated by certification that the device has been disinfected using validated procedures during regeneration or reconstitution and that validated procedures have been used to ensure that the devices and their component parts have been kept separate from devices and component parts used in non-potable water applications.

#### **5.2.1.4 Disinfection protection**

Compliance with the requirements of 4.2.1.4 for chemical disinfection procedures can be determined by testing for the disinfectant in the product water at the end of the disinfection procedure. If a commercially available chemical disinfectant, such as peracetic acid, is used, an established test for residual disinfectant shall be used according to the test manufacturer's instructions, and the residual level shall be less than that recommended by the manufacturer of the specific disinfectant.

When formaldehyde is used, residual levels can be determined by the Hantzsch reaction, Schiff's reagent, or by an equivalent test. Residual levels shall not exceed 3 mg/l or that stated in local requirements.

When sodium hypochlorite is used, the residual level shall be less than 0.1 mg/l.

Compliance with the requirements of 4.2.1.4 for high-temperature disinfection can be shown by demonstrating that the product water has returned to a safe temperature.

Compliance with the requirements of 4.2.1.4 for ozone disinfection can be shown by demonstrating that the ozone concentration in the product water has returned to a safe level (less than 0.1 mg/l).

Compliance with the patient protection requirements of 4.2.1.4 can be demonstrated by inspection.

#### **5.2.2 Backflow prevention devices**

Compliance with the requirements of 4.2.2 can be determined by visual inspection.

#### **5.2.3 Tempering valves**

Compliance with the requirements of 4.2.3 can be determined by visual inspection and review of manufacturer's specifications.

#### **5.2.4 Sediment filters**

Compliance with the requirements of 4.2.4 can be determined by visual inspection.

#### **5.2.5 Cartridge filters**

Compliance with the requirements of 4.2.5 can be determined by visual inspection.

#### **5.2.6 Softeners**

Compliance with the requirements of 4.2.6 can be determined by inspection.

### **5.2.7 Anion exchange resin tanks**

The performance of anion exchange resin tanks can be checked by periodically testing the feed and product water for total organic carbon (TOC) or tannins. Proper regeneration of the resin tank can be determined by monitoring salt usage and regeneration timer settings.

### **5.2.8 Carbon media**

Total chlorine removal can be used as an indication of carbon capacity. A DPD test kit selected for this purpose or a similar method shall be used to detect breakthrough of total chlorine, carbon exhaustion, or both. DPD materials shall be those designed for total chlorine detection and shall be used according to manufacturers' instructions. Alternatively, online monitors or "dip and read" test strips based on Michler's thioketone (MTK) can be used to measure the concentration of total chlorine. Tests for both free and total chlorine can also be performed to determine if chloramine is present. The difference between total chlorine and free chlorine is combined chlorine, which shall be considered chloramine. The utility of any test is dependent upon the sensitivity and detection limits of the analytical method used. Tests for total chlorine in product water shall have a sensitivity of at least 0.1 mg/l. Alternative tests (e.g. titrimetry) should be used to follow up questionable results. Tests are not required for organic or radioactive materials.

Compliance with the configuration requirements of 4.2.8 can be determined by inspection.

### **5.2.9 Chemical injection systems**

Compliance with the requirements of 4.2.9 can be determined by inspection.

### **5.2.10 Reverse osmosis**

Compliance with the performance requirement of 4.2.10 can be determined by the tests of 5.1.2 and 5.1.3.

Compliance with the alarm requirements of 4.2.10 can be determined by the tests of IEC 60601-1-8.

Conductivity, resistivity, or TDS measurements of product water of reverse osmosis devices can be accomplished by using conventional monitors that incorporate temperature compensation features. Compliance with this requirement and the other configuration requirements of 4.2.10 can be determined by inspection.

### **5.2.11 Deionization**

Resistivity measurements for product water of deionizers can be accomplished using conventional resistivity cells that incorporate temperature compensation features. The presence of required safety systems can be verified by inspection.

Compliance with the alarm requirements of 4.2.11 can be determined by the tests of IEC 60601-1-8.

### **5.2.12 Endotoxin-retentive filters**

Compliance with the requirements of 4.2.12 can be shown using the test methodologies for determining bacteria and endotoxin given in 5.1.2.

### **5.2.13 Storage and distribution of dialysis water**

#### **5.2.13.1 Piping systems**

The absence of copper, lead, and zinc and the configuration of a water treatment device or system can be determined by visual inspection. Non-contribution of bacteria and specific chemical contaminants to the water by the distribution system can be verified by using the tests described in 5.1.2 and 5.1.3.

#### **5.2.13.2 Storage tanks**

Compliance with the requirements of 4.2.13.2 can be determined by visual inspection.

#### **5.2.13.3 Ultraviolet irradiators**

Compliance with the requirements of 4.2.13.3 can be determined by visual inspection.

#### **5.2.13.4 Hot water disinfection systems**

Compliance with the requirements of 4.2.13.4 can be determined by measuring water temperatures in the fluid pathway being disinfected at the most distal point for the disinfection time specified by the manufacturer.

Compliance with the configuration requirements of 4.2.13.4 can be determined by inspection.

#### **5.2.13.5 Ozone disinfection systems**

Compliance with the requirements of 4.2.13.5 can be determined by using an online monitor for dissolved ozone or by analysis of water samples using test kits based on indigo trisulfonate or DPD chemistry.

Compliance with the configuration requirements of 4.2.13.5 can be determined by inspection.

## **6 Labelling**

### **6.1 General**

The term “labelling,” as used in this International Standard, includes any written material accompanying any water treatment device or system, such as instructions for use and operator's manuals, or any instructions or control feature markings attached to the device or system.

### **6.2 Device markings**

The following information shall accompany each water treatment device or system. Items a) to c) shall be directly affixed to the device or system or, in the case of disposable elements, to the immediate packaging, whereas items d) to f) can be provided in accompanying product literature.

- a) Name and address of manufacturer;
- b) Trade name and type of device;
- c) Model and serial number;
- d) A warning that product literature should be read before use (if appropriate);

- e) Prominent warnings about substances (e.g. germicides) needing to be removed from the device before using the product water for dialysis;
- f) Identification of fitting type or specification when necessary to prevent improper connections.

### 6.3 Product literature

The manufacturer shall provide literature to each user which contains, but is not necessarily limited to, the following information.

- a) Warnings that selection of water treatment equipment for dialysis is the responsibility of the user and that product water should be tested periodically.
- b) A description of the device or system, including a list of monitors, alarms, and ancillary devices provided as standard equipment.
- c) A schematic diagram of the device or system showing the location of any valves, online monitors, or sampling ports.
- d) Operating specifications, such as maximum and minimum input water temperature, pressure and flow rate, limits on input water quality, pressure of product water at various flow rates, and maximum output of product water.
- e) Detailed instructions for use, including initial start-up, testing, and calibration, operation and meaning of alarms, operational adjustments to monitors, alarms and controls, and connections to other equipment.
- f) For systems, the minimum quality of feed water required for the system to produce dialysis water meeting the chemical requirements of this International Standard.
- g) For systems, a warning that although a water treatment system produces water of sufficient quality to meet the requirements of this International Standard, distribution of that water could degrade its quality to the point where it no longer meets the requirements of the International Standard if the distribution system is not maintained appropriately.
- h) Safety features and warnings concerning the consequences if these features are circumvented.
- i) Information pertaining to online monitors of water quality, including operational factors that could affect monitor performance (e.g. temperature).
- j) In the case of systems whose product water is proportionally related to feed water quality, warnings that feed water quality shall be monitored. Since changes in product water could exceed acceptable limits if feed water deteriorates significantly, the user is responsible for monitoring.
- k) In the case of activated carbon beds, a warning that exhausted or contaminated carbon should be discarded and replaced with new beds.
- l) For devices regenerated or reconstituted offsite, instructions on how to safely reconnect the device to the water treatment system and how to remove any contaminant or disinfectant in the device before use.
- m) A statement on regenerated or reconstituted devices, such as deionizers, certifying that there was no intermixing of regenerated or reconstituted devices returned from medical or potable water users and devices returned from process or non-potable water users. A statement that a description of the methods used to ensure that no intermixing occurred is available on request.
- n) For automatically regenerated water treatment devices, identification of the mechanism (for example, lock-out valves) that prevents excessive levels of contaminants entering the product water during regeneration.

- o) In the case of deionizers, a warning that deionizers should be preceded by an activated carbon bed and a recommendation that they be followed by an endotoxin-retentive filter or other bacteria- and endotoxin-reducing device.
- p) In the case of ultraviolet (UV) irradiators, a requirement that the manufacturer disclose the effectiveness of the device in killing specific bacteria under specified operating conditions and a recommendation that UV irradiators be followed by an endotoxin-retentive filter or other bacteria- and endotoxin-reducing device.
- q) In the case of hot water disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions.
- r) In the case of ozone disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions and that he provide a warning that product water shall not be used until the minimum time required for ozone to dissipate has elapsed.
- s) In the case of hot water disinfection systems, a warning that appropriate heat-resistant materials be used for the fluid pathways to be disinfected with hot water.
- t) In the case of ozone disinfection systems, a warning that appropriate ozone-resistant materials be used for the fluid pathways to be disinfected with ozone.
- u) Construction materials, identified generically, that contact water.
- v) Typical life expectancy, capacity, or indication of the end of life of devices that are non-durable or require periodic regeneration or reconstitution and a statement that additional information on device life expectancy or capacity relative to the user's typical feed water is available upon request. The two principal mechanisms by which carbon removes contaminants from water is by adsorption and catalytic reduction. Organic compounds are removed by adsorption, while residual disinfectants are removed by catalytic reduction. In the case of carbon beds, manufacturers or suppliers should provide a warning that unexpected exhaustion could occur because of variable feed water characteristics. The only safeguard against such unforeseeable eventuality is diligent monitoring of carbon filter effluent by the user.
- w) Specified water supply or operating conditions that could cause the device to fail.
- x) Information about germicides and cleaning agents known to be compatible with materials used in the device, as well as information about chemicals with which materials used in the device are incompatible.
- y) If applicable, a method of cleaning and disinfecting the equipment, and of removing residual germicide, so that the system of which the equipment is part is capable of meeting the requirements for microbial and endotoxin contamination given in 4.1.2.
- z) Other maintenance and service instructions, including recommended preventive maintenance procedures and schedules, recommended monitoring schedules, troubleshooting guidelines intended for the user, service information, a recommended spare parts list, and a warning of the consequences if maintenance instructions are not followed.
- aa) A warning that if, after installation and subsequent use, any device in the water treatment system is changed or replaced, the user should conduct appropriate tests to ensure that the revised system meets the initial design criteria.
- bb) Information on storage, if allowed, of devices while not in use, including appropriate packing chemicals, storage conditions, and duration.



## **Annex A**

### **(informative)**

## **Rationale for the development and provisions of this International Standard**

### **A.1 Scope**

The items included within the scope of this International Standard are equipment used to treat water for the preparation of concentrates and dialysis fluid, or for the reprocessing of dialyzers for multiple uses, and the devices used to store and distribute this water.

This International Standard seeks to prevent the use of options that are hazardous to patients treated with hemodialysis and related therapies. For example, this International Standard is needed to prevent poisoning caused by formulation of dialysis fluid with water that contains high levels of certain contaminants.

Water treatment and distribution systems incorporate a variety of devices. These devices can be provided and installed by different vendors, making it difficult to assign responsibility for compliance with this International Standard to any one individual or company. To address this concern, primary responsibility for compliance with this International Standard was placed on the individual or company that specifies the water treatment and distribution system installed in a given situation. Responsibility could also lie with the vendor who assembles and installs the system and with the manufacturer of any individual device of the water treatment and distribution system if that manufacturer specifies that their device is intended for hemodialysis applications.

### **A.2 Requirements**

#### **A.2.1 Dialysis water quality requirements**

##### **A.2.1.1 General**

Individual water treatment devices might not provide water that meets the requirements of this International Standard in its entirety. ISO 13959 for dialysis water gives the requirement that a water system be maintained in a condition to continually meet ISO 13959-defined water quality without giving a method of accomplishing the requirements. This International Standard is directed at the manufacturer of the dialysis water treatment systems and defines the requirements that the manufacturer should meet prior to the user assuming responsibility for the water system. However, manufacturers of individual water treatment devices should be aware of the requirements for the final dialysis water and that they should be prepared to recommend other water treatment devices that might need to be used in conjunction with their device to produce water which meets the requirements of this International Standard.

##### **A.2.1.2 Microbiology of dialysis water**

The supplier of water treatment equipment is responsible for recommending a method of cleaning the equipment so that dialysis water meeting the microbial requirements of ISO 13959 can routinely be produced when typical feed water is presented. Beyond this qualification, it becomes the responsibility of the user of the system to monitor the system for ongoing compliance with ISO 11663. The rationale for these microbiological contaminant requirements is set forth in Annex A of ISO 13959:2014.

### **A.2.1.3 Maximum level of chemical contaminants**

The rationale for the chemical contaminant requirements is set forth in Annex A of ISO 13959:2014

Tables B.1 and B.2 should not be taken as a definitive list of harmful substances, but as a partial listing of those that might reasonably be expected to be present and have clinical implications. At the time this International Standard was prepared, it was not possible to specify threshold values for organic contaminants permitted in water used for the preparation of dialysis fluids, concentrates, and reprocessing of hemodialyzers. The issue of organic contaminants will be reassessed during the next revision of this International Standard.

Iron is not included because it does not enter the patient's blood in sufficient quantities to cause toxicity. Iron can, however, cause fouling of water treatment devices (see 4.2.1.1) or dialysis fluid supply systems. While a specific limit was not set, water treatment equipment suppliers are encouraged to consider the iron content of the feed water when recommending suitable equipment. A concern was raised regarding the injection of formulated phosphates (known as polyphosphates) primarily to bind iron and manganese to avoid the staining of fixtures and clothing. The concern was raised that this practice could cause significant problems in water treatment. Some municipal water suppliers were considering the use of chlorine dioxide as a disinfectant for potable water supplies. Chlorine dioxide breaks down in water to yield chlorite, chlorate, and chloride ions. Little information about the potential for chlorine dioxide and its daughter products to be toxic to hemodialysis patients could be found. A limited study of 17 patients unknowingly treated with water prepared by carbon and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects.<sup>[2]</sup> In that study, the water used to prepare dialysis fluid contained 0.02 mg/l to 0.08 mg/l of chlorite ions and no detectable chlorate ions. However, the patient population was small and potentially important hematological parameters were not measured. Further, there were only sparse data included on the removal of chlorine dioxide, chlorite ions, and chlorate ions by carbon and reverse osmosis, and it was not clear that sufficiently sensitive methods were available for their analysis in a dialysis facility. Therefore, there was no basis for setting maximum allowable levels of chlorine dioxide, chlorite ions, or chlorate ions in water to be used for dialysis applications or for making recommendations on methods for their removal at that time. However, in specifying water treatment systems, manufacturers of such systems should be aware of the possibility that municipal water suppliers can add chlorine dioxide to the water.

## **A.2.2 Water treatment equipment requirements**

### **A.2.2.1 General**

#### **A.2.2.1.1 Water treatment system**

The supplier of the complete water treatment system is responsible for assuring that the water produced by the system can routinely meet the maximum allowable chemical contaminant levels specified in Tables B.1 and B.2, or the prescription of the physician, at installation. Beyond this qualification, it becomes the responsibility of the physician in charge of dialysis to monitor the system to ensure that the treatment device or devices maintain an acceptable level of purity of the water. Variations in water quality or the presence of as-yet-unidentified toxic substances will obviously compromise the system's safety.<sup>[13]</sup> Such variations typically do occur, and while the supplier cannot be held accountable for the performance of the water treatment system during such variations, selection of water purification equipment should include careful consideration of methods to cope with such changes, many of which can be anticipated through consultation with state and local water authorities.

The medical director has the ultimate responsibility for the selection and use of water treatment devices on the basis of the supplier's recommendations. If a supplier is convinced that the local water quality is such that the selection of a minimum system does not provide an adequate margin of safety, then the supplier should recommend additions to the system or alternative systems with corresponding rationale. Continued monitoring of the water supply is necessary to maintain treatment methods consistent with safety.

#### **A.2.2.1.2 Materials compatibility**

Non-toxicity of construction materials for hemodialysis water treatment equipment is of major importance. Some well-recognized non-toxic materials include certain stainless steel formulations, silicon rubber, borosilicate glass, polypropylene, polyvinylchloride (PVC), chlorinated PVC (CPVC), polyvinylidene fluoride (PVDF), polyethylene, cross-linked polyethylene (PEX), and polytetrafluorethylene (PTFE). Data are now available that demonstrate that materials once regarded as inert can in fact be toxic in this application (e.g. copper leaches from copper conduits, especially in the presence of low pH, which can result when a deionizer is exhausted).<sup>[13]</sup> Other materials have been documented as being hazardous to the patient (e.g. brass, zinc, iron, and aluminium), and these materials should also be avoided. The hidden hazard with respect to construction materials derives from long-term cumulative toxicity. Hemodialysis is a long-term chronic treatment modality, and this fact should be acknowledged when selecting construction materials. A risk analysis according to ISO 14971 should be used to assess the suitability of materials based on existing data. If that analysis suggests the need for additional testing, that testing should be based on the approaches outlined in the ISO 10993 series of standards. Users of this document should be aware of the requirements of those standards.

Repeated exposure to ozone or hot water might have a deleterious effect on some plastic or metal materials. Therefore, manufacturers are required to include warnings that only ozone- or heat-compatible materials be used in piping systems intended for use with ozone or hot water disinfection devices, respectively (see 6.3).

#### **A.2.2.1.3 Regenerated or reconstituted devices**

Regenerated or reconstituted devices are subject to bacterial contamination that can cause excessive bacterial counts in product water (see 4.1.2). Disinfection procedures are required to minimize this risk. When devices are regenerated at a central facility, there is a risk of cross-contamination and improper disinfection and rinsing.<sup>[13]</sup> Some exchange-type deionizers are used for both dialysis and industrial recovery of plating metals, such as chromium and silver, from effluent process water. In some regeneration facilities, resins from both processes or non-potable users and from medical or potable users are regenerated together as a batch. Traces of these toxic metals will remain bound to the resins and could be eluted into water during subsequent use. For that reason, such mixed use is prohibited in this International Standard.

#### **A.2.2.1.4 Disinfection protection**

Disinfection procedures can render product water unsafe because of toxic chemicals or excessive temperatures. Therefore, provision was made for restoring the water treatment system to a safe condition after disinfection. Although the user is responsible for carrying out manual disinfection procedures, the manufacturer should demonstrate that recommended disinfection procedures meet the requirements of 4.2.1.4.

#### **A.2.2.2 Backflow prevention device**

A backflow prevention device isolates the water treatment system from the potable water supply, thereby protecting the potable water system from possible contamination in the event of a sudden reduction in pressure in the potable water supply.

#### **A.2.2.3 Tempering valves**

The performance of many water treatment devices is temperature sensitive. In less temperate climates, seasonal fluctuations in cold water temperature could impact the performance of these devices. A tempering valve can be used to blend hot and cold water to provide a constant feed water temperature independent of any seasonal changes in feed water temperature. Excessive water temperatures resulting from malfunction of a tempering valve can damage downstream devices, including reverse osmosis membranes and plastic pipes and pipe fittings. For that reason, consideration was given to requiring that tempering valves be fitted with a water temperature monitor that activates an audible alarm in the event that a high temperature is sensed. While recognizing the potential for equipment to be damaged by hot water, no consensus could be reached on the need for such a requirement.

#### **A.2.2.4 Sediment filters**

Accumulation of organics, bacteria, and algae in filters can lead to proliferation of bacteria to the point of overloading downstream devices or producing dangerous endotoxin levels. Use of opaque housings to reduce the light that promotes algae growth and differential pressure monitoring can reduce this risk.

#### **A.2.2.5 Cartridge filters**

Accumulation of organics, bacteria, and algae in filters can lead to proliferation of bacteria to the point of overloading downstream elements or producing dangerous endotoxin levels. Use of opaque housings to reduce the light that promotes algae growth and differential pressure monitoring can reduce this risk. In the pretreatment cascade, transparent filter housings can be useful because they allow any carbon or resin leakage to be seen without the need to break the integrity of the system. The housing can be cleaned to remove any growth when the filter cartridges are changed. For this reason, use of opaque housings for cartridge filters is recommended, but not required. If transparent housings are used, they should not be exposed to natural light, in order to minimize proliferation of algae.

#### **A.2.2.6 Softeners**

The process by which “hard” water (containing high levels of calcium and magnesium) is made “soft”, involves the exchange of sodium ions for the calcium and magnesium in the water supply. The resin should be regenerated with brine to sustain capacity for exchange. Regeneration can be either manual or automatic with a timer to regenerate outside operating hours. During regeneration, excess sodium can enter the product water stream if there is a temporary interruption of power, a malfunction in regeneration control, or inadequate water pressure. There are no monitors on a softener to detect excess sodium in the product water stream, and the physiological effects of excess sodium in the patient are severe.<sup>[18],[21]</sup> Therefore, protection against such excessive levels of sodium, as can occur during regeneration of a water softener, is required. An automatic bypass valve most easily provides this protection during the regeneration cycle.

#### **A.2.2.7 Anion exchange resin tank**

High levels of organic matter in the source water can foul carbon media. Organic molecules (usually very large) are attracted to carbon and become attached at the pore sites, effectively blocking the pore and sealing off the surface area within that pore. As organic molecules accumulate on the surface of the carbon, there is less surface area available for removal of chlorine. Organic scavengers operate similar to a water softener, exchanging anions and organic matter for chloride ions. Source water testing for organics (TOC or tannins) can indicate if an organic scavenger will help protect carbon media.

#### **A.2.2.8 Carbon media**

Carbon beds are particularly prone to bacterial growth because of their porosity and affinity for organics. More stringent requirements for the installation of carbon beds and their monitoring are included because of continued reports of clusters of hemolysis related to insufficient removal of chloramine from municipal water supplies.<sup>[8],[23],[27]</sup> In the United States, changes to the Safe Drinking Water Act, designed to eliminate lead and copper from tap water,<sup>[20]</sup> have reinforced the need for careful monitoring of carbon beds because the increase in water pH that can accompany the institution of these changes can decrease the capacity of carbon for chloramine.

Activated carbon can be regenerated by a number of techniques, including oxidation at high temperatures and stripping with low-pressure steam or solvents. Regeneration of activated carbon, also known as reactivation, is used in industrial applications where activated carbon can be used to remove organic and inorganic substances such as pollutants from process streams. No evidence that regenerated carbon was being used for hemodialysis applications could be found. However, it was deemed prudent to prohibit the use of regenerated carbon in hemodialysis applications to avoid any potential hazard resulting from residual toxins that could remain in the carbon following regeneration.

Depending on the source material used for its manufacture, and the manufacturing process, granular activated carbon can contain carbon fines and other contaminants, such as aluminium. If present, these substances will leach out of a carbon bed during the initial stages of operation. Carbon fines can contribute to fouling of reverse osmosis membranes downstream of the carbon beds and any metal ions can add to the burden of contaminants, which should be removed from the water. Acid washing of carbon minimizes the amount of fines and other contaminants, and a requirement for the use of acid-washed carbon was considered. No consensus could be reached on this issue because rinsing of carbon beds before they are placed online in a water treatment cascade will also effectively remove fines and other contaminants.

The requirement for two beds in series and a 10 min empty-bed-contact-time was waived for portable dialysis systems provided there is a redundant means of chloramine removal because of the impracticality of providing these features while retaining the portability of the system. Possible alternatives include a granular activated carbon bed followed by a dense carbon block and two carbon block filters in series. However, when a single carbon bed is used, it is important to ensure that the bed has adequate capacity to remove chloramine for the duration of an entire treatment given the typical feed water concentration of chloramine in the setting where the bed is being used.

Although treatment of water by carbon is the usual method of meeting the requirement of 4.1.3 when the feed water contains chloramine, in certain situations, such as acute or home dialysis with portable water treatment systems, it might not be practical to use the volume of carbon required for this purpose. In such circumstances, combining limited carbon with the addition of ascorbic acid to the acid concentrate has been used to eliminate chloramine from the final dialysis fluid.<sup>[27]</sup> It should be noted that some minimum contact time is required for ascorbic acid to neutralize chloramine in water. If ascorbic acid is being used to neutralize chloramine, and unexplained red blood cell destruction or anemia occurs, the effectiveness of the ascorbic acid neutralization of chloramine should be investigated.

In most circumstances, conventional carbon systems provide months of effective chlorine/chloramine removal. Occasionally, conventional carbon systems experience premature breakthrough necessitating carbon bed replacement/exchange within days rather than months. These occasions could be episodic or persistent in nature. Episodic carbon filter breakthrough is often associated with periodic municipal water treatment practices, such as short-term substitution of free chlorine for chloramine. Persistent difficulties with premature breakthrough of carbon systems could be related to the source water itself (pH, TOC level, etc.) or a routine municipal water treatment practice, such as the addition of corrosion inhibitors. The occurrence of these problems seemed to be increasing. Therefore, clauses on optional water purification system devices that might help address recurrent premature exhaustion of carbon media or enhance the efficiency of the carbon media were added. Two approaches were included: anion exchange resins that scavenge large organic molecules that can coat the carbon surface, and systems that inject sodium bisulfite, which reduces chloramine to chlorine, or acid to adjust the pH to the optimal range for removal of chloramine by carbon. Including the use of redox alloy media (RAM), also referred to as kinetic degradation fluxion (KDF), was also considered. This material can be an effective pretreatment for conventional carbon filters experiencing premature breakthrough due to municipal short-term substitution of free chlorine for chloramine or for supply waters having high organic loading. A disadvantage of KDF media is that both copper and zinc are eluted from the medium, albeit at very low levels. Concerns about how the eluted copper and zinc might affect downstream devices, together with questions about the effectiveness of KDF media, lead to the omission of this alternative.

#### **A.2.2.9 Chemical injection systems**

There were reservations about the addition of chemicals to the water. However, it was recognized that the addition of chemicals could be necessary in some circumstances if a facility is to meet the maximum contaminant levels set forth in 4.1.3. For example, if the municipal water contains high levels of *N*-chloramines or chloramine in the presence of orthophosphate or polyphosphate, injection of sodium bisulfite could be one of the few options available for chloramine removal. If chemical injection is used in the pretreatment cascade, users should ensure that the addition of the chemical does not interfere with the operation of subsequent purification processes, including the primary purification process. For example, the performance of thin-film composite reverse osmosis membranes can be

affected by the pH of the feed water. At pH levels below 7, the rejection of fluoride can be substantially reduced, compared to its rejection at a pH of 8.

#### A.2.2.10 Reverse osmosis

A reverse osmosis system should demonstrate delivery of water meeting the requirements of 4.1.2 and 4.1.3; otherwise, additional treatment devices should be recommended to the user. Monitoring requirements for reverse osmosis systems are recommended on the basis of totally different degradation characteristics of these systems as compared with deionizer systems. On initial setup, the reverse osmosis device should have a rejection rate that ensures that the product water of the water treatment system meets the requirements of 4.1.3. Because this rejection rate varies with different installations, an absolute level is not required. Monitoring is defined in terms of the salt passage rate or percent rejection and a threshold level of product water resistivity or conductivity. Compliance with both monitored parameters is required because an increase in feed water contaminants could result in product water unsuitable for hemodialysis applications even though the percent rejection of the membrane modules remains high.

Consensus could not be reached on how to establish the alarm limits for rejection and product water resistivity or conductivity. As noted above, changes in feed water quality will result in changes in product water quality even though rejection remains constant. Also, a significant change in the feed water concentration of one trace inorganic contaminant might not appreciably alter the product water resistivity even though the product water concentration of that contaminant exceeds the allowable limit. For that reason, some felt that routine analysis of feed water quality should be emphasized. Others felt that the rejection alarm limit could be set based on the reduction ratio for each contaminant that can be achieved by reverse osmosis<sup>[15]</sup> and the assumption that the feed water would meet the requirements of the *Safe Drinking Water Act* or other applicable standards. Either approach could be effective when incorporated into an overall monitoring programme designed to protect the patient against exposure to contaminant levels in excess of those listed in Tables B.1 and B.2.

Consensus could not be reached regarding the inclusion of a requirement that reverse osmosis systems incorporate as a means of diverting the product water to drain in the event of a product water conductivity or rejection rate alarm. Some felt that a divert-to-drain should be required because reverse osmosis is frequently the primary means of water purification. However, others felt that including a divert-to-drain should be optional. They pointed out that, because reverse osmosis membranes tend to fail gradually, the risk is different from exhaustion of a deionizer where very high levels of contaminants, such as fluoride, can occur abruptly in the product water because of competitive binding at the ion exchange sites of the deionizer resin. Furthermore, with direct feed water distribution systems, a divert-to-drain would cause an immediate alarm condition with all dialysis machines as a result of interrupting their water supply. Under such circumstances, the ability to discontinue dialysis effectively could pose the lowest risk to the patients. Therefore, a divert-to-drain was included as a recommendation and not as a requirement.

Requirements for alarm systems in medical electrical equipment are addressed in IEC 60601-1-8. During the 2012 revision of this International Standard, consideration was given to substituting reference to IEC 60601-1-8 for the alarm system requirements included in the 2009 version of the International Standard. Because reverse osmosis systems are often remote from the treatment area, an audible alarm in the treatment area was considered necessary if the reverse osmosis system did not have a means of preventing water from reaching the dialysis machine as its primary safety system should the product water conductivity exceed a preset value. There was concern that IEC 60601-1-8 did not necessarily require an audible alarm. Therefore, it was decided to retain the requirements for an audible alarm, in addition to the requirements of IEC 60601-1-8. IEC 60601-1-8 classifies alarms as low-priority, medium-priority, and high-priority based on potential harm to patients should a system failure occur. For reverse osmosis systems with a means of preventing water from entering the dialysis machine, if product water conductivity exceeded a preset value, a low-priority alarm was considered sufficient; whereas, for a reverse osmosis system without a means of preventing water from entering the dialysis machine if product water conductivity exceeded a preset value, i.e. one in which the alarm is the primary safety system, a medium priority alarm was required. A medium-priority, rather than a high-priority, alarm was chosen because the risk of immediate death or injury as the result of reverse osmosis system failure was considered to be very low. The question of whether or not audible alarms should be capable of being silenced provoked some discussion. On one hand, some felt that audible alarms should not be capable of being silenced because the alarm condition could be overlooked, allowing a dangerous

situation to ensue. On the other hand, an audible alarm capable of being temporarily silenced was suggested so that the operator would have a relatively unharried period of time to correct the fault condition. It was concluded that the ability to silence an audible alarm for up to 180 s was a reasonable requirement.

#### **A.2.2.11 Deionization**

Deionizer systems, during exhaustion, have the capability of releasing into the water potentially harmful contaminants at levels much higher than are present in the untreated feed water.<sup>[12],[6]</sup> The monitor level of 1 MΩ·cm specific resistivity was selected as the point at which most of the useful capacity of the deionizers used in dialysis water treatment has been consumed and below which rapid degradation of ion removal efficiency takes place; 1 MΩ·cm specific resistivity is not the minimum safe value for dialysis water, but deionizer systems producing water dropping below this value are in danger, during the following dialysis treatment, of producing water high in toxic contaminants as the final deterioration of resin accelerates. A requirement that the product water be diverted to drain was included because of the acute danger that an exhausted deionizer can pose to patients.<sup>[4]</sup> The requirement for activated carbon in advance of the deionizer prevents generation of possibly carcinogenic nitrosamines.<sup>[22]</sup> Deionizers are subject to bacterial contamination because of the porous structure of the resins. Although the level of bacterial contamination in product water from deionizers varies widely, it is generally highest after the deionizer has been idle for some time and lowest after continuous use. Because deionizers are usually placed last in a purification cascade, they should be followed by an endotoxin-retentive filter or another bacteria and endotoxin removing device to prevent bacterial contamination of the water storage and distribution system.

For the reasons outline in A.2.2.10 for reverse osmosis, it was decided to retain the requirements for an audible alarm in addition to requiring that the alarms comply with IEC 60601-1-8. High-priority alarms were selected for deionizers because of the risk of immediate death or injury should the product water specific resistivity drop below 1 MΩ·cm and the divert to drain fail.<sup>[4]</sup> The question of whether or not audible alarms should be capable of being silenced provoked some discussion. On one hand, some felt that audible alarms should not be capable of being silenced because the alarm condition could be overlooked, allowing a dangerous situation to ensue. On the other hand, an audible alarm capable of being temporarily silenced was suggested so that the operator would have a relatively unharried period of time to correct the fault condition. It was concluded that the ability to silence an audible alarm for up to 180 s was a reasonable requirement.

#### **A.2.2.12 Endotoxin-retentive filters**

Endotoxin-retentive filters are increasingly being used to provide water of high microbiologic quality for dialysis applications. Endotoxin-retentive filters include ultrafilters that remove endotoxin primarily by size exclusion, although some can also remove some endotoxin by adsorption to the membrane material, and microfilters that remove endotoxin primarily by adsorption to the membrane material. Because of the two different mechanisms of endotoxin removal, and because the role of endotoxin-retentive filters is to remove bacteria and endotoxins, they have been defined in these terms. This choice also provides a basis for monitoring the performance of endotoxin-retentive filters after they have been installed in a water treatment purification system. Consensus could not be reached regarding minimum performance criteria for the removal of bacteria and endotoxins by an endotoxin-retentive filter. One factor contributing to this impasse is the dependence of filter performance on the test conditions. Therefore, it was decided to require that manufacturers disclose the minimum performance of their device and that the device be required to perform to at least this level under stated operating conditions. Some considered that an endotoxin-retentive filter should be able to reduce the concentration of bacteria in the feed water to the filter by a factor of at least  $10^7$  and that of endotoxin by a factor of at least  $10^3$ . Methods for determining bacteria and endotoxin rejection by ultrafilters have been published by the Japanese Standards Institute<sup>[10],[11]</sup> and ASTM.<sup>[5]</sup>

The recommendation to use endotoxin-retentive filters in a cross-flow configuration is aimed at preventing excessive replacement of membrane modules, which could result from rapid fouling if the filter is operated in the dead-end mode. However, a dead-end configuration might perform satisfactorily in situations where the water quality is generally good (for example, as final filtration of water immediately before its use in dialyzer reprocessing equipment). Differential pressure measurements can be used to monitor fouling of both cross-flow and dead-end filters.

### **A.2.2.13 Storage and distribution**

#### **A.2.2.13.1 Piping systems**

The distribution system has been implicated in several bacterial contamination episodes involving dialysis patients.<sup>[19]</sup> Specific design criteria, such as minimum flow velocities, to minimize bacterial proliferation and biofilm formation<sup>[9]</sup> were considered. Desirable design criteria include use of a distribution loop, an absence of multiple branching and dead-ended pipes, the use of simple wall outlets with the shortest possible fluid path, a minimum of pipe fittings, and the use of valves with minimal dead space. Also, joints between sections of piping and between piping and fittings should be formed in a manner that minimizes the formation of crevices and other voids that could serve as sites for bacterial colonization. Agreement could not be reached concerning a minimum flow velocity. Some were of the opinion that the low shear stresses existing at the internal surface of a pipe operating at flow rates that are feasible in distribution systems for dialysis water are insufficient to prevent bacterial adhesion and biofilm formation. On the other hand, data from the semiconductor industry were presented showing that a Reynolds number of 3 000 in a piping system was sufficient to prevent bacterial contamination in water.<sup>[14]</sup> A Reynolds number of approximately Re 3 000 is obtained with a flow velocity of about 0.15 m/s in a 2 cm diameter pipe (0.5 ft/s in a 3/4" diameter pipe). However, even in systems operating with Re 3 000, biofilm was found on the internal surface of the pipes.<sup>[14]</sup> Further, in many dialysis facilities, there is no flow through the distribution system when the dialysis facility is not in operation, such as at night and on Sundays. Even if it were possible to specify a minimum flow velocity that was effective in reducing biofilm formation and bacterial contamination, use of such a minimum flow velocity would not provide a substitute for regular disinfection of the distribution system.

Direct feed systems commonly return water from the dialysis water distribution loop to the feed side of the reverse osmosis unit, before the pressurizing pump. With this configuration, it is possible for water from the feed side of the reverse osmosis unit to flow retrograde into the dialysis water distribution loop if the pressure in the distribution loop suddenly decreases as the result of a sudden increase in demand for dialysis water. Because retrograde flow allows contaminated water to enter the dialysis water distribution system, it was considered necessary to recommend some means of preventing retrograde flow. A common method is to include dual check valves at the end of the distribution loop. Some were concerned that there is no means of monitoring the integrity of these valves. A second approach is to return the dialysis water into a break tank at the inlet to the pressurizing pump of the reverse osmosis unit.

#### **A.2.2.13.2 Storage tanks**

When storage tanks form part of the water treatment infrastructure, the volume and low water velocities in such tanks predispose them to bacterial contamination. As a consequence, tanks should be designed with features that facilitate disinfection procedures and prevent the entry of bacteria.

#### **A.2.2.13.3 Ultraviolet irradiators**

The effectiveness of UV irradiation depends on the dose of radiant energy. Several studies have demonstrated that a dose of 30 mW sec/cm<sup>2</sup> will kill greater than 99.99 % of a variety of bacteria, including *Pseudomonas* species, in a flow-through device.<sup>[16],[17]</sup> However, certain gram-negative water bacteria appear to be more resistant to UV irradiation than others, and use of sub-lethal doses of UV radiation, or an insufficient contact time, could lead to proliferation of these resistant bacteria in the water system (Carson and Petersen<sup>[7]</sup>).

The radiant energy emitted by the mercury vapor lamps used in UV irradiators decreases with time. If the lamp is not replaced before its radiant energy decreases below the effective threshold, resistant bacteria could also develop. Therefore, the requirement for an online monitor of the radiant energy emitted by the lamp is included in this International Standard. Because the effectiveness of UV irradiation depends on the geometry of the device and the exposure time of water to the radiation, the manufacturer of a UV irradiation device is required to provide information on the killing of specific bacteria under specified operating conditions. Because UV irradiators do not eliminate endotoxin and could even increase endotoxin concentrations by killing bacteria, a recommendation was included that they be followed by an endotoxin-retentive filter. Use of an endotoxin-retentive filter was not made a requirement however, because reliance on an endotoxin-retentive filter to remove endotoxin should not be considered an alternative to identifying and eliminating the source of bacterial contamination.



Ultraviolet irradiation has also been used to eliminate chloramine as an alternative or adjunct to activated carbon. Ultraviolet irradiation at a wavelength of 254 nm converts chloramine (NH<sub>2</sub>Cl) to chloride and ammonium ions, which are easily rejected by reverse osmosis. Hard water, high total dissolved solids (TDS), or high levels of fluoride, iodine, iron, or manganese could interfere with penetration of ultraviolet irradiation through the water and inhibit the effectiveness of ultraviolet irradiation in eliminating chlorine/chloramine.

#### **A.2.2.13.4 Hot water disinfection systems**

Hot water disinfection of dialysis water storage and distribution systems is one means of controlling bacterial proliferation. The manufacturer of a hot water disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial levels and also disclose these operating specifications of the system. Repeated exposure to hot water might have a deleterious effect on some plastic piping. Therefore, a requirement that manufacturers of hot water disinfection systems include a warning in their product labelling about the need to use heat-resistant materials in piping systems to be disinfected with hot water was added to this International Standard.

#### **A.2.2.13.5 Ozone disinfection systems**

Ozonation is being introduced as a new means of controlling bacterial proliferation in dialysis water storage and distribution systems. This technology might have widespread applicability in dialysis facilities in light of the increased concern about endotoxin contamination of dialysis fluid. Insufficient data are available to set performance standards for such systems, such as ozone concentration and exposure time. Therefore, a requirement that the manufacturer of an ozone disinfection system disclose the operating specifications of the system until such time as performance criteria could be established was included. The manufacturer of an ozone disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial and, if applicable, endotoxin levels. The presence of ozone in dialysis water could be harmful to patients, however robust data demonstrating clinical effects is currently absent. It is, however, known that low levels of ozone have the potential to suppress immune system response.<sup>[30]</sup> Therefore, a requirement for manufacturers to include a warning that product water should not be used until ozone produced in the disinfection process has dissipated [see 6.3 item r)] was included. The manufacturer should validate that residual ozone in the product water falls to acceptable levels at the end of the recommended minimum elapsed time between disinfection and use of the product water. Alternatively, the manufacturer of an ozone disinfection system can provide the user with a means of verifying that the residual ozone is within acceptable limits before product water is used. Repeated exposure to ozone could have a deleterious effect on some plastic piping. Therefore, a requirement that manufacturers of ozonation systems include a warning in their product labelling about the need to use ozone-resistant materials in piping systems to be disinfected with ozone was added to this International Standard.

### **A.3 Tests**

#### **A.3.1 Compliance with dialysis water quality requirements — Microbiology of dialysis water**

The rationale for the culturing methods required in this International Standard is set forth in Annex A of ISO 13959:2014.

#### **A.3.2 Compliance with water treatment equipment requirements — Materials compatibility**

It has been argued that the biocompatibility tests outlined in the appropriate *pharmacopeia* were not useful for water treatment equipment because they were not sensitive enough to detect the presence of small amounts of toxin in large volumes of water. It was proposed that the appropriate *pharmacopeia* biocompatibility tests be replaced by leach testing and measurement of total organic carbon in the leachate. After discussion, this proposal was rejected because there was no clinical outcomes data suggesting a change was necessary and because no standardized methodology for such leach testing was available.

## A.4 Labelling

Some existing regulations contain requirements for the labelling of medical devices, including such information as name and address of manufacturer and lot number. Redundancy of these requirements was deemed preferable to omission however, and a requirement that some of the same information already mandated by other regulations was included. The provisions of the other requirements of 6.2 and 6.3 are intended to ensure that certain information specifically necessary for the safe and effective use of hemodialysis systems will be included in the device labelling. For most of this information, the underlying reasoning for the requirement is self-evident. Additional rationale for certain of these requirements is provided below.

Display of basic information about precautions before use is provided to ensure the safe and effective use of the device.

The quality of water used during dialysis is critical. Thus, certain information should be provided to the user so that appropriate precautions can be taken before the use of water for dialysis applications. The specialized information of 6.3 reflects an attempt to provide the user with sufficient information to minimize the risks of using improper water during dialysis.

## Annex B (informative)

### Reference tables from ISO 13959

NOTE The maximum allowable levels of contaminants listed in Tables B.1 and B.2 are identical to the reference tables in ISO 13959:2014. The values shown include the anticipated uncertainty associated with the analytical methodologies listed in Table B.3.

**Table B.1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water<sup>a</sup>**

| Contaminant                                                                                                                              | Maximum concentration<br>(mg/l) <sup>b</sup> |
|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| <b>Contaminants with documented toxicity in hemodialysis</b>                                                                             |                                              |
| Aluminium                                                                                                                                | 0.01                                         |
| Total chlorine                                                                                                                           | 0.1                                          |
| Copper                                                                                                                                   | 0.1                                          |
| Fluoride                                                                                                                                 | 0.2                                          |
| Lead                                                                                                                                     | 0.005                                        |
| Nitrate (as N)                                                                                                                           | 2                                            |
| Sulfate                                                                                                                                  | 100                                          |
| Zinc                                                                                                                                     | 0.1                                          |
| <b>Electrolytes normally included in dialysis fluid</b>                                                                                  |                                              |
| Calcium                                                                                                                                  | 2 (0.05 mmol/l)                              |
| Magnesium                                                                                                                                | 4 (0.15 mmol/l)                              |
| Potassium                                                                                                                                | 8 (0.2 mmol/l)                               |
| Sodium                                                                                                                                   | 70 (3.0 mmol/l)                              |
| NOTE This table is reproduced from ISO 13959.                                                                                            |                                              |
| <sup>a</sup> A dialysis facility's Medical Director has the ultimate responsibility for ensuring the quality of water used for dialysis. |                                              |
| <sup>b</sup> Unless otherwise noted.                                                                                                     |                                              |

**Table B.2 — Maximum allowable levels of other trace elements in dialysis water**

| Contaminant | Maximum concentration<br>(mg/l) |
|-------------|---------------------------------|
| Antimony    | 0.006                           |
| Arsenic     | 0.005                           |
| Barium      | 0.1                             |
| Beryllium   | 0.0004                          |

| Contaminant                                   | Maximum concentration<br>(mg/l) |
|-----------------------------------------------|---------------------------------|
| Cadmium                                       | 0.001                           |
| Chromium                                      | 0.014                           |
| Mercury                                       | 0.0002                          |
| Selenium                                      | 0.09                            |
| Silver                                        | 0.005                           |
| Thallium                                      | 0.002                           |
| NOTE This table is reproduced from ISO 13959. |                                 |

**Table B.3 — Analytical test methods for chemical contaminants**

| Contaminant    | Analytical technique                                                                                                                                | Reference, method number                                                                           |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Aluminium      | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                               | ISO 17294-2:2003<br>American Public Health Assn, #3113                                             |
| Antimony       | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (platform)                                                                     | ISO 17294-2:2003<br>US EPA, #200.9                                                                 |
| Arsenic        | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (gaseous hydride)                                                              | ISO 17294-2:2003<br>American Public Health Assn, #3114                                             |
| Barium         | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                               | ISO 17294-2:2003<br>American Public Health Assn, #3113                                             |
| Beryllium      | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (platform)                                                                     | ISO 17294-2:2003<br>US EPA, #200.9                                                                 |
| Cadmium        | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                               | ISO 17294-2:2003<br>American Public Health Assn, #3113                                             |
| Calcium        | Inductively-coupled plasma mass spectrometry or<br>EDTA titrimetric method or<br>atomic absorption (direct aspiration) or<br>ion specific electrode | ISO 17294-2:2003<br>American Public Health Assn, #3500-Ca D<br>American Public Health Assn, #3111B |
| Total chlorine | DPD ferrous titrimetric method or<br>DPD colorimetric method<br>TMK/MTK colorimetric method                                                         | American Public Health Assn, #4500-CI F<br>American Public Health Assn, #4500-CI G                 |
| Chromium       | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (electrothermal)                                                               | ISO 17294-2:2003<br>American Public Health Assn, #3113                                             |

| Contaminant | Analytical technique                                                                                                                           | Reference, method number                                                                                                                       |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Copper      | Inductively-coupled plasma mass spectrometry or Atomic absorption (direct aspiration), or neocuproine method                                   | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Cu D                                          |
| Fluoride    | Ion chromatography or Ion selective electrode method or sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalenedisulfonate (SPADNS) method | ISO 10304-1:2007<br><br>ISO 10359-1:1992<br><br>American Public Health Assn, #4500-F- C<br>American Public Health Assn, #4500-F- D             |
| Lead        | Inductively-coupled plasma mass spectrometry or Atomic absorption (electrothermal)                                                             | ISO 17294-2:2003<br><br>American Public Health Assn, #3113                                                                                     |
| Magnesium   | Inductively-coupled plasma mass spectrometry or Atomic absorption (direct aspiration)<br>Ion chromatography                                    | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br><br>EPA300.7;1986                                                                |
| Mercury     | Flameless cold vapor technique (atomic absorption)                                                                                             | American Public Health Assn, #3112                                                                                                             |
| Nitrate     | Ion chromatography or Spectrophotometric method using sulfosalicylic acid or Cadmium reduction method                                          | ISO 10304-1:2007<br><br>ISO 7890-3:1988<br><br>American Public Health Assn, #4500-NO3 E                                                        |
| Potassium   | Inductively-coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or flame photometric method or ion specific electrode    | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-K D<br>American Public Health Assn, #3500-K E |
| Selenium    | Inductively-coupled plasma mass spectrometry or Atomic absorption (gaseous hydride), or atomic absorption (electrothermal)                     | ISO 17294-2:2003<br><br>American Public Health Assn, #3114<br>American Public Health Assn, #3113                                               |
| Silver      | Inductively-coupled plasma mass spectrometry or Atomic absorption (electrothermal)                                                             | ISO 17294-2:2003<br><br>American Public Health Assn, #3113                                                                                     |
| Sodium      | Inductively-coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or flame photometric method or ion specific electrode    | ISO 17294-2:2003<br><br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Na D                                          |

| Contaminant        | Analytical technique                                                                                             | Reference, method number                                                                          |
|--------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Sulfate            | Ion chromatography or<br>Turbidimetric method                                                                    | ISO 10304-1:2007<br>American Public Health Assn, #4500-SO42-E                                     |
| Thallium           | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (platform)                                  | ISO 17294-2:2003<br>US EPA, #200.9                                                                |
| Total heavy metals | Colorimetric                                                                                                     | European Pharmacopoeia, 2.4.8<br>US Pharmacopoeia, < 231 >                                        |
| Zinc               | Inductively-coupled plasma mass spectrometry or<br>Atomic absorption (direct aspiration), or<br>dithizone method | ISO 17294-2:2003<br>American Public Health Assn, #3111<br>American Public Health Assn, #3500-Zn D |

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## Water testing methodologies

Approved 22 September 2014 by  
Association for the Advancement of Medical Instrumentation

**Abstract:** The Technical Information Report (TIR) includes common test methods used to monitor hemodialysis water treatment systems and product water. The TIR identifies the contaminants; provides the maximum allowable levels and action levels from various standards (AAMI/ISO) and other references as applicable; describes symptoms that hemodialysis patients might experience with exposure to the contaminant; describes effects of the contaminant on hemodialysis equipment and water treatment systems; lists common test methodologies used for analysis/detection of the contaminant at the laboratory and clinic level; notes test interferences that can be associated with a specific test method.

**Keywords:** hemodialysis water, product water, chemical contaminants, test methods, test interference, clinical exposure symptoms, dialysis equipment, water treatment system

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Although the material presented in a TIR may need further evaluation by experts, releasing the information is valuable because the industry and the professions have an immediate need for it.

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A TIR is not subject to the same formal approval process as a standard. However, a TIR is approved for distribution by a technical committee and the AAMI Standards Board.

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Comments on this technical information report are invited and should be sent to AAMI, Attn: Standards Department, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633.

### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-556-6

| <b>Contents</b>                                           | <b>Page</b> |
|-----------------------------------------------------------|-------------|
| Glossary of equivalent standards.....                     | iv          |
| Committee representation.....                             | v           |
| Foreword.....                                             | vi          |
| Acknowledgment .....                                      | vi          |
| Introduction .....                                        | vii         |
| 1      Scope .....                                        | 1           |
| 2      Applicability and use .....                        | 1           |
| 3      Acronyms and definitions.....                      | 1           |
| 4      Guide to Table 1—Water testing methodologies ..... | 8           |
| Table 1 .....                                             | 9           |
| Cited references .....                                    | 44          |
| Bibliography .....                                        | 49          |

## **Glossary of equivalent standards**

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

**[www.aami.org/standards/glossary.pdf](http://www.aami.org/standards/glossary.pdf)**

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Renal Disease and Detoxification Committee

This technical information report was developed by the AAMI Renal Disease and Detoxification Committee. Committee approval of this technical information report does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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NOTE—Participation by federal agency representatives in the development of this technical information report does not constitute endorsement by the federal government or any of its agencies.

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## Foreword

This technical information report was developed by the AAMI Renal Disease and Detoxification Committee. The objective is to provide dialysis practitioners with additional information and background related to recommendations made in ANSI/AAMI/ISO and ANSI/AAMI standards, in particular, the contaminants in water, the test methodologies available and suitable for testing to the requirements of these standards to keep dialysis patients safe. Some of the methods are complex, requiring sophisticated instrumentation and these are noted as laboratory test methods to distinguish them from those that can be done at the clinic level. Maximum allowable levels as well as action levels where applicable are provided and the source of the limits noted. The limits are often based on those specified for drinking water with a safety margin to allow for the larger exposure volume of this water to hemodialysis patients. Agents that can interfere with the accuracy and validity of a given type of test method are noted where relevant. Any adverse effects of a contaminant on components of the water treatment or hemodialysis delivery systems are also covered. Emphasis is placed upon known toxicities to hemodialysis patients, but other contaminants that may affect the dialysis treatment are also provided.

This TIR is intended to be used as supplementary to other ANSI/AAMI/ISO and ANSI/AAMI standards and provides information in an easy-to-refer-to-and-use chart for quick reference and to better understand the requirements and their rationales.

As used within the context of this document, “should” indicates that among several possibilities one is recommended as particularly suitable without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but not prohibited. “May” is used to indicate that a course of action is permissible within the limits of the TIR. “Can” is used as a statement of possibility and capability. “Must” is used only to describe “unavoidable” situations, including those mandated by government regulations.

Suggestions for improving this TIR are invited. Comments and suggested revisions should be sent to Technical Programs, AAMI, 4301 N. Fairfax Dr., Suite 301, Arlington, VA 22203-1633.

NOTE This foreword does not contain provisions of AAMI TIR58, but does provide important information about the development and intended use of the document.

## Acknowledgment

The AAMI Renal Disease and Detoxification Committee would like to thank the team led by Jo-Ann B. Maltais, Ph.D. including Vern Taaffe and Organizational Member Liaisons Paul Smith and Mark Rolston, who worked tirelessly to bring this much needed TIR to completion.

## Introduction

While the ANSI/AAMI/ISO Standard 13959:2009 specifies the maximum allowable levels of chemical contaminants acceptable in water used for hemodialysis and the recommended frequency of testing, it does not necessarily provide all the information that would be useful to the hemodialysis clinic personnel regarding water testing. This TIR provides maximum allowable levels, notes clinical symptoms in dialysis patients exposed to the various contaminants, provides toxic levels where available and applicable, and lists the updated test methods and any interfering substances that can result in inaccurate analysis. In addition, while ANSI/AAMI/ISO 13959 provides a list of acceptable tests, these have often been replaced by more up-to-date methods and techniques that are now commonly used by the testing labs providing such analyses to the hemodialysis community. Given that the typical hemodialysis clinic personnel may not be skilled in or have the necessary knowledge of the test methods, this updated list will ensure that the hemodialysis clinic personnel can assess whether the testing lab is using the appropriate testing methodologies. Historically, the AAMI Renal Disease and Detoxification Committee has recommended certain acceptable levels based on known toxicities and/or EPA Drinking Water requirements, adding a safety margin based on the increased exposure volume for a hemodialysis patient during treatment. The committee has not evaluated methods for sensitivity and accuracy. Thus, there is a need, and a TIR is the appropriate vehicle to inform/educate the hemodialysis community regarding the nuances of testing for contaminants in water and what levels are known or suspected to be hazardous to the hemodialysis patient.

NOTE The Centers for Medicare and Medicaid Services (CMS) currently references ANSI/AAMI RD52, *Dialysate for Hemodialysis* and ANSI/AAMI RD62, *Water Treatment Equipment for Hemodialysis Applications*, in their Conditions for Coverage. These American National Standards have been superseded by ANSI/AAMI/ISO 11663, *Quality of dialysis fluid for hemodialysis and related therapies*, ANSI/AAMI/ISO 13959, *Water for hemodialysis and related therapies*, ANSI/AAMI/ISO 23500, *Guidance for the preparation and quality management of fluids for hemodialysis and related therapies*, and ANSI/AAMI/ISO 26722, *Water treatment equipment for hemodialysis applications and related therapies*.





# Testing methodologies for water

## 1 Scope

This Technical Information Report (TIR) identifies common contaminants as well as the test methods commonly used to monitor contaminants in a hemodialysis water treatment system and product water. The TIR will: 1) identify each contaminant with its chemical symbol, as applicable; 2) list maximum allowable levels and action levels as applicable as found in AAMI/ISO Standards and other pertinent references; 3) identify symptoms in hemodialysis patients associated with exposure to a given contaminant; 4) describe adverse effects of a contaminant on hemodialysis equipment and the water treatment system; and 5) identify test(s) used to detect the contaminants while describing the pros and cons of each method, e.g. interference elements.

This document in no way supersedes *Standard Methods for the Examination of Water and Wastewater*<sup>1</sup> but rather provides common test methods used within the dialysis industry. The reader is advised to reference FDA approval as appropriate or for those tests that CMS requires FDA approved methods (i.e. bacteria and endotoxin testing). This document excludes sampling recommendations. Check the manufacturer's instructions for use, test kit or test method instructions, AAMI and/or ISO documents, CMS regulations as applicable for sampling guidance.

## 2 Applicability and use

This TIR contains information intended to assist end users in making informed decisions regarding which test methodologies are useful to test for the presence of specific contaminants commonly found in water in settings where hemodialysis is delivered, allowable limits and action levels and substances that can interfere with accurate test results.

Disclaimer: Users of any selected test methodology must understand the level of sensitivity, precision, and accuracy and how the test results will correlate to the selected action level/maximum allowable limits.

## 3 Acronyms and definitions

For the purposes of this AAMI TIR, the following acronyms and definitions apply.

### 3.1

#### **AAMI**

Association for the Advancement of Medical Instrumentation

### 3.2

#### **accuracy**

closeness of agreement between a measured quantity value and a true quantity value of a measurement

NOTE A measurement is said to be more accurate when it has a smaller measurement error [bias].

### 3.3

#### **acid**

chemical substance having a pH of less than 7 that neutralizes alkalis, dissolves some metals, and turns litmus red; typically, a corrosive or sour-tasting liquid of this kind

### 3.4

#### **Act**

Federal Food, Drug, and Cosmetic Act which establishes the US Food and Drug Administration as the law enforcement agency with the authority to regulate food, drugs, and device manufacturing through a comprehensive Code of Federal Regulations (CFR)

### 3.5

#### **action level(s)**

#### **action limit(s)**

#### **control level(s)**

#### **control limit(s)**

concentration of a contaminant at which steps should be taken to interrupt the trend towards higher, unacceptable levels

### 3.6

#### **activated carbon**

carbon that has been oxidized with steam or carbon dioxide at 800 - 1000°C. The treatment results in a highly porous charcoal. These tiny holes give the charcoal a surface area of 300-2,000 m<sup>2</sup>/g, allowing liquids or gases to pass through the charcoal and interact with the exposed carbon. The carbon adsorbs or chemically reacts with a wide range of impurities and contaminants, including chlorine, organics, odors, and pigments

### 3.7

#### **adsorption**

attraction and subsequent attachment of atoms, ions, or molecules from a gas, liquid, or dissolved solid to a surface. This process creates a film of the *adsorbate* on the surface of the *adsorbent* (*Activated Carbon for example*)

### 3.8

#### **algae**

any of various chiefly aquatic, eukaryotic, photosynthetic organisms, ranging in size from single-celled forms to the giant kelp. Algae were once considered to be plants but are now classified separately because they lack true roots, stems, leaves, and embryos

### 3.9

#### **alkali**

basic, ionic salt of an alkali metal or alkaline earth metal chemical element. Alkali can also be defined as a base that dissolves in water. A solution of a soluble base has a pH greater than 7.0

### 3.10

#### **amphoteric**

chemical species that behaves both as an acid and as a base is called amphoteric. This property depends upon the medium in which the species is present

### 3.11

#### **anion**

ion carrying a negative charge. Negatively charged atom or molecule

### 3.12

#### **assay**

test for a particular contaminant or effect

### 3.13

#### **ASTM**

American Society for Testing and Materials

### 3.14

#### **bacteria**

very large group of microorganisms comprising one of the three domains of living organisms. They are prokaryotic, unicellular, and either free-living in soil or water or parasites of plants or animals

### 3.15

#### **base**

chemical substance having a pH greater than 7.0, that neutralizes acids to form salts, turns litmus blue, in aqueous solution, is slippery to the touch, tastes bitter and promotes certain chemical reactions (base catalysis)

### 3.16

#### **biofilm**

coating on the surfaces that consists of microcolonies of bacteria embedded in a protective extracellular matrix. The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants

Microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

NOTE 1 The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

NOTE 2 A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling. Accumulated biomass of bacteria and extracellular material that is tightly adhered to a surface and cannot be easily removed<sup>2</sup>

NOTE 3 Some microscopic organisms have the ability, when growing in water or water solutions or *in vivo* (e.g., the bloodstream), to adhere to a surface and then exude over themselves a polysaccharide matrix. The matrix contains cells, living and dead, as well as polysaccharide (sometimes referred to as glycocalyx) and prevents antimicrobial agents such as sterilants, disinfectants, and antibiotics, from reaching the microbial cells.

NOTE 4 The biomass may consist of one or multiple bacterial or yeast species or both

### **3.17**

#### **brackish water**

water containing dissolved solids in the range of 1000 – 15000 ppm

### **3.18**

#### **buffer**

solution that resists changes in pH when acid or alkali is added to it. Buffers typically involve a weak acid or alkali together with one of its salts

### **3.19**

#### **carcinogen /carcinogenic**

cancer causing substance

### **3.20**

#### **cation**

ion carrying a positive charge. Positively charged atom or molecule

### **3.21**

#### **chloramines**

organic compound containing a chlorine atom bonded to nitrogen, especially any of a group of sulfonamide derivatives used as antiseptics and disinfectants. Compounds formed by the reaction of aqueous chlorine with ammonia. Used in water treatment as an alternative or complementary agent to hypochlorite compounds (bleach)

### **3.22**

#### **chlorine, combined**

chlorine that is chemically combined, such as in chloramines compounds. Where chloramines are used to disinfect water supplies, chloramines is usually the principal component of combined chlorine

NOTE There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

### **3.23**

#### **chlorine, free**

dissolved molecular chlorine. Concentration of residual chlorine in water that is present as dissolved gas ( $\text{Cl}_2$ )

NOTE Three forms of free chlorine exist together in equilibrium. Their relative proportions are determined by the pH and temperature of the water. Chlorine can be present in water as dissolved molecular chlorine ( $\text{Cl}_2$ ), hypochlorous acid ( $\text{HOCl}$ ) and hypochlorite ion ( $\text{OCl}^-$ ).

### **3.24**

#### **chlorine, total**

sum of free and combined chlorine

NOTE Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

### 3.25

#### **chromatography**

method of separating and analyzing mixtures of chemicals. The separation of closely related compounds, by allowing a solution or mixture to seep through an absorbent (such as clay, gel, or paper) so each compound becomes absorbed into a separate, often colored layer

### 3.26

#### **colony forming unit (CFU)**

measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

NOTE Colonies can also form from groups of organisms when they occur in aggregates.

### 3.27

**colorimetric measurement** A means of measuring unknown chemical concentrations in water by measuring a sample's color intensity. The specific color of the sample, developed by addition of chemical reagents, is measured with a photoelectric colorimeter or is compared with "color standards" (disc, vial or chart) using or corresponding with known concentrations of the chemical

### 3.28

#### **contaminant**

substance that makes water impure

### 3.29

#### **Delta P ( $\Delta P$ )**

change in pressure, or pressure drop, that occurs across a piece of control equipment due to accumulation of material or fouling resulting in increased resistance

### 3.30

#### **dilution**

process of reducing the concentration of a solute in solution, usually achieved by adding/mixing with more water (solvent)

### 3.31

#### **disinfection**

process that kills most recognized pathogenic microorganisms but not necessarily all microbial forms, such as bacterial spores. or renders them inert by physical, thermal or chemical means

NOTE Disinfection processes are less lethal than sterilization and do not ensure the margin of safety associated with sterilization processes. This definition of "disinfection" is equivalent to low-level disinfection in the Spaulding classification. There are also intermediate and high-level disinfection categories in the Spaulding classification.

### 3.32

#### **dissolved solids**

name that refers to matter which was formerly solid but is now dissolved in water

### 3.33

#### **distilled water**

water that has many of its impurities removed through distillation. Distillation involves boiling the water and then condensing the steam into a clean container

Water that has been heated to the boiling point, vaporized to remove non-volatile impurities, cooled, condensed into a liquid condensate, and collected so that no impurities are reintroduced

### 3.34

#### **DPD**

N-diethyl-p-phenylene-diamine is a reagent used to measure residual chlorine in water

### 3.35

#### **electrolyte**

compound that ionizes when dissolved in suitable ionizing solvents such as water.

Ion capable of transferring or exchanging electrons. Upon dissociation of salts in water, electrolytes or charged ions result. These ions are responsible for the conductivity of a solution

### 3.36

#### element

substance that cannot be chemically interconverted or broken down into simpler substances and are primary constituents of matter. Each element is distinguished by its atomic number, i.e., the number of protons in the nuclei of its atoms. Elements are typically those found in the periodic table. The periodic table is a tabular arrangement of the chemical elements, organized on the basis of their atomic numbers, electron configurations, and recurring chemical properties

### 3.37

#### endotoxin

major component of the outer cell wall of gram-negative bacteria. Endotoxins are high molecular weight lipopolysaccharide complexes, which consist of a polysaccharide chain covalently bound to lipid A. They are heat-stable and is released from the cell wall upon lysis of the bacterial cell. Endotoxins can acutely activate both humoral and cellular host defenses, leading to a syndrome characterized by fever, shaking chills, hypotension, multiple organ failure and even death if allowed to enter the circulation in a sufficient dose

Long –term exposure to low levels of endotoxin has been implicated in a chronic inflammatory response, which may contribute to some of the long-term complications seen in hemodialysis (RD62).

Endotoxins specifically interact with Limulus amoebocyte lysate (LAL).<sup>3</sup>

### 3.38

#### endotoxin retentive filter (ETRF)

membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

NOTE 1 The performance of an endotoxin-retentive filter is usually expressed as the logarithmic reduction value (LRV) defined as  $\log_{10}$  (inlet concentration)/(outlet concentration).

NOTE 2 Endotoxin-retentive filters may be configured in a cross-flow or dead-end mode. Some endotoxin retentive filters also remove endotoxins by adsorption.

NOTE 3 Endotoxin removal can be accomplished by size exclusion or adhesion to the membrane surface of the filter.

NOTE 4 Because endotoxins differ in their activity on a mass basis, their activity is referred to as a standard endotoxin. The relationship between mass of endotoxin and its activity varies with both the lot of LAL and the lot of control standard endotoxin being used. The relationship between mass and activity of endotoxin has been designated as 10 EU/ng since the endotoxin standards were harmonized in 1983.

### 3.39

#### endotoxin units (EU)

units assayed by the Limulus amoebocyte lysate (LAL) test when testing for endotoxins

NOTE 1 Because the activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to as a standard endotoxin unit as extracted from *Escherichia coli* O113:H10.

NOTE 2 In some countries, endotoxin concentrations are expressed as international units (IU) and in others as endotoxin units (EU). EU and IU are equivalent.

### 3.40

#### EPA

U.S. Environmental Protection Agency

### 3.41

#### feed water

water supplied to a water treatment system or an individual component of a water treatment system

### 3.42

#### filtration

mechanical or physical process to separate solid particulates from fluids

### 3.43

#### fungus

large group of eukaryotic microorganisms that includes yeast, mold and mushrooms. Some species have been implicated as contaminants of water used in hemodialysis

**3.44****grains per gallon (GPG)**

unit of measure for hardness 17.1 mg/L = 1 GPG

**3.45****halogen**

any of a group of five chemically related nonmetallic elements found in group 17 of the periodic table and includes fluorine, chlorine, bromine, iodine, and astatine

**3.46****hardness**

concentration of calcium and magnesium ions in water expressed as parts per million (ppm) or milligrams per liter (mg/L) of calcium carbonate ( $\text{CaCO}_3$ ) equivalents

**3.47****heavy metals**

metallic elements with atomic weight greater than 5, e.g. mercury, chromium, cadmium, arsenic, and lead. Heavy metals can be toxic to living organisms at low concentrations and tend to accumulate in the food chain.

**3.48****hydrophilic**

having a strong affinity (liking) for water

**3.49****hydrophobic**

having a strong aversion (dislike) for water. Not readily absorbing water; insoluble in water

**3.50****hypochlorous acid (HOCl)**

dominant reaction product of chlorine in water at a pH of less than 7, however, as you continue to lower the pH, especially below a pH of 2, the dominant chlorine species is chlorine not hypochlorous acid

**3.51****Langelier saturation index (LSI)**

calculated number used to predict the calcium carbonate ( $\text{CaCO}_3$ ) stability in water; that is, whether the water will precipitate, dissolve, or be in equilibrium with calcium carbonate

**3.52****limulus amoebocyte lysate Test**

assay used to detect endotoxin. Exploits the immune response of the horseshoe crab to endotoxin. Reagent made by lysing amoebocytes of the horseshoe crab, *Limulus polyphemus*, and used to detect and quantify endotoxin

NOTE 1 The detection method uses the chemical response of an extract from blood cells of the horseshoe crab (*Limulus polyphemus*) to endotoxin.

**3.53****mass spectrometry (MS)**

instrumental method for identifying the chemical constitution of a substance by means of the separation of gaseous ions according to their differing mass and charge

**3.54****nephelometric turbidity unit (NTU)**

standard unit of measurement used to measure turbidity in water. It is a measure of the light scattering effect of fine suspended particles in a light beam

**3.55****PPM****parts per million**

way to quantify very low concentrations of substances. For example, 1 ppm is equivalent to 1 milligram per liter (abbreviated as mg/L)

**3.56****pH (potential of hydrogen)**

expression of the acidity of a solution; the negative logarithm of the hydrogen ion concentration (pH 1 very acidic; pH 14, very basic; pH 7, neutral). e.g., pH 5 is 10 times the acidity of 6 and 100 times the acidity of 7. pH is a measure of intensity and not capacity. It is the logarithm of the reciprocal of the hydrogen ion concentration of a solution. The neutral point of 7 indicates the presence of equal concentrations of free hydrogen and free hydroxide ions. Number denoting level of acidity or alkalinity

NOTE 1 The pH scale is logarithmic and runs from 0 to 14; the neutral point is 7. Numbers below 7.0 indicate acidity, and those above 7.0 indicate alkalinity

**3.57****potable water**

water which is considered safe and fit for human consumption, culinary and domestic purposes and meets the requirements of the health authority having jurisdiction. Water that has been treated and delivered in a manner so that meets the requirements as suitable for drinking

**3.58****precision**

precision of a measurement system, also called reproducibility or repeatability, is the degree to which repeated measurements under unchanged conditions show the same results. Closeness of agreement between measured values obtained by replicate measurements on the same or similar objects under specified conditions

**3.59****product water**

water produced by a water treatment system or individual component thereof

**3.60****raw water**

untreated water from wells or from surface sources or any water before it reaches a water treatment device or process

**3.61****RO (reverse osmosis)**

process for the removal of dissolved ions from water, in which pressure is used to force the water through a semi-permeable membrane, which will transmit the water but reject most other suspended and dissolved materials. It is called reverse osmosis because mechanical pressure is used to force the water to flow in the direction that is the reverse of natural osmosis, namely from the dilute to the concentrated solution

Membrane separation process for purifying water that is based on molecular sieving and ionic rejection and that is effective in removing ions as well as dissolved organic contaminants with molecular weights above 100

**3.62****Safe Drinking Water Act (SDWA)**

Safe Drinking Water Act (SDWA) is the principal federal law in the United States intended to ensure safe drinking water for the public. Pursuant to the act, the Environmental Protection Agency (EPA) is required to set standards for drinking water quality and oversee all states, localities, and water suppliers who implement these standards

**3.63****sensitivity**

lowest concentration of a substance that can be reliably measured by a given analytical method

**3.64****softened water**

water that is treated to reduce hardness minerals to 1.0 GPG (17.1 mg/L) or less, expressed as calcium carbonate

**3.65****Standard Methods for the Examination of Water and Wastewater**

joint publication of the American Public Health Association, American Water Works Association, and the Water Pollution Control Federation outlining the procedures used to analyze the impurities in water and wastewater

**3.66****total dissolved solids (TDS)**

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

NOTE TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of  $\text{CaCO}_3$ , NaCl (equivalents in ppm, KCl, or 442 equivalents, in milligrams per liter (mg/L). 442 is a solution of sodium sulfate (40%), sodium bicarbonate (40%), and sodium chloride (20%) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.

### **3.67**

#### **total organic carbon (TOC)**

amount of carbon covalently bound in organic compounds in a water sample. The measurement of carbon dioxide produced from organic matter when a water sample is atomized in a combustion chamber. Measure of both natural and synthetic organic substances that are residual from natural plant and animal decomposition

### **3.68**

#### **trihalomethanes (THM)**

group of organic chemicals known to be carcinogenic in more than trace amounts which are produced during the process of chlorination. They reduce the germicidal activity of chlorine in alkaline water

### **3.69**

#### **turbidity**

measure of the amount of finely divided suspended matter in water, which causes the scattering and absorption of light rays. Turbidity is usually reported in arbitrary Nephelometric turbidity units (NTU) determined by measurements of light scattering. NTU should not exceed 0.5 in potable water. Turbidity can protect bacteria from disinfection

### **3.70**

#### **virus**

smallest form of life known to be capable of producing disease or infection, usually considered to be of large molecular size. Viruses multiply by assembly of component fragments in living cells, rather than by cell division, as do most bacteria. Being parasitic, infectious microbes, they are much smaller than bacteria

## **4 Guide to Table 1—Water testing methodologies**

### **4.1 Column 1**

Lists elemental, organic and microbial contaminants with their chemical symbol or commonly used acronym. These are used for testing during the design, operational monitoring, and/or troubleshooting phases of a water treatment and distribution system lifecycle.

### **4.2 Column 2**

Lists Maximum Allowable Levels, Action Limits and/or clinically significant levels for each contaminant, as applicable, from ANSI/AAMI, ANSI/AAMI/ISO and other reputable documents and references.

### **4.3 Column 3**

Describes the documented clinical symptoms and levels of the contaminant at which the symptoms occur when a hemodialysis patient is exposed.

### **4.4 Column 4**

Describes effects the contaminant can have on the various components involved in production of water used to prepare dialysis fluid/dialysate and delivery of dialysis fluid/dialysate to the hemodialysis patient during a hemodialysis treatment. Systems affected could include the water treatment system, concentrate preparation and storage, water and concentrate delivery systems and dialysate proportioning by the hemodialysis machine.

### **4.5 Column 5**

Describes the various test methods that can be used to detect or test for a given contaminant. The test method should be sensitive enough to detect below the maximum allowable contaminant levels as described in the applicable ANSI/AAMI or ANSI/AAMI/ISO standard. Known interference problems associated with certain test methodologies are noted.



**Table 1—Water testing methodologies**

| 1                               | 2                                     | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 5                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels              | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Test Methodologies                                                                                                                                                                                                                                                                                                                            |
| Aluminum (Al)                   | 0.01 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <p><b><u>Observed in the setting of hemodialysis:</u></b><br/>Uptake of aluminum from dialysate prepared with water contaminated with aluminum is associated with anemia, dialysis encephalopathy syndrome (usually fatal).<sup>4,5,6</sup></p> <p>10-13 mEq/L deferoxamine (DFO) test result can indicate clinical problems such as bone disease in dialysis patients.</p> <p>The combination of a baseline immunoreactive parathyroid hormone level of less than 200 mEq/mL and a change in serum aluminum value of 200 ng/mL after deferoxamine is 90% specific and has a positive predictive value of 85% for aluminum toxicity.<sup>7</sup></p> <p>Aluminum toxicity may be chronic or acute.</p> <p>Symptoms are varied and include:</p> <p>Neurological:<br/>speech disorders, personality</p> | <p>Aluminum is a large amphoteric molecule meaning that in different pH environments aluminum presents in different forms and causes different problems for water system components.</p> <p>Aluminum's major problem is fouling or interfering with the performance of water system components such as GAC (granular activated carbon) tanks and ROs (reverse osmosis membranes).</p> <p>&gt;0.1 mg/L as colloidal aluminum can cause fouling<sup>8</sup></p> <p>Aluminum can leach from aluminum containing pump components or aluminum silicate sand filters inappropriately used in the water treatment systems or loops.</p> | <p><b><u>Onsite Testing:</u></b><br/>Colorimeter/aluminon reagent method.</p> <p><b><u>Laboratory Testing:</u></b><br/>Inductively coupled plasma spectrometry –Mass Spectrometry (ICP-MS)<sup>9</sup></p> <p>Atomic absorption (electrothermal)]<sup>10</sup></p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

\* SW = U.S. EPA Solid Waste Methods; SM = Standard Methods; CMS = Centers for Medicare and Medicaid Services

NOTE Unless a chemical contaminant is part of the AAMI profile, an EPA testing laboratory that is licensed by their state for the contaminants in question should be consulted.

**Table 1—Water testing methodologies**

| 1                               | 2                                      | 3                                                                                                                                                                                                                                                                                                                                                                                                                              | 4                                         | 5                                                                                                                                                                                                                                                                                         |
|---------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels               | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                     | Effect of Contaminant on Dialysis Systems | Test Methodologies                                                                                                                                                                                                                                                                        |
|                                 |                                        | <p>changes, hallucinations, seizures, agitation, confusion, obtundation or dialysis dementia, muscle spasms, and intellectual impairment abnormal EEG coma, encephalopathy that can be fatal.<sup>11</sup></p> <p>Musculo-skeletal - bone pain, fractures, osteomalacia, osteodystrophy, myoclonic jerks.</p> <p>Hematological: microcytic anemia, EPO resistance or hyporesponse.</p> <p>Lowest toxicity level 0.06 mg/L.</p> |                                           |                                                                                                                                                                                                                                                                                           |
| Antimony (Sb)                   | 0.006 mg/L<br>ANSI/AAMI/ISO 13959:2009 | No data to indicate concern in a hemodialysis setting.                                                                                                                                                                                                                                                                                                                                                                         | N/A                                       | <p><b>Onsite Testing:</b><br/>N/A</p> <p><b>Laboratory Testing:</b><br/>Inductively coupled plasma spectrometry –Mass spectrometry (ICP-MS)<sup>9</sup></p> <p>Atomic absorption (platform)<sup>12</sup></p> <p>Can also be measured as part of the total heavy metals with a maximum</p> |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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**Table 1—Water testing methodologies**

| 1                               | 2                                      | 3                                                                                                                                                                                                            | 4                                                                                                                                                                                                                                                                                                                                                                                                                             | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels               | Clinical Symptoms Associated with Exposure                                                                                                                                                                   | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                     | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                 |                                        |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                               | allowable level of <0.1mg/L. <sup>13</sup><br>Usually included in laboratory AAMI water quality compliance tests.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Arsenic (As)                    | 0.005 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <b><u>Observed from all types of exposure:</u></b><br>Fatigue, loss of energy, vomiting, diarrhea, burning abdominal pain, throat constriction, dehydration, pulmonary edema and liver failure <sup>14</sup> | Presence of arsenic in particulate (insoluble) form may contribute to fouling large pore size membrane filters (i.e. ultrafilters, microfilters). Water sources containing high levels of dissolved organic carbon may reduce the effectiveness of membrane filtration of arsenic due to membrane fouling. <sup>15</sup><br><br>In combination with aluminum in a low pH environment (<6.0) may foul water system components. | <b><u>Onsite Testing:</u></b><br>Despite the test not being EPA approved analytical method anodic stripping voltammetry appears to be suited for onsite analysis for the presence of arsenic in water. <sup>16</sup><br><br>1. Test Strips<br>2. Color comparator (disc)<br><br><b><u>Laboratory Testing:</u></b><br>Inductively coupled plasma/mass spectrometry (ICP/MS) <sup>9,17</sup><br><br>Inductively coupled plasma/atomic emission spectrometry (ICP/AES) <sup>18,19,20</sup><br><br>Graphite furnace atomic absorption spectrometry (GFAA) <sup>12, 10, 21,22</sup><br><br>Gaseous hydride atomic adsorption (GHAA) <sup>23,24,25,26</sup><br><br>Anodic stripping voltammetry (ASV) <sup>27</sup> |

- \* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.
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NOTE Unless a chemical contaminant is part of the AAMI profile, an EPA testing laboratory that is licensed by their state for the contaminants in question should be consulted.

**Table 1—Water testing methodologies**

| 1                               | 2                                       | 3                                                                                                                                                                 | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 5                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                | Clinical Symptoms Associated with Exposure                                                                                                                        | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Test Methodologies                                                                                                                                                                                                                                                                                                                                                      |
|                                 |                                         |                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p>The test methodologies outlined above are most suitable in the laboratory setting as dialysis clinics may not have the equipment necessary to perform the test.</p> <p>Can also measure as part of the total heavy metals with a maximum allowable level of &lt;0.1mg/L.<sup>13</sup></p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |
| Barium (Ba)                     | 0.1 mg/L<br>ANSI/AAMI/ISO<br>13959:2009 | <p><b><u>Observed from all types of exposure:</u></b><br/>Vomiting, diarrhea, abdominal pain, tremors, convulsions, hypertension, cardiac arrest<sup>14</sup></p> | Concentrated barium in quantities of 2ppm or greater will likely precipitate out within cation exchange softening or deionization, reverse osmosis and distillation. In the presence of sulfates (typically >2ppm) barium sulfate precipitate will most likely form. Barium sulfate can lead to coating and fouling of the system or its components. Barium sulfate removal can be very difficult due to compound being very insoluble often leading to replacement of membrane modules, resin or other system components. | <p><b><u>Onsite Testing:</u></b><br/>N/A</p> <p><b><u>Laboratory Testing:</u></b><br/>ICP-MS<sup>9</sup></p> <p>Atomic absorption (electrothermal)<sup>10</sup></p> <p>Can also be measured as part of the total heavy metals with a maximum allowable level of &lt;0.1mg/L<sup>13</sup></p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |

- \* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.
- \* SW = U.S. EPA Solid Waste Methods; SM = Standard Methods; CMS = Centers for Medicare and Medicaid Services

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**Table 1—Water testing methodologies**

| 1                               | 2                                       | 3                                                                                                                                                                                                         | 4                                                                                  | 5                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                | Clinical Symptoms Associated with Exposure                                                                                                                                                                | Effect of Contaminant on Dialysis Systems                                          | Test Methodologies                                                                                                                                                                                                                                                                                                                                        |
|                                 |                                         |                                                                                                                                                                                                           | Scales RO membranes and interferes with DI resin regeneration.                     |                                                                                                                                                                                                                                                                                                                                                           |
| Beryllium (Be)                  | 0.0004 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <b><u>Observed from all types of exposure:</u></b><br>Acute toxicity 130ug/l<br>Chronic toxicity 5ug/l; <sup>1</sup> No data to indicate a concern in a hemodialysis setting.                             | N/A                                                                                | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>ICP-MS <sup>9</sup><br><br>Atomic absorption (platform) <sup>12</sup><br><br>Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup><br><br>Usually included in laboratory AAMI water quality compliance tests. |
| Cadmium (Cd)                    | 0.001 mg/L<br>ANSI/AAMI/ISO 13959:2009  | <b><u>Observed from all types of exposure:</u></b><br>Vomiting, diarrhea, abdominal cramps, dry throat, cough, dyspnea (difficulty breathing), headache, bone decalcification, shock, coma. <sup>14</sup> | Can interfere with GAC adsorption.<br>Foul RO membranes in certain pH environments | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Electrothermal atomic adsorption spectrometric method (EAASM) <sup>28</sup><br><br>Flame atomic absorption spectrometric (FAAS) <sup>28, 29</sup>                                                                                                                        |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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NOTE Unless a chemical contaminant is part of the AAMI profile, an EPA testing laboratory that is licensed by their state for the contaminants in question should be consulted.

**Table 1—Water testing methodologies**

| 1                               | 2                                                                                   | 3                                                                                                                                                                                                                                            | 4                                                       | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                                                            | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                   | Effect of Contaminant on Dialysis Systems               | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                 |                                                                                     |                                                                                                                                                                                                                                              |                                                         | <p>Inductively coupled plasma method (ICP)<sup>20, 31</sup></p> <p>Anodic stripping voltammetry can provide acceptable results but is prone to interference from copper, silver, gold and organic compounds.<sup>32</sup></p> <p>In the absence of EAASM or ICP and if a lower precision is acceptable the dithizone method may be suitable.<sup>1</sup></p> <p>Can also be measured as part of the total heavy metals with a maximum allowable level of &lt;0.1mg/L.<sup>13</sup></p> <p>ICP-MS,<sup>9</sup></p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |
| Calcium (Ca <sup>++</sup> )     | AAMI RD62/2006 & ANSI/AAMI/ISO 13959:2009<br>Ca <sup>++</sup> 2 mg/L (0.05 mmol/L). | <p><b><u>Observed from all types of exposure:</u></b></p> <p>Excess calcium can cause nausea, vomiting, muscle weakness, severe headaches, skin flushing and low or high blood pressure, lethargy, flushing, itching, tachycardia, coma,</p> | Will foul RO membranes and reduce RO percent rejection. | <p><b><u>Onsite Testing:</u></b><br/>N/A</p> <p><b><u>Laboratory Testing:</u></b><br/>Usually included in laboratory AAMI water quality compliance tests.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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**Table 1—Water testing methodologies**

| 1                               | 2                        | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 4                                         | 5                                                                                                                                                                                                                                                                    |
|---------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Effect of Contaminant on Dialysis Systems | Test Methodologies                                                                                                                                                                                                                                                   |
|                                 |                          | <p>pancreatitis, abnormal bone mineralization, soft tissue calcification leading to blocked blood vessel cells, gangrene, loss of limbs.<sup>33</sup> Calcium plays a critical role in bone disorders associated with renal disease.</p> <p><b><u>Observed in the setting of hemodialysis:</u></b><br/> Hypercalcemia—too much <math>\text{Ca}^{++}</math> in dialysate can lead to adverse GI effects such as nausea, vomiting, anorexia and central nervous system effects such as confusion, irritability and potentially result in coma.<sup>33</sup></p> <p>Lowest toxicity level 88 mg/L as <math>\text{Ca}^{++}</math><br/> A 10ppm difference in Ca in dialysis water can result in a 20% error in dialysate <math>\text{Ca}^{++}</math>; A 2ppm difference results in a less than 5% error risk in dialysate <math>\text{Ca}^{++}</math>.</p> <p>If left unmanaged, calcium (<math>\text{Ca}^{++}</math>) levels in water can alter the final dialysate delivered to the patient. For</p> |                                           | <p><b><u><math>\text{Ca}^{++}</math></u></b><br/> Ethylenediaminetetraacetic acid (EDTA) titrimetric method<sup>29, 34</sup>.<br/> Atomic absorption (direct aspiration)</p> <p>Ion specific electrode</p> <p>ICP (direct aspiration)</p> <p>ICP-MS.<sup>9</sup></p> |

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**Table 1—Water testing methodologies**

| 1                                          | 2                                                                                                      | 3                                                                                                                                                                                                                                                                                                     | 4                                                                                                                                                                                                                                                                                                               | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant            | Maximum Allowable Levels                                                                               | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                            | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                       | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                            |                                                                                                        | example: 10ppm of Ca++ in water used to prepare dialysate solutions could increase the dialysate Ca++ concentration by as much as 20% (assuming a target dialysate prescription of 2.5mEq/L). Similarly, 2ppm of Ca++ in water could increase the dialysate Ca++ concentration by as much as 4%.      |                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Chlorine (Cl <sub>2</sub> )<br>Free, Total | Free chlorine 0.5 mg/L<br>AAMI RD62:2006<br><br>Total chlorine 0.1 mg/L<br>ANSI/AAMI/ISO<br>13959:2009 | <b><u>Observed from all types of exposure:</u></b><br>Shortness of breath, headache, malaise, nausea, vomiting, abdominal pain, back pain, or chest pain, cardiac arrhythmia, hypertension, hyperkalemia, methemoglobinemia. Symptoms are due to protein denaturing and hemolysis of red blood cells. | Removed using carbon adsorption; sodium metabisulfite; ascorbic acid; ultraviolet light; or redox alloy media. Removing chlorine causes these media (including UV lamps) to be exhausted over time and require replacement.<br><br>Has been shown to cause degradation damage to certain types of RO membranes. | <b><u>Onsite Testing:</u></b><br>Syringaldazine (FACTS) based test strips for free chlorine.<br><br>Tetramethylbenzidine (TMB) based chlorine test strips for free chlorine.<br><br>Thio-Michler's Ketone (TMK/MTK) based chlorine test strips for total chlorine.<br><br>DPD (N-Diethyl-p-phenylenediamine) ferrous colorimetric/titrimetric based assay or test strips for free and/or total chlorine. Manganese & organic chloramines interference is a common issue with DPD tests.<br><br>Amperometric titration inline continuous |

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**Table 1—Water testing methodologies**

| 1                                | 2                                                   | 3                                                                                                                                                                                                                                                                                                                                                                                                 | 4                                                                                                                                                                                                                                                                                                                  | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant  | Maximum Allowable Levels                            | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                        | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                          | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                  |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                    | monitoring instrument for free and/or total chlorine.<br><br><b>Laboratory Testing:</b><br>Not recommended due to volatility of chlorine.                                                                                                                                                                                                                                                                                                                                                |
| Chloramines (NH <sub>2</sub> Cl) | Total chlorine 0.1 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <b>Observed from all types of exposure:</b><br>Symptoms include: shortness of breath, headache, malaise, nausea, vomiting, abdominal pain, back pain, or chest pain, cardiac arrhythmia, hypertension, hyperkalemia, and methemoglobinemia. Symptoms are due to protein denaturing and hemolysis of red blood cells.<br><br>Hemolytic anemia <sup>35</sup><br><br>Lowest toxicity level 0.25 mg/L | Removed using carbon adsorption; sodium metabisulfite; ascorbic acid; ultraviolet light; or redox alloy media. Removing chloramines causes these media (including UV lamps) to be exhausted over time and require replacement.<br><br>Has been shown to cause degradation damage to certain types of RO membranes. | <b>Onsite Testing:</b><br>Thio-Michler's Ketone (TMK/MTK) based chlorine test strips for total chlorine.<br><br>DPD (N-Diethyl-p Phenylenediamine) Ferrous Colorimetric/Titrimetric Total Chlorine. Manganese & organic chloramines interference is a common issue with DPD tests.<br><br>Amperometric titration inline continuous monitoring instrument for free and/or total chlorine.<br><br><b>Laboratory Testing:</b><br>Not recommended due to volatility of chlorine/chloramines. |
| Chromium (Cr)                    | 0.014 mg/L<br>ANSI/AAMI/ISO 13959:2009              | <b>Observed from all types of exposure:</b><br>Skin diseases <sup>14</sup>                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                    | <b>Onsite Testing:</b><br><u>N/A</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**Table 1—Water testing methodologies**

| 1                               | 2                                                                                                                                                                                                                                                                                                                                                                                                                                     | 3                                                                                                                                                                                                                                                                                                                    | 4                                         | 5                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                                                                                                                                                                                                                                                                                                                                                                                                              | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                           | Effect of Contaminant on Dialysis Systems | Test Methodologies                                                                                                                                                                                                                                                                                                                   |
|                                 | This level is set at 28% above the U.S. EPA maximum allowable level in drinking water as it is not expected to pass from dialysate made with water at this level to blood.                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                      | N/A                                       | <b><u>Laboratory Testing:</u></b><br>Atomic absorption (electrothermal) <sup>10</sup> .<br>ICP-MS. <sup>9</sup><br>Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup>                                                                                                  |
| Disinfectant Byproducts (DBP)   | Not defined by AAMI/ISO. <u>EPA Drinking Water Standard Maximum Contaminant Level (MCL)</u> :<br>Disinfectant byproducts result from the use of chemical disinfectants such as chlorine, chloramines, chlorine dioxide, or ozone to disinfect source water to improve the quality of drinking water for public health protection purposes. When these disinfectants combine with naturally occurring materials in the water including | <b><u>Observed from all types of exposure:</u></b><br>Possible cancer causing agents (THM, HAA5, Bromate).<br><br>Bromate may cause gastrointestinal and central nervous system problems, kidney failure and irreversible hearing loss. Chlorite may induce adverse neurodevelopmental effects and anemia (per EPA). | N/A                                       | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Trihalomethanes (THM) <sup>36</sup> [U.S. EPA 500 series methods]<br><br>Haloacetic acids (HAA5) <sup>37</sup> [U.S. EPA 550 series methods]<br><br>Bromate <sup>38</sup> [U.S. EPA 317 method]<br><br>Chlorite <sup>39</sup> [U.S. EPA 327 method] |

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**Table 1—Water testing methodologies**

| 1                                    | 2                                                                                                                                                                                                              | 3                                                                                                                                                                      | 4                                                                                          | 5                                                                                                                                                                    |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant      | Maximum Allowable Levels                                                                                                                                                                                       | Clinical Symptoms Associated with Exposure                                                                                                                             | Effect of Contaminant on Dialysis Systems                                                  | Test Methodologies                                                                                                                                                   |
|                                      | <p>microorganisms, disinfectant byproducts are formed which include:</p> <p>Trihalomethanes (THM) 80 ppb MCL</p> <p>Haloacetic Acids (HAA5) 0 ppb MCL.</p> <p>Bromate 10 ppb MCL</p> <p>Chlorite 1 ppm MCL</p> |                                                                                                                                                                        |                                                                                            |                                                                                                                                                                      |
| Organic Chloramines (RNHCl)          | Not defined by AAMI/ISO.                                                                                                                                                                                       | <b><u>Observed from all types of exposure:</u></b><br>Marginally mutagenic. Cytotoxic and cytostatic.                                                                  | Low biocidal activity. Shown to cause false positive for certain chlorine tests, e.g. DPD. | <p><b><u>Onsite Testing:</u></b><br/>Colormetric test using DPD (N-Diethyl-p phenylenediamine) and MonochlorF methods.</p> <p><b>Laboratory Testing:</b><br/>N/A</p> |
| Chlorine Dioxide (ClO <sub>2</sub> ) | <p>Not defined by AAMI/ISO.</p> <p>EPA maximum contaminant level (MCL) is 0.8 mg/L</p>                                                                                                                         | <p><b><u>Observed in the setting of hemodialysis:</u></b><br/>A limited study of 17 patients unknowingly treated with dialysis water prepared by carbon adsorption</p> | Has been shown to cause degradation damage to certain types of RO membranes.               | <p><b><u>Onsite Testing:</u></b><br/>Chlorine dioxide specific test strips (may need to use glycine to neutralize chlorine interference).</p>                        |

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**Table 1—Water testing methodologies**

| 1                               | 2                                               | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4                                         | 5                                                                                                                                                             |
|---------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                        | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Effect of Contaminant on Dialysis Systems | Test Methodologies                                                                                                                                            |
|                                 | Test to be certain amount is less than 0.8 mg/L | <p>and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects [Ames and Stratton, 1987]<sup>40</sup>. In that study, the dialysis water used to prepare dialysis fluid contained 0.02 mg/L to 0.08 mg/L of chlorite ions and no detectable chlorate ions. However, the patient population was small, and potentially important hematological parameters were not measured.</p> <p><b><u>Observed from all types of exposure:</u></b><br/> Michael et al. (1981)<sup>41</sup> found that chlorine dioxide in drinking water rapidly disappeared from the stored water (within 2-4 hours) and chlorite levels concomitantly increased. Numerous animal studies have examined toxicity of chlorine dioxide and chlorite. These studies show a decrease in weight, decrease in motor activity, decreased erythrocyte counts, hemoglobin levels, and hematocrit; increased methemoglobin levels (males) and decreased</p> |                                           | <p><b><u>Laboratory Testing:</u></b><br/> Ion Chromatography.</p> <p>Spectrometry (colorimetry)</p> <p>Amperometric Titration</p> <p>Iodometric Titration</p> |

- \* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.
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|---------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels              | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                     | Effect of Contaminant on Dialysis Systems                                                                                                                                                 | Test Methodologies                                                                                                                                                                                                                                                                                                                |
|                                 |                                       | <p>methemoglobin levels (females). Histologic alterations of the stomach consisted of squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation and edema.</p> <p>EPA lists anemia and nervous system effects under health effects of chlorite.</p>                                                                                                                                                                    |                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                   |
| Copper (Cu)                     | 0.10 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <p><b><u>Observed in the setting of hemodialysis:</u></b><br/>Nausea, vomiting, diarrhea, and stomach cramps, chills, flushing, headache, hypotension, leukocytosis, hemolytic anemia, metabolic acidosis and pancreatitis<sup>11, 42</sup> Liver and kidney damage with high level long term exposure.</p> <p>Can also produce acute and sometimes fatal hemolysis.<sup>43</sup></p> <p>Lowest toxicity level 0.49 mg/L.<sup>44, 45</sup></p> | <p>In normal pH ionized heavy metals do not present problems for dialysis water treatment systems.</p> <p>Copper leaches into the water if the pH of the water is acidic<sup>46</sup></p> | <p><b><u>Onsite Testing:</u></b><br/>Bi-cinchonate reagent with color disc test.</p> <p><b><u>Laboratory Testing:</u></b><br/>Atomic absorption (direct aspiration)<sup>47</sup></p> <p>Neocuproine method<sup>48</sup></p> <p>ICP-MS.<sup>9</sup></p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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|---------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels             | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Effect of Contaminant on Dialysis Systems                                                                                                                                                         | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Fluoride (F <sup>-</sup> )      | 0.2 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <p><b><u>Observed in the setting of hemodialysis:</u></b></p> <p>Overfluoridation at levels up to 50mg/L (50ppm) were reported to have caused hemodialysis patient death<sup>49</sup> [CDC, 1980]</p> <p><b><u>Observed from all types of exposure:</u></b></p> <p>Shortness of breath, chest pain, nausea, vomiting, diarrhea, hypotension, headache, weakness, numbness, itching, parathyroid disease, muscle twitching, seizures. Patients exposed to high levels of fluoride may show evidence of uremic bone disease such as osteosclerosis.<sup>42, 50</sup></p> <p>Patients exposed to very high levels of fluoride far exceeding the levels of fluorinated drinking water may experience ventricular fibrillation and/or death.<sup>49</sup> Levels of fluoride as high as 22.5 mg/L resulted in 12 of 15</p> | <p>Literature review did not demonstrate any known effects on dialysis systems due to fluoride.</p> <p>The RO membrane's ability to reject decreases substantially as the pH drops below 6.0.</p> | <p><b><u>Onsite Testing:</u></b> N/A</p> <p><b><u>Laboratory Testing:</u></b></p> <p>Ion-selective electrode method<sup>52, 53</sup></p> <p>SPADNS colorimetric method<sup>53, 54</sup></p> <p>Complexone Method<sup>55</sup></p> <p>Ion-selective electrode flow injection analysis<sup>56, 57</sup></p> <p>Ion chromatography</p> <p>Part of the AAMI Profile Testing for Chemical Contaminants in Dialysis Water.</p> <p>Tube Test Kits</p> <p>Drop Count and diskette comparator test</p> <p>Digital Colorimeter</p> <p>Usually included in laboratory AAMI water quality compliance tests.</p> |

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|---------------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant             | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                      | Effect of Contaminant on Dialysis Systems               | Test Methodologies                                                                                                                                                                                             |
|                                             |                          | patients becoming ill; 3 died from ventricular fibrillation due to the use of exhausted deionizer resin beds. <sup>51</sup> There is no consensus as to whether there is an association between fluoride exposure and uremic bone disease.      |                                                         |                                                                                                                                                                                                                |
| Iron Oxide (FeO <sub>2</sub> )              |                          | <b><u>Observed from all types of exposure:</u></b><br>Ferric Iron (Fe <sup>+++</sup> ) can cause hypoxia. Excessive iron storage can occur in the liver with GI distress, hemolytic anemia and liver damage.                                    | Can cause fouling of water treatment system components. | <b><u>Onsite Testing:</u></b><br>Phenanthroline reagent with:<br><br>- Color comparator disc<br><br>- Iron test strips<br><br><b><u>Laboratory Testing:</u></b><br>Standard methods such as mass spectroscopy. |
| Iron (Fe <sup>2+</sup> , Fe <sup>3+</sup> ) | N/A                      | <b><u>Observed from all types of exposure:</u></b><br>Ferric Iron (Fe <sup>+++</sup> ) can cause hypoxia. Excessive iron storage can occur in the liver with GI distress, hemolytic anemia and liver damage.<br><br>Can be fatal. <sup>11</sup> | Can cause fouling of water treatment system components. | <b><u>Onsite Testing:</u></b><br>Phenanthroline reagent with:<br><br>- Color comparator disc<br><br>- Iron test strips                                                                                         |

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|---------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                                          | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                               | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                 |                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                         | <b>Laboratory Testing:</b><br>Standard methods such as mass spectroscopy                                                                                                                                                                                                                                                                                                                                                                               |
| Lead (Pb)                       | 0.005 mg/L<br>ANSI/AAMI/ISO 13959:2009                            | <b><u>Observed from all types of exposure:</u></b><br>Neurological damage including personality changes, metallic taste, anorexia, constipation and hemolytic anemia can occur. <sup>14, 42</sup><br><br>Abdominal pain and muscle weakness have been attributed to lead levels of 52 µg/L to 65 µg/L in dialysis fluid. <sup>58</sup> No toxicity at levels below 5ug/L.<br><br>High levels can interfere with blood cell formation and vitamin D metabolism. Accumulation can cause brain damage and even death. <sup>14</sup> | Literature review did not demonstrate any known effects on dialysis systems due to lead.<br><br>Generally, ionized heavy metals do not present problems for dialysis water treatment systems providing the pH is with normal range 6-8. | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b>Laboratory Testing:</b><br><br>Atomic-absorption spectrophotometry; <sup>59,60</sup> electrothermal <sup>28</sup><br><br>Differential pulse anodic stripping voltammetry <sup>61</sup><br><br>Dithizone Method <sup>62</sup><br><br>ICP-MS <sup>9</sup><br><br>Part of the AAMI Profile for Testing for Chemical Contaminants in Dialysis Water<br>Tube Test Kits<br>Color comparator disk with reagent |
| Magnesium (Mg <sup>++</sup> )   | ANSI/AAMI/ISO 13959:2009<br>Mg <sup>++</sup> 4 mg/L (0.15 mmol/L) | <b><u>Observed from all types of exposure:</u></b><br>Excess magnesium can cause                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Will foul RO membranes and reduce RO percent rejection.                                                                                                                                                                                 | <b><u>Onsite Testing:</u></b><br>N/A                                                                                                                                                                                                                                                                                                                                                                                                                   |

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| Chemical Element or Contaminant                                             | Maximum Allowable Levels                | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                        | Effect of Contaminant on Dialysis Systems                                                                                                                     | Test Methodologies                                                                                                                                                                                                                                           |
|                                                                             |                                         | nausea, vomiting, muscle weakness, severe headaches, skin flushing and low or high blood pressure, lethargy, flushing, itching, tachycardia, coma, pancreatitis, abnormal bone mineralization, soft tissue calcification leading to blocked blood vessels, gangrene, loss of limbs. <sup>33</sup> |                                                                                                                                                               | <b>Laboratory Testing:</b><br>Usually included in laboratory AAMI water quality compliance tests.<br><br><b>Mg<sup>++</sup></b><br>Atomic Absorption (direct aspiration). <sup>47</sup><br>ICP (direct aspiration).<br>ICP-MS <sup>9</sup>                   |
| Manganese (Mn <sup>2++</sup> ) and Manganese Screening (MN <sup>2++</sup> ) | N/A                                     | <b>Observed from all types of exposure:</b><br>Irritates mucous membranes.                                                                                                                                                                                                                        | Manganese oxide can foul GAC beds, other system components. Oxidized forms of manganese such as manganese oxide gives a false positive DPD test for chlorine. | <b>Onsite Testing:</b><br>Color comparator disc with reagent<br>Digital colorimeter with reagent<br>Standard Method using potassium iodide and sodium arsenite additives.<br><br><b>Laboratory Testing:</b><br>Standard methods such as ICP-MS or equivalent |
| Mercury (Hg)                                                                | 0.0002 mg/L<br>ANSI/AAMI/ISO 13959:2009 | <b>Observed from all types of exposure:</b><br>Acute: Vomiting and diarrhea, salivating, abdominal pain, burning                                                                                                                                                                                  | N/A                                                                                                                                                           | <b>Onsite Testing:</b><br>N/A                                                                                                                                                                                                                                |

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| Chemical Element or Contaminant                              | Maximum Allowable Levels                | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                 | Effect of Contaminant on Dialysis Systems                                       | Test Methodologies                                                                                                                                                                                                                                                                                                           |
|                                                              |                                         | mouth. <sup>14</sup><br><br>Chronic: Gum inflammation, mental disturbances, neurological problems <sup>14</sup>                                                                                                                                                                                                                            |                                                                                 | <b>Laboratory Testing:</b><br>Flameless cold vapor technique (atomic absorption) <sup>63</sup><br><br>ICP-MS <sup>9</sup><br><br>Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup><br><br>Usually included in laboratory AAMI water quality compliance tests. |
| Nitrate (NO <sub>3</sub> <sup>-</sup> )<br>(as Nitrogen (N)) | 2 mg/L<br>ANSI/AAMI/ISO<br>13959:2009   | <b>Observed in the setting of hemodialysis:</b><br>Acute hemolysis, hemolytic anemia, persistent hypotension, nausea, vomiting, lethargy, weakness, mental confusion, cyanosis (bluish skin, gums, lips, fingernail beds. <sup>48, 42</sup> Also causes methemoglobinemia. <sup>43</sup><br><br>Lowest toxicity level 21 mg/L as Nitrogen. | N/A                                                                             | <b>Onsite Testing:</b><br>N/A<br><br><b>Laboratory Testing:</b><br>Cadmium reduction method <sup>64</sup><br><br>Ion chromatography <sup>57</sup><br><br>Usually included in laboratory AAMI water quality compliance tests.                                                                                                 |
| Ozone (O <sub>3</sub> )                                      | <0.1 ppm<br>ANSI/AAMI/ISO<br>26722:2009 | <b>Observed from all types of exposure:</b><br>Becker et. Al. <sup>65</sup> report suppression of the immune system response at levels as low as 0.1 mg/L.                                                                                                                                                                                 | May degrade many plastic materials including PVC and elastomeric seals/O-rings. | <b>Onsite Testing:</b><br><br>Ozone in water test strips<br><br>Indigo colorimetric method                                                                                                                                                                                                                                   |

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| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                   | Test Methodologies                                                                                                                                                                                                                                                                                                                                     |
|                                 |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p>ORP (Redox) probe method</p> <p>Colormetric using DPD (N-Diethyl-p phenylenediamine) and MonochlorF methods (water must be free of other disinfectants).</p> <p>Amperometric analyzers</p> <p><b>Laboratory Testing:</b><br/>Not recommended due to short half-life of ozone in water.</p>                                                          |
| pH                              | 6.0 – 8.0*               | <p><b>Observed in the setting of hemodialysis:</b><br/>Kidney failure is associated with failure of hydrogen ion excretion and bicarbonate regeneration, causing metabolic acidosis. Dialysate provides a source of buffer to correct the metabolic acidosis either directly as bicarbonate or indirectly as acetate, citrate or lactate. Metabolic acidosis is associated with respiratory adaptation, manifested by hyperventilation. Inadvertent exposure to dialysate deficient in buffer capacity is associated with</p> | <p>The rate of the oxidation-reduction reaction responsible for the removal of chlorine and chloramines slows as pH increases. The pH of the water can interfere with RO membrane performance as well. Generally low pH water corrodes plumbing fixtures and faucets. Basic (pH&gt;7) water can cause incrustation and scaling problems.</p> <p>Low pH water could cause bicarbonate concentrates and dialysate to precipitate as well.</p> | <p><b>Onsite Testing:</b><br/>- pH Strips*<br/>- Color disc comparator*<br/>- pH Met</p> <p>pH test devices were so inaccurate they continue to influence perceptions of current devices with new technologies that have eliminated most if not all of the earlier problems.</p> <p><b>Laboratory Testing:</b><br/>Standard methods to assess both</p> |

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**Table 1—Water testing methodologies**

| 1                               | 2                        | 3                                                                                                                                                                                           | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                  | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                 |                          | more profound respiratory adaptation, and if the patient's ability to maintain hyperventilation is impaired, because of fatigue or obtundation, profound acidemia may occur <sup>95</sup> . | Removal of fluoride by RO is reduced at acidic pH.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | alkalinity and acidity*.<br><br>pH should be tested onsite due to a sample holding time of only 15 minutes.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Phosphorus (P)                  | N/A                      | <b><u>Observed in the setting of hemodialysis:</u></b><br>No known documented toxicity in hemodialysis.                                                                                     | Phosphate compounds are used in potable water purification for: <sup>76</sup> <ul style="list-style-type: none"> <li>Sequestering</li> <li>Deflocculation</li> <li>Chlorine stabilization</li> </ul> Phosphates may provide a nutrient source for microorganisms promoting increased biological growth in the water supply and subsequent bio-fouling of water purification. <sup>15</sup><br>Phosphate can load anion resins and cause fouling. <sup>75</sup><br>Interferes or prevents cation exchange water softening.<br>Combines with KDF byproducts to form alkali elements. | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Vanadomolybdophosphoric acid colorimetric method <sup>66</sup><br><br>Stannous Chloride Method <sup>67</sup><br><br>Ascorbic acid method <sup>68</sup><br><br>Automated Ascorbic Acid Reduction <sup>69</sup><br><br>Flow Injection analysis of Orthophosphate <sup>70</sup><br><br>Manual digestion and flow injection analysis for total phosphorus <sup>71</sup><br><br>In-line UV/Persulfate digestion and flow injection analysis for total phosphorus <sup>72</sup> |

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**Table 1—Water testing methodologies**

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|--------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant            | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                              | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                     | Test Methodologies                                                                                                                                                                                                                                                                                                               |
|                                            |                          |                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                               | ICP-MS. <sup>9</sup><br><br>Persulfate method for simultaneous determination of total nitrogen and total phosphorus <sup>72</sup><br><br>Ion chromatography <sup>74</sup><br><br>1. Ascorbic Acid Photometer<br>2. Tube Test Kits<br>3. Drop Count with disk comparator                                                          |
| Phosphate (PO <sub>4</sub> <sup>3-</sup> ) | N/A                      | <u><b>Observed in the setting of hemodialysis:</b></u><br>No known documented toxicity in hemodialysis. | Phosphate compounds are used in potable water purification for: <sup>76</sup><br>Sequestering<br>Deflocculation<br>Chlorine stabilization<br><br>Phosphates may provide a nutrient source for microorganisms promoting increased biological growth in the water supply and subsequent bio-fouling of water purification. <sup>15</sup><br><br>Phosphate can load anion resins | <u><b>Onsite Testing:</b></u><br>N/A<br><br><u><b>Laboratory Testing:</b></u><br>Vanadomolybdophosphoric acid colorimetric method <sup>66</sup><br><br>Stannous Chloride Method <sup>67</sup><br><br>Ascorbic acid method <sup>68</sup><br><br>Automated Ascorbic Acid Reduction <sup>69</sup><br><br>Flow Injection analysis of |

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**Table 1—Water testing methodologies**

| 1                               | 2                                               | 3                                                                                                                                                                                                                                                           | 4                                                                                                                                                            | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                        | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                  | Effect of Contaminant on Dialysis Systems                                                                                                                    | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                 |                                                 |                                                                                                                                                                                                                                                             | and cause fouling. <sup>75</sup><br><br>Interferes or prevents cation exchange water softening.<br><br>Combines with KDF byproducts to form alkali elements. | Orthophosphate <sup>70</sup><br><br>Manual digestion and flow injection analysis for total phosphorus <sup>71</sup><br><br>In-line UV/Persulfate digestion and flow injection analysis for total phosphorus <sup>72</sup><br><br>Persulfate method for simultaneous determination of total nitrogen and total phosphorus <sup>73</sup><br><br>Ion chromatography <sup>74</sup><br><br>1. Ascorbic Acid Photometer<br>2. Tube Test Kits<br>3. Drop Count with disk comparator |
| Potassium (K)                   | 8 mg/L (0.2 mmol/L)<br>ANSI/AAMI/ISO 13959:2009 | <b><u>Observed from all types of exposure:</u></b><br>Hypokalemia—too little potassium resulting in abnormal heart rhythms, arrhythmia, cardiac arrest, muscle weakness, fatigue, EKG changes, arrhythmias, cardiac arrest and death often without warning. | N/A                                                                                                                                                          | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Atomic absorption (direct aspiration) <sup>47</sup><br><br>Flame photometric method <sup>778</sup><br>Ion specific electrode <sup>77</sup>                                                                                                                                                                                                                                                  |

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| 1                                           | 2                                                                                                                                                                       | 3                                                                                                                                                                                                                                                                                                                                                        | 4                                                                                                                                                                                                                                                                | 5                                                                                                                                                                                             |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant             | Maximum Allowable Levels                                                                                                                                                | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                               | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                        | Test Methodologies                                                                                                                                                                            |
|                                             |                                                                                                                                                                         | Can have an adverse effect on hemodialysis patients if present in excess in dialysate.<br><br>Hyperkalemia—muscle weakness, heart may stop; most often no symptoms.                                                                                                                                                                                      |                                                                                                                                                                                                                                                                  | ICP (direct aspiration)<br><br>ICP-MS. <sup>9</sup><br><br>Usually included in laboratory AAMI water quality compliance tests.                                                                |
| Potassium Permanganate (KMNO <sub>4</sub> ) | N/A                                                                                                                                                                     | <b><u>Observed from all types of exposure:</u></b><br>Potassium permanganate is an oxidizing agent that can cause hemolysis of red blood cells. It also stains hands and clothing as it is reduced to MnO <sub>2</sub> . Clothing stains may be washed away using acetic acid.<br><br>Skin stains, which are typically brown, disappear within 48 hours. | Highly oxidative element that GAC prefers to chloramines thus it interferes with chloramines adsorption.<br><br>Will damage RO membranes with moderate exposure<br><br>Potassium permanganate can give a positive test result in both DPD- and MTK-based assays. | <b><u>Onsite Testing:</u></b><br>Cold Periodate reagent with Color comparator disc<br><br><b><u>Laboratory Testing:</u></b><br>N/A                                                            |
| Selenium (Se)                               | 0.09 mg/L<br>ANSI/AAMI/ISO 13959:2009<br><br>Set at “no transfer level”. This is above the U.S. EPA maximum allowable level since no passage from dialysate to blood is | <b><u>Observed from all types of exposure:</u></b><br>Loss of hair and nails, dyspnea (difficulty breathing), nausea <sup>14</sup>                                                                                                                                                                                                                       | N/A                                                                                                                                                                                                                                                              | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Atomic absorption (gaseous hydride <sup>23</sup> or electrothermal) <sup>10</sup><br><br>ICP-MS <sup>9</sup> |

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| Chemical Element or Contaminant | Maximum Allowable Levels                | Clinical Symptoms Associated with Exposure                                                                                                                                                                            | Effect of Contaminant on Dialysis Systems                                                                                                                                                      | Test Methodologies                                                                                                                                                                                                                                                                                                                                               |
|                                 | expected to occur at this level.        |                                                                                                                                                                                                                       |                                                                                                                                                                                                | Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup><br><br>Usually included in laboratory AAMI water quality compliance tests.                                                                                                                                                                      |
| Silica (Si)                     | N/A                                     | N/A                                                                                                                                                                                                                   | Added to water for corrosion inhibition, iron and manganese control and as a coagulant. Can cause fouling of water treatment system pre-treatment components and result in RO membrane scaling | Heteropoply Blue Amino Acid<br><br>Comparative Test Kits<br><br>Photometer                                                                                                                                                                                                                                                                                       |
| Silver (Ag)                     | 0.005 mg/L<br>ANSI/AAMI/ISO 13959: 2009 | <b><u>Observed from all types of exposure:</u></b><br>Vomiting, diarrhea, shock, vertigo (dizziness), convulsions. <sup>14</sup> Can cause permanent blue-gray discoloration of skin and eyes (argyria). <sup>1</sup> | N/A                                                                                                                                                                                            | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Atomic absorption (electrochemical) <sup>10</sup><br><br>ICP-MS <sup>9</sup><br><br>Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup><br><br>Usually included in laboratory AAMI water quality compliance tests. |

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|------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant          | Maximum Allowable Levels                         | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                 | Effect of Contaminant on Dialysis Systems                                                           | Test Methodologies                                                                                                                                                                                                                                                                                                                           |
| Sodium (Na)                              | 70 mg/L (3.0 mmol/L)<br>ANSI/AAMI/ISO 13959:2009 | <p><b><u>Observed from all types of exposure:</u></b><br/>Increased thirst, headache, hypertension, crenation (shriveling of RBCs)—hypernatremia.</p> <p>Nausea, vomiting, headache, mental confusion, tremors, seizures—hyponatremia, also termed “dialysis disequilibrium syndrome”.<sup>42, 80</sup><br/>Other symptoms of sodium imbalance are pulmonary edema, shortness of breath, tachycardia, and coma.</p> <p>Lowest toxicity level 300 mg/L.</p> | N/A                                                                                                 | <p><b><u>Onsite Testing:</u></b><br/>N/A</p> <p><b><u>Laboratory Testing:</u></b><br/>Atomic absorption (direct aspiration)<sup>47</sup><br/>Flame photometric method<sup>81</sup><br/>Ion specific electrode<br/>ICP (direct aspiration)<br/>ICP-MS<sup>9</sup><br/>Usually included in laboratory AAMI water quality compliance tests.</p> |
| Sulfate (SO <sub>4</sub> <sup>-2</sup> ) | 100 mg/L ANSI/AAMI/ISO 13959:2009.               | <p><b><u>Observed from all types of exposure:</u></b><br/>High levels can cause laxative effect. Nausea, vomiting and metabolic acidosis at levels &gt;200 mg/ and disappear below 100mg/L.<sup>42, 50</sup></p> <p>Lowest toxicity level 200 mg/L.</p>                                                                                                                                                                                                    | Major contaminant in influent municipal water supplies; removed by reverse osmosis or deionization. | <p><b><u>Onsite Testing:</u></b><br/>N/A</p> <p><b><u>Laboratory Testing:</u></b><br/>Turbidimetric method<sup>79</sup><br/>Ion chromatography<sup>57</sup><br/>Usually included in laboratory AAMI water quality compliance tests.</p>                                                                                                      |

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|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant          | Maximum Allowable Levels                                                                                                              | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                  | Effect of Contaminant on Dialysis Systems                                                                                                                                          | Test Methodologies                                                                                                                                                                                                                                                                                                                                        |
| Sulfite (SO <sub>3</sub> <sup>-2</sup> ) |                                                                                                                                       | <b><u>Observed from all types of exposure:</u></b><br>Causes asthma like symptoms if inhaled.                                                                                                                                               | Used to remove disinfectants such as chlorine and chlorine dioxide from influent water. Forms sulfates or chlorides on reacting with oxidizing agents. Can be removed by RO or DI. | Iodometric color disc                                                                                                                                                                                                                                                                                                                                     |
| Thallium (Tl)                            | 0.002 mg/L<br>ANSI/AAMI/ISO 13959:2009                                                                                                | <b><u>Observed in the setting of hemodialysis:</u></b><br>There is no data to indicate concern in a dialysis setting.                                                                                                                       | N/A                                                                                                                                                                                | <b><u>Onsite Testing:</u></b><br>N/A<br><br><b><u>Laboratory Testing:</u></b><br>Atomic absorption (platform) <sup>12</sup><br><br>ICP-MS <sup>9</sup><br><br>Can also be measured as part of the total heavy metals with a maximum allowable level of <0.1mg/L. <sup>13</sup><br><br>Usually included in laboratory AAMI water quality compliance tests. |
| Total Hardness (CaCO <sub>3</sub> )      | 1 grain/gal (17 mg/L)<br>Unless otherwise specified by the manufacturer of the reverse osmosis equipment.<br>ANSI/AAMI/ISO 23500:2011 | <b><u>Observed from all types of exposure:</u></b><br>Excess water hardness due to high calcium or magnesium levels above the AAMI maximum levels can cause “hard water syndrome” in dialysis patients. .<br>Acute symptomology of includes | Daily test post softener per ANSI/AAMI/ISO 23500, Table C.1, <sup>84</sup><br><br>Will foul RO membranes and reduce RO percent rejection.                                          | <b><u>Onsite Testing:</u></b><br>Water Hardness Test Strips<br><br>Ethylenediaminetetraacetic acid (EDTA) Titrimetric Method <sup>82</sup>                                                                                                                                                                                                                |

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| Chemical Element or Contaminant | Maximum Allowable Levels             | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                  | Effect of Contaminant on Dialysis Systems                       | Test Methodologies                                                                                                                                                                                                                                                                                                                                              |
|                                 |                                      | nausea and vomiting, headache, muscular weakness, flushing, lethargy, pruritus, tachycardia, severe hypertension leading to vasodilation, and coma. Chronic symptoms appear as abnormal bone mineralization, soft tissue calcifications, and pancreatitis. <sup>82,83</sup> |                                                                 |                                                                                                                                                                                                                                                                                                                                                                 |
| Zinc (Zn)                       | 0.10 m/L<br>ANSI/AAMI/ISO 13959:2009 | <b><u>Observed from all types of exposure:</u></b><br>Chronic anemia, hemolytic anemia, nausea, vomiting, fever and chills; methemoglobinemia <sup>11,85</sup><br><br>Lowest toxicity level 0.2 mg/L. <sup>44,45</sup>                                                      | Zinc oxide can interfere with carbon and ion exchange softener. | <b><u>Onsite Testing:</u></b><br>- Zincon reagent with color comparator disc<br>- Digital colorimeter with Zincon reagent<br><br><b><u>Laboratory Testing:</u></b><br><br>Atomic absorption (direct aspiration) <sup>48</sup><br><br>ICP-MS <sup>9</sup><br><br>Zincon <sup>86</sup><br><br>Usually included in laboratory AAMI water quality compliance tests. |

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| Chemical Element or Contaminant | Maximum Allowable Levels                                                                                            | Clinical Symptoms Associated with Exposure                      | Effect of Contaminant on Dialysis Systems                                                                                                                        | Test Methodologies                                                                                                                                                                                                                                       |
| <b>Organics:</b>                |                                                                                                                     |                                                                 |                                                                                                                                                                  |                                                                                                                                                                                                                                                          |
| Total Organic Carbon (TOC)      | N/A                                                                                                                 | N/A                                                             | N/A                                                                                                                                                              | N/A                                                                                                                                                                                                                                                      |
| Tannins & Lignin (HPLC)         | <2 PPM*                                                                                                             | <b><u>Observed from all types of exposure:</u></b><br>Acidosis. | Causes fouling of pretreatment components affecting performance and if allowed to reach the RO will foul membranes and provide a food source for microorganisms. | <b><u>Onsite Testing:</u></b><br>Organic assays are available but cannot differentiate between the different species of organics; thus will give a TOC result.<br><br><b><u>Laboratory Testing:</u></b><br>Standard Method such as radio diffusion assay |
| Turbidity (NTU)                 | 1 Nephelometric Turbidity Unit (NTU)*<br>unless the manufacturer's instructions for use allow for a different level | N/A                                                             | Indicator for rate of component and RO membrane fouling. Measures clarity of water (suspended particles).                                                        | <b><u>Onsite Testing:</u></b><br>- Turbidimeter also called Nephelometer which measures scattering of light by particles in the sample.<br><br><b><u>Laboratory Testing:</u></b><br>N/A                                                                  |
| Silt Density Index (SDI)        | < 5*<br>* RO membranes show very low fouling at a feed                                                              | N/A                                                             | Membrane fouling is the main cause of permeate flux decline and loss of product quality in reverse osmosis (RO) systems, so                                      | <b><u>Onsite Testing:</u></b><br>A Silt Density Index (SDI) test measures the time required to filter a fixed volume of water through a                                                                                                                  |

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| Chemical Element or Contaminant  | Maximum Allowable Levels                                                | Clinical Symptoms Associated with Exposure                                | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Test Methodologies                                                                                                                                                                                                                                                                                           |
|                                  | SDI of less than 5 providing microbiological growth is moderate or low. |                                                                           | <p>fouling control should dominate RO system design and operation.</p> <p>Fouling by particulates (silt), bacteria and organics generally affects the first components in the water system the most.</p> <p>Scaling is worsened with more concentrated feed solutions; therefore the last components in the water system (RO) are most affected, because they are exposed to the most concentrated feed water.</p> <p>RO membranes show very low fouling at a feed SDI of less than 5 providing microbiological growth is moderate or low.</p> | <p>standard 0.45µm microfiltration membrane with a constant given pressure of 30 psi (2,07 bar). The difference between the initial time and the time of a second measurement after normally 15 minutes (after silt-built up) represents the SDI value.</p> <p><b><u>Laboratory Testing:</u></b><br/>N/A</p> |
| Langelier Saturation Index (LSI) | N/A                                                                     | <b><u>Observed from all types of exposure:</u></b><br>Hard water syndrome | The LSI is probably the most widely used indicator of water scale potential. It is purely an equilibrium index and deals only with the thermodynamic driving                                                                                                                                                                                                                                                                                                                                                                                   | Water analysis to include data on pH, conductivity, alkalinity, temperature and total hardness is required to be able to use the formula for determination of LSI.<br>LSI = pH – pH <sub>s</sub> . See links such as                                                                                         |

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|---------------------------------|--------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                 |                          |                                            | <p>force for calcium carbonate scale formation and growth. It provides no indication of how much scale or calcium carbonate will actually precipitate to bring water to equilibrium. Determination of the LSI requires data on pH, conductivity, total dissolved solids, alkalinity, temperature and total hardness of the water being used.</p> <p>If LSI is negative: No potential to scale, the water will dissolve <math>\text{CaCO}_3</math>.</p> <p>If LSI is positive: Scale can form and <math>\text{CaCO}_3</math> precipitation may occur.</p> <p>If LSI is close to zero: Borderline scale potential. RO membranes show very low fouling at a feed SDI of less than 5 providing microbiological growth is moderate or low.</p> <p>Water quality or changes in</p> | <p><a href="http://www.lenntech.com/ro/index/langelier-explanation.htm">http://www.lenntech.com/ro/index/langelier-explanation.htm</a> for the complete formula.</p> <p><b>Onsite Testing:</b><br/>Typically done by the water treatment system manufacturer/installer to determine what type of water pretreatment may be needed in the system. Test kits and instrumentation may be required to gather all the data needed.</p> <p><b>Laboratory Testing:</b><br/>Some of the data required to determine the LSI can be gleaned from a typical water analysis done by laboratories qualified to do such testing. However, temperature at least will likely need to be measured on site within the dialysis setting.</p> |

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**Table 1—Water testing methodologies**

| 1                               | 2                                                                                                                                                                                                                                            | 3                                                                                                                                                                                                                                                                                                                                                                                                                         | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 5                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                                                                                                                                                                                                                     | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                           |
|                                 |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                           | <p>temperature, or evaporation could change the index.</p> <p>RO membranes, piping and filters in the water distribution system are subject to fouling due to accumulation of <math>\text{CaCO}_3</math> (scaling). This can also result in metal corrosion.</p>                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Microbiology</b>             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                              |
| Bacteria                        | <p><u>Water</u></p> <p>&lt;100 CFU/mL (max allowable level); 50 CFU/mL (action level)<br/>ANSI/AAMI/ISO 23500:2011</p> <p>&lt;200 CFU/mL (max allowable level); 50 CFU/mL (action level)<br/>ANSI/AAMI RD 52:2004<br/>CMS VTags 256-V257</p> | <p><b><u>Observed in the setting of hemodialysis:</u></b><br/>Symptoms range from those associated with the chronic inflammatory response to bacteremia (no symptoms or chills and fever) to sepsis.<sup>43</sup></p> <p>Sepsis symptoms can include fever, hyper or hypotension, rapid heart rate, rapid breathing rate, abnormally high or low number of white blood cells.<sup>87</sup></p> <p>Nausea and vomiting</p> | <p>Microorganisms can proliferate to such an extent as to affect water system component performance and contaminate downstream distribution and delivery systems for dialysis water and dialysate/dialysis fluid prepared from such water.</p> <p>The ability of bacteria to grow through membranes and past brine seals with non-full-fit membranes and form biofilm in water and ultimately dialysate/dialysis fluid prepared from such water increases the patient risk for pyrogenic</p> | <p><b><u>On-Site Testing:</u></b><br/>Dip Samplers are not recommended;<sup>88</sup> requires independent verification by an outside testing laboratory.</p> <p><b><u>Laboratory Testing:</u></b><br/>Heterotrophic or Standard Plate Count (HPC/SPC)<br/>Spread Plate<br/>Membrane Filtration.</p> <p>Media:<sup>89, 90</sup><br/>TSA (Tryptic Soy Agar)<br/>Plate Count Agar<br/>Standard Methods Agar</p> |

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**Table 1—Water testing methodologies**

| 1                               | 2                                                                                                            | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 4                                                                                                                                                                                                                                                                                                                                                                                              | 5                                                                                                                                                                                                                                                                                 |
|---------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels                                                                                     | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                                                                                                      | Test Methodologies                                                                                                                                                                                                                                                                |
|                                 |                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | reactions, and chronic microinflammation leading to both acute and chronic comorbidities and mortality.                                                                                                                                                                                                                                                                                        | Incubation: 35°C, 48hrs<br>Media: <sup>91 92</sup><br>TGEA (Tryptone Glucose Extract Agar)<br>R2A (Reasoner's R2A)<br>Incubation: 17-23°C, 7 days                                                                                                                                 |
| Endotoxin                       | <u>Water</u><br><br><0.25EU/mL (max allowable level); 0.125 EU/mL (action level)<br>ANSI/AAMI/ISO 23500:2011 | <u><b>Observed in the setting of hemodialysis:</b></u><br>Similar to bacterial symptoms above.<br><br>Highly contaminated water can lead to contaminated dialysate/dialysis fluid which can cause a rapid patient reaction (fever and chills) within 2 minutes of initiating dialysis; complement-mediated reactions are more delayed (15–30 minutes) in onset. <sup>94</sup><br><br>However, use of even grossly contaminated dialysis solution usually has no acute clinical consequences; the higher the bacterial and endotoxin | Endotoxins in the pretreatment side of the RO are not problematic because the RO will exclude >99%.<br><br>The organisms that manage to grow through or pass through the RO membrane can establish biofilms in the downstream water distribution system and dialysis machines.<br><br>Biofilm bacteria will generate endotoxin at the end of their life cycle and be dispersed into the water. | <u><b>On-Site Testing:</b></u><br>Typically Gel Clot, single tube method<br><br><u><b>Laboratory Testing:</b></u><br>LAL (Limulus Amoebocyte Lysate) test <sup>93</sup><br><br>Kinetic test(chromogenic or turbidimetric)<br><br>Gel Clot Test<br><br>Recombinant Factor C assays |

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**Table 1—Water testing methodologies**

| 1                               | 2                        | 3                                                                                                                                                                                                                                                                      | 4                                                                                                                                                                                                                                                                                                        | 5                                                                                                                                                                                                                               |
|---------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                             | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                                                | Test Methodologies                                                                                                                                                                                                              |
|                                 |                          | levels are, the greater the risk is of a reaction. <sup>93</sup><br><br>Hypotension, nausea, vomiting, fever and chills. <sup>42</sup>                                                                                                                                 | The endotoxins if present in the water used to prepare dialysate can pass through the dialyzer membrane directly to the patient's blood via backfiltration, causing pyrogenic reactions or chronic micro-inflammation if not removed prior to the dialyzer by a bacteria and endotoxin retentive filter. |                                                                                                                                                                                                                                 |
| Algae                           | No limits specified.     | <b><u>Observed from all types of exposure:</u></b><br>Unknown except those containing Cyanobacteria, which produces several toxins, neurotoxins, or hepatotoxins (CDC).<br><br>May give pyrogenic reactions no known association with concentration; blue green algae. | A multicelled organism that presents multiple problems for water systems components including accumulation on surfaces of transparent filter cartridge housing or tubing exposed to natural light.                                                                                                       | Sight<br>Microscopic analysis; no recommended limits<br>Bluegreen algal toxins should not be in the treated water.<br>LC/MS<br><br>Mouse bio-assay.<br><br>Time-resolved fluoroimmunoassay (TR-FIA), ELISA, GC-ECD, HPLC, GC-MS |
| Mold                            | No limits specified.     | <b><u>Observed from all types of exposure:</u></b><br>Unknown.<br>Fungemia (fever, rigors).                                                                                                                                                                            | Common infestations usually include the walls of storage or mixing tanks.                                                                                                                                                                                                                                | Should be part of the total count (Use HPC limits)                                                                                                                                                                              |
| Fungus                          | No limits specified.     | <b><u>Observed from all types of exposure:</u></b><br>Unknown<br>Fungemia.                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                          | Culture                                                                                                                                                                                                                         |

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**Table 1—Water testing methodologies**

| 1                               | 2                        | 3                                                                                                                                                                                                                                                                                                                                     | 4                                                                                                                                                                                                                                                                        | 5                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                                                                                                                                                                                                                                            | Effect of Contaminant on Dialysis Systems                                                                                                                                                                                                                                | Test Methodologies                                                                                                                                                                                                                                                                                                                                                                                                |
| Biofilm                         | Not specified.           | <u><b>Observed from all types of exposure:</b></u><br>Unknown.                                                                                                                                                                                                                                                                        | Fouling and ultimately complete breakdown of water treatment system components, product water delivery systems and hemodialysis machines.<br><br>Can reduce efficiency of equipment, be a source of bacteria and endotoxin to downstream water and ultimately dialysate. | Heterotrophic or Standard Plate Count (HPC/SPC)<br><br>Swabbing or scraping of tubing or piping surfaces followed by HPC or SPC analysis<br><br>Look for instances of erratic colony counts/spikes in CFU or persistence of high levels (above action levels) in spite of frequent and aggressive disinfection. <sup>89</sup><br><br>Robbins devices or coupons for insertion into flowpath. Analysis by HPC/SPC. |
| Exotoxin                        |                          | <u><b>Observed from all types of exposure:</b></u><br>Unknown with viable suspects being studied.<br><br>Chronic inflammatory response can occur. Exotoxin A has exactly the same mechanism of action as the diphtheria toxin; it is a virulence factor for <i>Pseudomonas aeruginosa</i> ; there are a number of different bacterial |                                                                                                                                                                                                                                                                          | No commercially available test methods for detection in water.<br><br>Much discussion but most not sure whether to go above route or try to measure another way since they may be organism specific.                                                                                                                                                                                                              |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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**Table 1—Water testing methodologies**

| 1                               | 2                        | 3                                                                                                                      | 4                                         | 5                  |
|---------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------|
| Chemical Element or Contaminant | Maximum Allowable Levels | Clinical Symptoms Associated with Exposure                                                                             | Effect of Contaminant on Dialysis Systems | Test Methodologies |
|                                 |                          | exotoxins (Clostridium difficile, Bacillus anthracis, Group A Streptococcus, Corynebacteria diphtheriae, for example). |                                           |                    |

\* The test method should be sensitive enough to detect below the maximum allowable contaminant levels in water as described in Tables 1 and 2 of ISO 13959, *Water for hemodialysis and related therapies*, 2009.

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# Ultrapure dialysate for hemodialysis and related therapies

Approved 23 September 2011 by  
**Association for the Advancement of Medical Instrumentation**

**Abstract:** Addresses preparation and use of ultrapure fluids to perform hemodialysis. Fluids include water and dialysate. Includes the definition of ultrapure fluids, the rationale for their use, and the means by which they can be prepared. Does not cover peritoneal dialysis fluids.

**Keywords:** fluid, preparation, use, water

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Dr., Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

**ISBN 1-57020-421-7**

# Contents

|                                                                                                                                                                     | Page |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Glossary of equivalent standards.....                                                                                                                               | iv   |
| Committee representation.....                                                                                                                                       | vi   |
| Foreword.....                                                                                                                                                       | vii  |
| Introduction.....                                                                                                                                                   | viii |
| 1 Scope.....                                                                                                                                                        | 1    |
| 1.1 Inclusions.....                                                                                                                                                 | 1    |
| 1.2 Exclusions.....                                                                                                                                                 | 1    |
| 2 Definitions.....                                                                                                                                                  | 1    |
| 3 Rationale for the use of ultrapure dialysate.....                                                                                                                 | 2    |
| 3.1 Exposure to microbiological contaminants in dialysate.....                                                                                                      | 2    |
| 3.2 Sources of microbial contamination.....                                                                                                                         | 2    |
| 3.3 Bacterial products can cross both low-flux and high-flux membranes fabricated from cellulose and synthetic polymers and stimulate an inflammatory response..... | 3    |
| 3.4 Use of ultrapure dialysate reduces long-term morbidity associated with inflammation.....                                                                        | 4    |
| 3.5 Current status of the use of ultrapure dialysate for standard dialysis.....                                                                                     | 5    |
| 4 Strategies to achieve ultrapure dialysate.....                                                                                                                    | 5    |
| 4.1 System design.....                                                                                                                                              | 5    |
| 4.2 Strategies for reducing biofilm formation.....                                                                                                                  | 6    |
| 4.2.1 Basic design considerations.....                                                                                                                              | 6    |
| 4.3 Disinfection method.....                                                                                                                                        | 7    |
| 4.3.1 Hot water disinfection.....                                                                                                                                   | 7    |
| 4.3.2 Ozonation.....                                                                                                                                                | 7    |
| 4.4 System maintenance.....                                                                                                                                         | 8    |
| 4.4.1 System disinfection.....                                                                                                                                      | 9    |
| 4.4.2 Filter maintenance.....                                                                                                                                       | 9    |
| 4.4.3 Chemical quality of water.....                                                                                                                                | 9    |
| 5 Demonstrating compliance with recommendations for the microbiological quality of dialysate.....                                                                   | 9    |
| 5.1 Monitoring bacterial levels.....                                                                                                                                | 9    |
| 5.2 Monitoring for endotoxin levels.....                                                                                                                            | 11   |
| 5.3 Monitoring biofilm.....                                                                                                                                         | 12   |
| 5.4 Recommended monitoring frequencies.....                                                                                                                         | 12   |
| Bibliography.....                                                                                                                                                   | 14   |
| Tables                                                                                                                                                              |      |
| 1 Microbiological techniques for monitoring water and dialysate.....                                                                                                | 10   |

## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation. The code in the US column, "(R)20xx" indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

| International designation                         | U.S. designation                                                                                         | Equivalency                                                     |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| IEC 60601-1:2005<br>Technical Corrigendum 1 and 2 | ANSI/AAMI ES60601-1:2005 and ANSI/AAMI ES60601-1:2005/A2:2010<br>ANSI/AAMI ES60601-1:2005/C1:2009 (amdt) | Major technical variations<br>C1 Identical to Corrigendum 1 & 2 |
| IEC 60601-1-2:2007                                | ANSI/AAMI/IEC 60601-1-2:2007                                                                             | Identical                                                       |
| IEC 60601-2-2:2009                                | ANSI/AAMI/IEC 60601-2-2:2009                                                                             | Identical                                                       |
| IEC 60601-2-4:2010                                | ANSI/AAMI/IEC 60601-2-4:2010                                                                             | Identical                                                       |
| IEC 60601-2-16:2008                               | ANSI/AAMI/IEC 60601-2-16:2008                                                                            | Identical                                                       |
| IEC 60601-2-19:2009                               | ANSI/AAMI/IEC 60601-2-19:2009                                                                            | Identical                                                       |
| IEC 60601-2-20:2009                               | ANSI/AAMI/IEC 60601-2-20:2009                                                                            | Identical                                                       |
| IEC 60601-2-21:2009                               | ANSI/AAMI/IEC 60601-2-21:2009                                                                            | Identical                                                       |
| IEC 60601-2-24:1998                               | ANSI/AAMI ID26:2004/(R)2009                                                                              | Major technical variations                                      |
| IEC 60601-2-27:2011                               | ANSI/AAMI/IEC 60601-2-27:2011                                                                            | Identical                                                       |
| IEC 60601-2-47:2001                               | ANSI/AAMI EC38:2007                                                                                      | Major technical variations                                      |
| IEC 60601-2-50:2009                               | ANSI/AAMI/IEC 60601-2-50:2009                                                                            | Identical                                                       |
| IEC 80001-1:2010                                  | ANSI/AAMI/IEC 80001-1:2010                                                                               | Identical                                                       |
| IEC 80601-2-30:2009 and Technical Corrigendum 1   | ANSI/AAMI/IEC 80601-2-30:2009 and ANSI/AAMI/IEC 80601-2-30:2009/ C1:2009 (amdt) – consolidated text      | Identical (with inclusion)<br>C1 Identical to Corrigendum 1     |
| IEC 80601-2-58:2008                               | ANSI/AAMI/IEC 80601-2-58:2008                                                                            | Identical                                                       |
| IEC/TR 60878:2009                                 | ANSI/AAMI/IEC TIR60878:2003                                                                              | Identical                                                       |
| IEC/TR 62296:2009                                 | ANSI/AAMI/IEC TIR62296:2009                                                                              | Identical                                                       |
| IEC 62304:2006                                    | ANSI/AAMI/IEC 62304:2006                                                                                 | Identical                                                       |
| IEC/TR 62348:2006                                 | ANSI/AAMI/IEC TIR62348:2006                                                                              | Identical                                                       |
| IEC/TR 62354:2009                                 | ANSI/AAMI/IEC TIR62354:2009                                                                              | Identical                                                       |
| IEC 62366:2007                                    | ANSI/AAMI/IEC 62366:2007                                                                                 | Identical                                                       |
| IEC/TR 80002-1:2009                               | ANSI/IEC/TR 80002-1:2009                                                                                 | Identical                                                       |
| ISO 5840:2005                                     | ANSI/AAMI/ISO 5840:2005/(R)2010                                                                          | Identical                                                       |
| ISO 7198:1998                                     | ANSI/AAMI/ISO 7198:1998/2001/(R)2010                                                                     | Identical                                                       |
| ISO 7199:2009                                     | ANSI/AAMI/ISO 7199:2009                                                                                  | Identical                                                       |
| ISO 8637:2010                                     | ANSI/AAMI/ISO 8637:2010                                                                                  | Identical                                                       |
| ISO 8638:2010                                     | ANSI/AAMI/ISO 8638:2010                                                                                  | Identical                                                       |
| ISO 10993-1:2009                                  | ANSI/AAMI/ISO 10993-1:2009                                                                               | Identical                                                       |
| ISO 10993-2:2006                                  | ANSI/AAMI/ISO 10993-2:2006/(R)2010                                                                       | Identical                                                       |
| ISO 10993-3:2003                                  | ANSI/AAMI/ISO 10993-3:2003/(R)2009                                                                       | Identical                                                       |
| ISO 10993-4:2002 and Amendment 1:2006             | ANSI/AAMI/ISO 10993-4:2002/(R)2009 and Amendment 1:2006/(R)2009                                          | Identical                                                       |
| ISO 10993-5:2009                                  | ANSI/AAMI/ISO 10993-5:2009                                                                               | Identical                                                       |
| ISO 10993-6:2007                                  | ANSI/AAMI/ISO 10993-6:2007/(R)2010                                                                       | Identical                                                       |
| ISO 10993-7:2008                                  | ANSI/AAMI/ISO 10993-7:2008                                                                               | Identical                                                       |
| ISO 10993-9:2009                                  | ANSI/AAMI/ISO 10993-9:2009                                                                               | Identical                                                       |
| ISO 10993-10:2010                                 | ANSI/AAMI/ISO 10993-10:2010                                                                              | Identical                                                       |
| ISO 10993-11:2006                                 | ANSI/AAMI/ISO 10993-11:2006/(R)2010                                                                      | Identical                                                       |
| ISO 10993-12:2007                                 | ANSI/AAMI/ISO 10993-12:2007                                                                              | Identical                                                       |
| ISO 10993-13:2010                                 | ANSI/AAMI/ISO 10993-13:2010                                                                              | Identical                                                       |
| ISO 10993-14:2001                                 | ANSI/AAMI/ISO 10993-14:2001/(R)2006                                                                      | Identical                                                       |
| ISO 10993-15:2000                                 | ANSI/AAMI/ISO 10993-15:2000/(R)2006                                                                      | Identical                                                       |
| ISO 10993-16:2010                                 | ANSI/AAMI/ISO 10993-16:2010                                                                              | Identical                                                       |
| ISO 10993-17:2002                                 | ANSI/AAMI/ISO 10993-17:2002/(R)2008                                                                      | Identical                                                       |
| ISO 10993-18:2005                                 | ANSI/AAMI BE83:2006                                                                                      | Major technical variations                                      |
| ISO/TS 10993-19:2006                              | ANSI/AAMI/ISO TIR10993-19:2006                                                                           | Identical                                                       |
| ISO/TS 10993-20:2006                              | ANSI/AAMI/ISO TIR10993-20:2006                                                                           | Identical                                                       |
| ISO 11135-1:2007                                  | ANSI/AAMI/ISO 11135-1:2007                                                                               | Identical                                                       |
| ISO/TS 11135-2:2008                               | ANSI/AAMI/ISO TIR11135-2:2008                                                                            | Identical                                                       |

| International designation               | U.S. designation                                       | Equivalency                 |
|-----------------------------------------|--------------------------------------------------------|-----------------------------|
| ISO 11137-1:2006                        | ANSI/AAMI/ISO 11137-1:2006/(R)2010                     | Identical                   |
| ISO 11137-2:2006 (2006-08-01 corrected) | ANSI/AAMI/ISO 11137-2:2006                             | Identical                   |
| ISO 11137-3:2006                        | ANSI/AAMI/ISO 11137-3:2006/(R)2010                     | Identical                   |
| ISO 11138-1:2006                        | ANSI/AAMI/ISO 11138-1:2006/(R)2010                     | Identical                   |
| ISO 11138-2:2006                        | ANSI/AAMI/ISO 11138-2:2006/(R)2010                     | Identical                   |
| ISO 11138-3:2006                        | ANSI/AAMI/ISO 11138-3:2006/(R)2010                     | Identical                   |
| ISO 11138-4:2006                        | ANSI/AAMI/ISO 11138-4:2006/(R)2010                     | Identical                   |
| ISO 11138-5:2006                        | ANSI/AAMI/ISO 11138-5:2006/(R)2010                     | Identical                   |
| ISO/TS 11139:2006                       | ANSI/AAMI/ISO 11139:2006                               | Identical                   |
| ISO 11140-1:2005                        | ANSI/AAMI/ISO 11140-1:2005/(R)2010                     | Identical                   |
| ISO 11140-3:2007                        | ANSI/AAMI/ISO 11140-3:2007                             | Identical                   |
| ISO 11140-4:2007                        | ANSI/AAMI/ISO 11140-4:2007                             | Identical                   |
| ISO 11140-5:2007                        | ANSI/AAMI/ISO 11140-5:2007                             | Identical                   |
| ISO 11607-1:2006                        | ANSI/AAMI/ISO 11607-1:2006/(R)2010                     | Identical                   |
| ISO 11607-2:2006                        | ANSI/AAMI/ISO 11607-2:2006/(R)2010                     | Identical                   |
| ISO 11663:2009                          | ANSI/AAMI/ISO 11663:2009                               | Identical                   |
| ISO 11737-1:2006                        | ANSI/AAMI/ISO 11737-1:2006                             | Identical                   |
| ISO 11737-2:2009                        | ANSI/AAMI/ISO 11737-2:2009                             | Identical                   |
| ISO/TS 12417:2011                       | ANSI/AAMI/ISO TIR12417:2011                            | Identical                   |
| ISO 13408-1:2008                        | ANSI/AAMI/ISO 13408-1:2008                             | Identical                   |
| ISO 13408-2:2003                        | ANSI/AAMI/ISO 13408-2:2003                             | Identical                   |
| ISO 13408-3:2006                        | ANSI/AAMI/ISO 13408-3:2006                             | Identical                   |
| ISO 13408-4:2005                        | ANSI/AAMI/ISO 13408-4:2005                             | Identical                   |
| ISO 13408-5:2006                        | ANSI/AAMI/ISO 13408-5:2006                             | Identical                   |
| ISO 13408-6:2006                        | ANSI/AAMI/ISO 13408-6:2006                             | Identical                   |
| ISO 13485:2003                          | ANSI/AAMI/ISO 13485:2003/(R)2009                       | Identical                   |
| ISO 13958:2009                          | ANSI/AAMI/ISO 13958:2009                               | Identical                   |
| ISO 13959:2009                          | ANSI/AAMI/ISO 13959:2009                               | Identical                   |
| ISO 14155:2011                          | ANSI/AAMI/ISO 14155:2011                               | Identical                   |
| ISO 14160:1998                          | ANSI/AAMI/ISO 14160:1998/(R)2008                       | Identical                   |
| ISO 14161:2009                          | ANSI/AAMI/ISO 14161:2009                               | Identical                   |
| ISO 14708-3:2008                        | ANSI/AAMI/ISO 14708-3:2008                             | Identical                   |
| ISO 14708-4:2008                        | ANSI/AAMI/ISO 14708-4:2008                             | Identical                   |
| ISO 14708-5:2010                        | ANSI/AAMI /ISO 14708-5:2010                            | Identical                   |
| ISO 14937:2009                          | ANSI/AAMI/ISO 14937:2009                               | Identical                   |
| ISO/TR 14969:2004                       | ANSI/AAMI/ISO TIR14969:2004                            | Identical                   |
| ISO 14971:2007                          | ANSI/AAMI/ISO 14971:2007/(R)2010                       | Identical                   |
| ISO 15223-1:2007 and A1:2008            | ANSI/AAMI/ISO 15223-1:2007 and A1:2008                 | Identical                   |
| ISO 15223-2:2010                        | ANSI/AAMI/ISO 15223-2:2010                             | Identical                   |
| ISO 15225:2010                          | ANSI/AAMI/ISO 15225:2010                               | Identical                   |
| ISO 15674:2009                          | ANSI/AAMI/ISO 15674:2009                               | Identical                   |
| ISO 15675:2009                          | ANSI/AAMI/ISO 15675:2009                               | Identical                   |
| ISO 15882:2008                          | ANSI/AAMI/ISO 15882:2008                               | Identical                   |
| ISO 15883-1:2006                        | ANSI/AAMI ST15883-1:2009                               | Major technical variations  |
| ISO/TR 16142:2006                       | ANSI/AAMI/ISO TIR16142:2005                            | Identical                   |
| ISO 17664:2004                          | ANSI/AAMI ST81:2004                                    | Major technical variations  |
| ISO 17665-1:2006                        | ANSI/AAMI/ISO 17665-1:2006                             | Identical (with inclusions) |
| ISO/TS 17665-2:2009                     | ANSI/AAMI/ISO TIR17665-2:2009                          | Identical                   |
| ISO 18472:2006                          | ANSI/AAMI/ISO 18472:2006/(R)2010                       | Identical                   |
| ISO/TS 19218-1:2011                     | ANSI/AAMI/ISO TIR19218:2011                            | Identical                   |
| ISO 20857:2010                          | ANSI/AAMI/ISO 20857:2010                               | Identical                   |
| ISO 22442-1:2007                        | ANSI/AAMI/ISO 22442-1:2007                             | Identical                   |
| ISO 22442-2:2007                        | ANSI/AAMI/ISO 22442-2:2007                             | Identical                   |
| ISO 22442-3:2007                        | ANSI/AAMI/ISO 22442-3:2007                             | Identical                   |
| ISO/TR 22442-4:2010                     | ANSI/AAMI/ISO TIR22442-4:2010                          | Identical                   |
| ISO 23500:2011                          | ANSI/AAMI/ISO 23500:2011                               | Identical                   |
| ISO 25539-1:2003 and A1:2005            | ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009 | Identical                   |
| ISO 25539-2:2008                        | ANSI/AAMI/ISO 25539-2:2008                             | Identical                   |
| ISO 26722:2009                          | ANSI/AAMI/ISO 26722:2009                               | Identical                   |
| ISO 27186:2010                          | ANSI/AAMI/ISO 27186:2010                               | Identical                   |
| ISO 80369-1:2010                        | ANSI/AAMI/ISO 80369-1:2010                             | Identical                   |
| ISO 81060-1:2007                        | ANSI/AAMI/ISO 81060-1:2007                             | Identical                   |
| ISO 81060-2:2009                        | ANSI/AAMI/ISO 81060-2:2009                             | Identical                   |

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Renal Disease and Detoxification Committee

This Technical Information Report was developed by the AAMI Renal Disease and Detoxification Committee. Committee approval of the Technical Information Report does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

*Cochairs:*           Conor Curtin  
                          Richard A. Ward, PhD

*Members:*           G. Steven Acres, Carolina Regional Nephrology Associates  
                          Larry Alexander, Florian Services  
                          James W. Baker, AmeriWater  
                          Robert Berube, Church & Dwight Company Inc.  
                          Arnold Boehnlein, Baxter Healthcare Corporation  
                          Judy Brown, Ascend Clinical LLC  
                          Karla Byrne, Rockwell Medical Inc  
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                          Conor Curtin, Fresenius Medical Care North America  
                          Jim Curtis, Home Dialysis Plus LTD  
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                          Robert Dudek, Siemens Water Technologies Corporation  
                          Gema Gonzalez, U.S. Food and Drug Administration/Center for Devices and Radiological  
                              Health/Office of Device Evaluation  
                          Elizabeth Howard, Davita Inc.  
                          Byron Jacobs, CBET, Sanford USD Medical Center  
                          David Katz, El Camino Hospital  
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NOTE—Participation by federal agency representatives in the development of this recommended practice does not constitute endorsement by the federal government or any of its agencies.

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## Foreword

This technical information report was developed by the AAMI Renal Disease and Detoxification Committee. The objective is to provide dialysis practitioners with additional background information related to the recommendation made in ANSI/AAMI/ISO 23500:2011, *Guidance for the preparation and quality management of fluids for hemodialysis and related therapies*, that ultrapure dialysate should be used for routine hemodialysis.

As used within the context of this document, “should” indicates that among several possibilities one is recommended as particularly suitable without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but not prohibited. “May” is used to indicate that a course of action is permissible within the limits of the TIR. “Can” is used as a statement of possibility and capability. “Must” is used only to describe “unavoidable” situations, including those mandated by government regulations..

Suggestions for improving this TIR are invited. Comments and suggested revisions should be sent to Technical Programs, AAMI, 4301 N. Fairfax Dr., Suite 301, Arlington, VA 22203-1633.

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NOTE—This foreword does not contain provisions of AAMI TIR43:2011, *Ultrapure dialysate for hemodialysis and related therapies*, but it does provide important information about the development and intended use of the document.

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## Introduction: Need for this AAMI TIR

Hemodialysis patients are directly exposed to large volumes of dialysis fluid, with the dialyzer membrane being the only barrier against the transfer of hazardous contaminants from the dialysis fluid to the patient. It has long been known that there could be contaminants in dialysis fluid that are hazardous to patients. To minimize this hazard, ANSI/AAMI/ISO 11663, *Quality of dialysis fluid for hemodialysis and related therapies*, establishes quality requirements for dialysis fluid used in hemodialysis and related therapies. These quality requirements define two classes of dialysis fluid: standard dialysis fluid and ultrapure dialysis fluid. The maximum allowable levels of chemical contaminants are the same for both standard dialysis fluid and ultrapure dialysis fluid; however, they differ in the maximum allowable levels of microbial contaminants. According to ANSI/AAMI/ISO 23500, *Guidance for the preparation and quality management of fluids for hemodialysis and related therapies*, dialysis fluid complying with the requirements for standard dialysis fluid is the minimum quality acceptable for routine hemodialysis. However, it recommends that ultrapure dialysis fluid be used, even for routine hemodialysis. The recommendation is based on clinical and experimental observations that improving the microbiological purity of dialysis fluid is associated with reduced levels of inflammation and a reduction in morbidities associated with inflammation. These apparent advantages of ultrapure dialysis fluid might not be widely appreciated, and implementing the routine use of ultrapure dialysis fluid could require changes in dialysis unit practices. For these reasons, this Technical Information Report was developed to provide background information on ultrapure dialysis fluid, and to review strategies that could be helpful in implementing its routine use.

This Technical Information Report is directed at healthcare professionals involved in the management of dialysis facilities and the routine care of patients treated in dialysis facilities, because they are responsible for the final preparation of dialysis fluid.

# Ultrapure dialysate for hemodialysis and related therapies

## 1 Scope

This Technical Information Report (TIR) addresses the preparation of ultrapure dialysate from water and concentrates and its use in performing hemodialysis and related therapies.

### 1.1 Inclusions

The Technical Information Report includes the definition of ultrapure dialysate, the rationale for its use, and some means by which it can be prepared.

### 1.2 Exclusions

This Technical Information Report does not cover peritoneal dialysis fluids or prepackaged fluids, such as those used in continuous renal replacement therapies (CRRT).

## 2 Definitions

For the purposes of this technical information report, the following definitions apply.

NOTE: Ultrapure dialysate is defined by the level of microbiological contamination. While chemical contaminants in the dialysate can harm patients, as yet there is no evidence to show that reducing their levels below those specified in ANSI/AAMI/ISO 13959, *Water for hemodialysis and related therapies*, for water used to prepare dialysate and concentrates improves patient outcomes. Therefore, this clause is limited to defining different levels of dialysate quality based on microbiological contaminants.

### 2.1 conventional dialysate

Conventional dialysate, also referred to as standard dialysate, is dialysate meeting the minimum acceptable quality requirements for hemodialysis. The International Organization for Standardization (ISO) recommends maximum allowable levels of 100 CFU/mL for total viable microbial count and 0.5 EU/mL for endotoxin (ISO 11663:2009). The United States adopted these recommendations in 2010. Standards in other countries and regions are more rigorous. For example, the limits recommended by the European Renal Association and the Japanese Society for Dialysis Therapy are 100 CFU/mL and 0.25 EU/mL, respectively, for total viable microbial count and endotoxin (European Renal Association, 2002; Kawanishi, et al., 2009).

NOTE Prior to 2010, the microbial quality of conventional dialysate in the United States was defined in ANSI/AAMI RD52:2004, *Dialysate for hemodialysis*. Those requirements specified a total viable microbial count lower than 200 CFU/mL and an endotoxin concentration lower than 2 EU/mL (AAMI, 2004).

Some standards include action levels for total viable microbial count and endotoxin in conventional dialysate. The purpose of action levels is to trigger a corrective action, such as disinfection and retesting, before levels of bacteria or endotoxin reach the maximum allowable level. The ISO and Japanese Society for Dialysis Therapy standards recommend setting action levels at 50 % of the maximum allowable level (ISO, 2009; Kawanishi, et al., 2009).

NOTE Prior to the adoption of ISO 11663 in 2010, recommended action levels in the United States were 50 CFU/mL and 1 EU/mL for the total viable microbial count and the endotoxin concentration, respectively (ANSI/AAMI, 2004).

### 2.2 ultrapure dialysate

Ultrapure dialysate refers to dialysate meeting more rigorous standards for microbiological quality than conventional dialysate. One widely used definition of ultrapure dialysate limits the total viable microbial count to less than 0.1 CFU/mL (100 CFU/L) and the endotoxin concentration to less than 0.03 EU/mL (Ledebro and Nystrand, 1999). This definition has been adopted by the European Renal Association (European Renal Association, 2002) and ISO (ISO, 2009). The Japanese Society for Dialysis Therapy recommends an even lower maximum allowable concentration for

endotoxin of 0.001 EU/mL (Kawanishi, et al., 2009). No action limits are set for ultrapure dialysate, as the recommended maximum allowable levels for bacteria and endotoxin are close to the lower limits of detection for commonly available assays.

### **2.3 ultrapure dialysis water**

Ultrapure dialysis water refers to dialysis water meeting more rigorous standards for microbiological quality than conventional dialysis water. One widely used definition of ultrapure dialysis water limits the total viable microbial count to less than 0.1 CFU/mL (100 CFU/L) and the endotoxin concentration to less than 0.03 EU/mL (Ledebø and Nystrand, 1999).

### **2.4 substitution solution for use in on-line convective therapies**

Convective therapies, such as hemodiafiltration and hemofiltration, require substitution solution to maintain fluid balance in the presence of high ultrafiltration rates. On-line convective therapies may exchange 20 – 70 liters of fluid in a single treatment, depending on whether the therapy is performed in the pre-dilution or post-dilution mode (Ledebø, 1998). Because it is not practical to provide the volume of fluids required using pre-packaged, terminally sterilized bags, substitution solution is usually produced on-line from dialysate by a process of sequential filtration through bacteria- and endotoxin-retentive membranes. Substitution solution prepared in this manner should be sterile and non-pyrogenic; that is, the equivalent of on-line prepared substitution fluid as described in clause 4.1.4 of ANSI/AAMI/ISO 11663:2009. Compliance with this requirement cannot be demonstrated by culturing. Therefore, dialysate for infusion should be produced by a device or process that has been validated by the manufacturer to produce fluid meeting the above recommendations for a specified time or number of treatments when supplied with dialysate of a specified quality. The user should follow the manufacturer's instructions for installation and use of the validated system, and the user's monitoring and maintenance schedule should conform to the manufacturer's instructions and be designed to confirm that the dialysate used to prepare the dialysate for infusion continues to meet the specifications of the manufacturer of the device or process.

## **3 Rationale for the use of ultrapure dialysate**

### **3.1 Exposure to microbiological contaminants in dialysate**

Water constitutes 95 % of dialysate (Ledebø and Nystrand, 1999) and is used in the preparation of dialysate concentrates, reprocessing of dialyzers for reuse, and for disinfecting and cleaning distribution systems and dialysis machines. The quality of the water impacts each of those processes and ultimately has a cumulative effect on the quality of the therapy delivered. As many as 200 different species of microorganisms have been identified in water used to prepare dialysate and in the dialysate itself, including several pseudomonads (*Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Brevundimonas vesicularis*, etc.) and other gram-negative species such as *Alcaligenes* species, *Moraxella*, *Corynebacteria*, and fungi (molds or filamentous fungi and yeast) (Gomlia, et al., 2005; Nystrand, 2008; Pass, et al., 1996; Arvanitidou, et al., 2000).

In the United States, the average person consumes approximately 14 liters of water per week. Hemodialysis patients are exposed to an additional 400 – 500 liters per week during dialysis treatments via dialysate that is separated from the patient's blood by only a semi-permeable dialyzer membrane. (Sorbent-based systems might have a different level of exposure.) Dialysis patients are typically immunocompromised to some degree as well. Thus, exposure to any bacteria, viable and non-viable, pathogenic and opportunistic, and their degradation products such as endotoxin, peptidoglycan, exotoxins, and DNA fragments in the water used to prepare dialysate, puts dialysis patients at risk. On-line convective therapies, such as hemofiltration or hemodiafiltration, might put patients at additional risk, because substitution solution derived from dialysate is introduced directly into the blood in on-line convective therapies. Thus, the quality of dialysate becomes more critical with these latter therapies.

### **3.2 Sources of microbial contamination**

In the United States, incoming water to a dialysis clinic should meet the United States Environmental Protection Agency's (EPA) Primary Drinking Water Standard (U.S. EPA, 1996). Those regulations address the presence of total coliforms, including *Escherichia coli*, in drinking water as an indicator of fecal contamination. In general, no specific testing is required for other microbial contaminants or for the total bacterial content. However, if the water is derived from surface sources, control measures are required to be in place for *Cryptosporidium*, *Giardia lamblia*, and *Legionella*, and the heterotrophic plate count should not exceed 500 CFU/mL.

Because the water treatment system removes germicides, such as chlorine and chloramine, from the municipal water (Ismail, et al., 1996), and because bacteria may enter the treated water storage and distribution system through gaps in system integrity, there is potential for bacterial growth, endotoxin production, biofilm development, and accumulation of microbial debris in the water distribution system and at points of use.

Biofilm is the most common source of microbial contaminants in the dialysate. Biofilms form when bacteria in a fluid adhere to a surface and generate a protective shield of extracellular polymer termed a glycocalyx. Biofilm is the preferred habitat for bacteria in fluid systems (Sutherland, 2001; Donlan, 2002). In addition to bacteria and their debris, such as peptidoglycan, lipopolysaccharides, lipid A, and DNA and RNA fragments, the glycocalyx also traps exotoxins and other low molecular weight by-products of bacterial metabolism. As a biofilm matures, it can slough off portions of itself in an unpredictable manner, releasing many of these trapped materials, as well as viable bacteria, into the water or dialysate. Many of these bacterial products are undetectable by currently available techniques but are potentially harmful to the patient. Biofilm can form anywhere that a non-sterile fluid flows over a hard surface and thus may become established within the distribution systems for both treated water and bicarbonate concentrate, as well as in the final dialysate pathway.

### **3.3 Bacterial products can cross both low-flux and high-flux membranes fabricated from cellulose and synthetic polymers and stimulate an inflammatory response**

The ability of a dialyzer membrane to function as a barrier against bacterial products in the dialysate was long relied upon empirically, although not without some controversy. Widespread adoption during the 1980s of bicarbonate dialysate, which is a good bacterial culture medium (Ebben, et al., 1987), and the increasing use of high-flux membranes, prompted more careful investigation of the potential for transfer of bacterial products from the dialysate into the blood compartment.

Several *in vitro* studies have shown that bacterial products can cross both high-flux and low-flux membranes (Laude-Sharp, et al., 1990; Urena, et al., 1992). Intact bacteria are too large to cross the dialyzer membrane, as are some bacterial products, such as lipopolysaccharide (LPS, > 100 kD) and exotoxin A (71 kD), even though hemodialysis patients are reported to have endotoxin antibodies specific to endotoxins extracted from bacteria isolated from dialysate (Gazendfeldt-Gazit and Eliahou, 1969; Yamagami, et al., 1990). However, bacterial products of smaller molecular size, including small fragments of endotoxin and fragments of bacterial DNA and other microbial products (Lonnemann, et al., 1992; Schindler et al. 2004; Jochimsen, et al., 1998; Selenic, et al., 2004; Bossola, et al., 2009), can cross dialyzer membranes from dialysate to the blood compartment and elicit an inflammatory response. These small bacterial products are termed “cytokine-inducing substances” (CIS) and cross the dialyzer membrane by both backfiltration and diffusion (Lonnemann, 2000). A role for diffusion was demonstrated by Pereira, et al. who observed that cytokine production by peripheral blood mononuclear cells (PBMC) – a sensitive marker of the presence of endotoxin – increased within the first hour of dialysis in the strict absence of backfiltration. *In vitro* studies have shown that specific membrane characteristics determine the amount of CIS appearing in the blood compartment of dialyzers (Henrie, 2008). The thickness of a membrane influences its pyrogen permeability, because membrane thickness is one of the factors that determine diffusive resistance. Also, the permeability of a membrane is influenced by its physico-chemical composition. Synthetic membranes such as polysulfone and polyamide contain hydrophobic domains that can bind hydrophobic pyrogens (e.g. lipids like LPS fragments) (Hayama, et al., 2003). The high porosity of membranes provides a large surface area for adsorption of pyrogens to these hydrophobic domains, and they are routinely used as effective bacterial- and endotoxin-retentive filters for the production of ultrapure dialysate and substitution fluid for on-line convective therapies. However there are exceptions and at least one polysulfone-based membrane (DIAPES) has been reported to be somewhat permeable to CIS (Lonnemann, et al. 2001; Schindler, et al., 2003; Weber, et al., 2004). High-flux and low-flux cellulose membranes tend to be less of a barrier to CIS (Lonnemann, et al., 1992). Low-flux cellulosic membranes are thinner (6.5 – 8 µm) than synthetic membranes, (40 – 60 µm), and cellulosic membranes generally lack the hydrophobic domains that bind hydrophobic pyrogens.

Microorganisms in contaminated dialysate release several different CIS. Depending on the level of bacteria and endotoxin in the dialysate, patient exposure to such substances may elicit an immediate effect, such as a pyrogenic reaction, cardiovascular instability, headache, nausea, and cramps (Dawids and Vejlsgaard, 1976; Favero, et al., 1974). At lower levels, CIS stimulate synthesis of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and interleukin-1 (IL-1) (Lonnemann, et al., 1992; Pereira, et al., 1995; Schindler, et al., 1996).

This ability to provoke inflammation is the basis for hypotheses that link dialysate contamination with dialysis-associated morbidity. The “interleukin hypothesis” links cytokines induced by bioincompatibilities to fever and hypotension during or after a hemodialysis session (Henderson, et al., 1983), while the malnutrition, inflammation and atherosclerosis (MIA) syndrome (Stenvinkel, et al., 1999; Stenvinkel, et al., 2000) has been proposed to explain some of the more chronic consequences of long-term hemodialysis. Part of the rationale for both these hypotheses is that long term exposure to low levels of microbial contaminants and debris that can cross the dialyzer membrane by backfiltration contributes to a chronic state of micro-inflammation. While these hypotheses have not been tested in long-term, prospective, placebo-controlled clinical trials, small prospective and retrospective studies, as well as anecdotal data gathered over the past 20 years, support that microbial contamination of water and dialysate contribute to a number of intradialytic complications seen in dialysis patients. These include dialysis-related amyloidosis, atherosclerosis, malnutrition, inflammation, anemia expressed as resistance to erythropoietin therapy, and increased ferritin levels, muscle protein wasting, protein catabolism, and bone disease as reviewed by Lonnemann (2000) and in 3.4.

### 3.4 Use of ultrapure dialysate reduces long-term morbidity associated with inflammation

Patients treated with hemodialysis have been observed to manifest a state of chronic inflammation characterized by increased plasma concentrations of pro-inflammatory cytokines and acute phase proteins, such as C-reactive protein (Herbelin, et al., 1991; Kimmel, et al., 1998; Owen and Lowrie, 1998). An improvement in this inflammatory state has been reported in numerous studies where bacterial and endotoxin levels have been systematically reduced (Schindler, et al., 1994; Sitter, et al., 2000; Schiffli, et al., 2001; Matsuhashi and Yoshioka, 2002; Arizono, et al., 2004; Hsu, et al., 2004; Rahmati, et al., 2004; Furuya, et al., 2005; Molina, et al., 2007; Go, et al., 2007). Reactive carbonyl compounds (RCOs) are precursors of uremia-associated advanced glycation end products (AGEs). Pentosidine is an AGE that correlates highly with precursor RCOs and is used as a surrogate marker for plasma carbonyl stress, which has been implicated in the development of uremic complications, such as atherosclerosis. Use of ultrapure dialysate has been associated with improved carbonyl stress, evidenced by a decrease in plasma pentosidine concentrations (Furuya, et al., 2005; Izuhara, et al., 2004). Other studies have suggested that a variety of outcomes linked to inflammation are also improved when patients are treated with dialysate of high microbial quality. The preponderance of data are in three main areas as reviewed by Ward (2004): nutrition (Schiffli, et al., 2001; Arizono, et al., 2004; Rahmati, et al., 2004; Ouseph, et al., 2007); responsiveness to erythropoietin (Sitter, et al., 2000; Matsuhashi and Yoshioka, 2002; Arizono, et al., 2004; Hsu, et al., 2004; Rahmati, et al., 2004; Molina, et al., 2007; Go, et al., 2007); and,  $\beta_2$ -microglobulin amyloidosis (Baz, et al., 1991; Schiffli, et al., 2000). There are also preliminary data suggesting that ultrapure dialysate may be of benefit in preserving residual renal function (Schiffli, et al., 2002; McKane, et al., 2002), in reducing cardiovascular morbidity (Lederer and Schiffli, 2002; Blagg, et al., 2003) and risk factors for cardiovascular morbidity (Oka, et al., 2004; Schiffli and Lang, 2009; Honda, et al., 2009), and in improving responsiveness to vaccines (Schiffli, et al., 2002).

Nutritional status is thought to be a predictor of long-term outcomes in hemodialysis patients. Schiffli and colleagues evaluated the role of ultrapure dialysate in nutritional status. Changing from conventional to ultrapure dialysate resulted in significant increases in estimated dry body weight, mid-arm muscle circumference, serum albumin concentration, levels of humoral factors, and protein catabolic rate (Schiffli, et al., 2001). Their conclusion was that cytokine induction by microbiologically contaminated dialysate has a negative impact on nutritional parameters and that the microbiological quality of the dialysate represents an independent determinant of the nutritional status in addition to other factors, such as under dialysis and the choice of dialyzer membrane. Other investigators have also reported an increase in serum albumin concentrations with the use of ultrapure dialysate (Arizono, et al., 2004; Rahmati, et al., 2004; Ouseph, et al., 2007). Ouseph, et al. (2007) also noted that the introduction of ultrafiltered dialysate was associated with a significant increase in muscle mass as indicated by an increase in creatinine generation rate.

Uremia is characterized by anemia, which is corrected by administration of erythropoietin-stimulating agents (ESA). The effectiveness of ESA therapy is thought to be compromised by inflammation and several reports indicate an improvement in the effectiveness of ESAs when patients are treated with ultrapure dialysate compared to conventional dialysate. This improved effectiveness may be manifest as a decrease in the dose needed to achieve a target hemoglobin or hematocrit (Sitter, et al., 2000; Matsuhashi and Yoshioka, 2002; Hsu, et al., 2004; Molina, et al., 2007) or an increase in hemoglobin or hematocrit at a constant ESA dose (Arizono, et al., 2004; Rahmati, et al., 2004; Go, et al., 2007). In two observational studies (Matsuhashi and Yoshioka, 2002; Molina, et al., 2007) and two small randomized trials (Sitter, et al., 2000; Hsu, et al., 2004), the ESA doses needed to achieve a given level of anemia correction could be reduced by 16 to 34 percent with the use of ultrapure dialysate. In three observational studies where the ESA dose did not change, hemoglobin levels were reported to increase by about 10 percent over 6 to 24 months (Arizono, et al., 2004; Rahmati, et al., 2004; Go, et al., 2007).

End-stage renal failure is associated with the development of a unique type of amyloidosis that may lead to complications, such as carpal tunnel syndrome (CTS) and the formation of bone cysts with consequence of bone destruction and an increased risk of bone fractures (Miyata, et al., 1998; Lonnemann and Koch, 2002). Highly permeable synthetic membranes have been shown to reduce circulating levels of  $\beta_2$ -microglobulin ( $\beta_2m$ ) by approximately 20 % to 30 %. A small number of studies have investigated whether improved bacteriologic quality of dialysate is also associated with reduced incidence or severity of complications associated with retention of  $\beta_2m$ . In prospective observational studies, treatment with ultrapure dialysate has been shown to reduce  $\beta_2m$  concentrations in serum (Quellhorst, et al., 1998; Ouseph, et al., 2007). In a small randomized clinical trial, Schiffli, et al. (2002) reported a decreased incidence of  $\beta_2m$  amyloidosis, assessed by the need for carpal tunnel surgery or the presence of arthropathy or bone cysts, in patients treated with ultrapure dialysate compared to those treated with intermittently contaminated dialysate. In addition, several retrospective studies have described a beneficial role for improved dialysate quality on the incidence of CTS (Baz, et al., 1991; Kleophas, et al., 1998; Koda, et al., 1997). Lonnemann and Koch (2002) analyzed the latter three studies and concluded that the findings were highly suggestive of a beneficial effect of improved bacterial quality of dialysate on the incidence of CTS.

It should be noted that not all studies that have examined these three potential benefits of ultrapure dialysate have yielded positive findings. For example, two studies failed to find an improvement in the effectiveness of ESA therapy with ultrapure dialysate (Ouseph, et al., 2007; Lamas, et al., 2006). Similarly, three studies failed to find an increase in serum albumin concentration with the introduction of ultrapure dialysate (Furuya, et al., 2005; Izuhara, et al., 2004;

Lamas, et al., 2006). There is no clear explanation for these discrepant findings. However, it may be significant that the use of ultrapure dialysate was not associated with a reduction in inflammation, as assessed by plasma levels of CRP and IL-6, in the two studies that failed to find an improvement in the effectiveness of ESA therapy; whereas, reductions in CRP and IL-6 were reported in all the studies that did show an improvement in ESA utilization [Sitter, et al., 2000; Matsuhashi and Yoshioka, 2002; Arizono, et al., 2004; Rahmati, et al., 2004; Hsu, et al., 2004; Molina, et al., 2007; Go, et al., 2007).

### **3.5 Current status of the use of ultrapure dialysate for standard dialysis**

In spite of the considerable number of reports of improvements in dialysis patients' morbidity and mortality when dialysis is performed using ultrapure dialysate, ultrapure dialysate therapy has not been widely adopted, particularly in the United States. Important questions remain unanswered. For example, questions remain about the appropriate parameters to use for defining the microbial quality of dialysate, and there is little information about the relationship between levels of those parameters and clinical outcomes. Moreover, none of the studies reported to date provides definitive evidence of a cause and effect relationship between dialysate purity and clinical outcomes in dialysis patients (Ward, 2004). Many studies were retrospective (Sitter, et al., 2000; Rahmati, et al., 2004; Kleophas, et al., 1998; Baz, et al., 1991; Schiffli, et al., 2000), lacked an adequate comparison group, or were poorly controlled (Rahmati, et al., 2004; Kleophas, et al., 1998). Some studies are confounded by differences in variables other than dialysate quality (McKane, et al., 2002; Baz, et al., 1991). The prospective studies were relatively small in size and included a limited number of centers (Sitter, et al., 2000; Schiffli, et al., 2001; Matsuhashi and Yoshioka, 2002; Schiffli, et al., 2002). Dialysate quality is often not provided in these studies, but only referred to as mildly contaminated or "ultrapure" based on having been passed through an ultrafilter at point of use. The relative importance of dialysate quality as a trigger of inflammation is also not clear.

While it seems logical that improvement in the microbiological quality of dialysate would likely be beneficial and the means to achieve ultrapure dialysate are available, the utilization of ultrapure dialysate for routine hemodialysis has not yet become the standard of care in most hemodialysis facilities.

## **4 Strategies to achieve ultrapure dialysate**

Achieving ultrapure dialysate on a routine basis is dependent on proper system design, effective maintenance practices, a validated cleaning and disinfection regimen for all components of the system, and monitoring on a regular basis to ensure that the system is under control (Canaud, et al., 2000). All of these aspects of dialysate preparation should be incorporated into a formal written plan that provides a structured and systematic approach to the management of dialysate quality. The plan should cover equipment installation, performance validation, verification of continued performance through routine monitoring, and periodic revalidation. The basics of establishing such a quality management program are outlined in ISO 23500, *Guidance for the preparation and quality management of fluids for hemodialysis and related therapies*.

### **4.1 System design**

All ultrapure fluids for hemodialysis and related therapies can begin with water that complies with any of the current standards for dialysis water, that is, water with less than 100 CFU/mL of bacteria and less than 0.25 EU/mL of endotoxin (ISO 13959:2009). The water is then mixed with concentrates that also comply with current standards in a flow path designed with appropriate selection of materials and components. After the concentrates are mixed, the fluid can be filtered in a controlled step of filtration with bacteria- and endotoxin-retentive filters. One or more filters are used depending on the quality of final fluid desired, the system design architecture, and the quality of water achieved prior to mixing with dialysate concentrates. Bacteria- and endotoxin-retentive filters do not reduce the level of chemical contaminants in the fluid, but do remove the vast majority of the bacteria and bacterial products (Tsuchida, et al., 2009). The water used for ultrapure fluids can be of the same chemical purity as the water for hemodialysis and no additional treatment is required to improve chemical purity in order to generate ultrapure dialysate. Special attention should always be paid to using water with a minimum amount of microbial contaminants. Bacteria- and endotoxin-retentive filters can become overloaded with bacterial products and particulates after a certain period of use and can cause the fluid quality to suffer. Also, a long period without use can allow microbial growth on the membrane that can affect its endotoxin retentive capacity. Also, polysulfone-based membranes are degraded by bleach. The performance of bacteria- and endotoxin-retentive filters is validated by the manufacturer for a certain time or number of treatments when used according to the manufacturer's instructions, including disinfection. If a machine and filter are subjected to more frequent disinfection with bleach or disinfection with higher concentrations of bleach as part of an effort to reduce bacterial contamination, consideration should be given to replacing the filter sooner than the manufacturer's recommendation based on its cumulative exposure to bleach. Thus, the strategy for ultrapure dialysate is to use water treatment equipment that reduces both chemical and microbial contaminants from feed water before the final stage of filtration, incorporating design features in the hemodialysis system that help reduce biofilm formation and implementing specific disinfection and filter replacement procedures that remove and reduce microbial load on the system.

The equipment commonly used to reduce levels of chemical contaminants during the production of standard quality water for hemodialysis includes deionizers, water softeners, granular activated carbon, and reverse osmosis (RO). Deionizers, water softeners and carbon do not remove microbial entities and in many instances contribute to the load of microbial contaminants. However, these components can be required for reduction of chemical contaminants that are not removed effectively by RO. Chlorine and chloramines are examples of contaminants that can usually be removed by carbon filtration that can affect the performance of RO membranes. Water softeners and carbon beds are generally placed before the RO unit. RO reduces both chemical and microbial contamination in water. RO units by themselves can produce ultrapure water if properly maintained, but normal use of these systems and only periodic disinfection cycles make it difficult for them to do so reliably or for the fluid to remain ultrapure when the water is mixed with concentrates. One of the important features of bicarbonate-based hemodialysis machines affecting dialysate quality is the way bicarbonate concentrate is supplied to the machine. The use of liquid bicarbonate concentrate made at the dialysis unit from packaged powder and treated water is common in the United States, whereas, use of on-line concentrate generators is more common in Europe and Japan. There have been many incidents of microbial contamination occurring with bicarbonate concentrate prepared from powder and water at the dialysis facility. While most of these situations could have been prevented by better training and more rigorous procedures, batch preparation of bicarbonate concentrate at dialysis facilities is associated with increased microbial loads in the system. Although these loads are acceptable for standard dialysate, that might preclude the production of ultrapure dialysate. Because it is desirable to decrease the microbial load wherever possible to eliminate any opportunity for biofilm formation, on-line bicarbonate concentrate generators are recommended for the production of ultrapure dialysate. On-line bicarbonate concentrate generators can minimize the microbial load substantially compared with liquid concentrates prepared at the dialysis facility. Daily disinfection of the apparatus that holds the concentrate generator reduces the microbial load on the system.

Reverse osmosis cannot be used in the hemodialysis machine as a final filter for the dialysate, because it would change the chemical composition of the dialysate along with reducing microbial contaminants. Thus, there is a need for a bacteria- and endotoxin retentive filter as the last filter in the generation of ultrapure dialysate.

## 4.2 Strategies for reducing biofilm formation

### 4.2.1 Basic design considerations

On-line water treatment systems consist of a series of components connected with piping, monitors, pumps and recirculation loops that process water and generate product water and, often, waste water streams. The water treatment system should incorporate all the components necessary to produce water meeting all applicable chemical and microbiological quality requirements. The product water distribution system should have few or no piping dead legs, because it can be difficult to introduce disinfecting agents into such areas where flow is stagnant or reduced compared to the main recirculation loop. (A dead leg is defined as a length of piping greater than or equal to 6X the diameter of the pipe (National Institutes of Health, 2008); wherever possible, it is recommended that dead legs not exceed 2X the diameter of the pipe (American Society of Mechanical Engineers, 2007).) The system design should maximize use of recirculation loops to prevent stagnation. The choice of piping material should be predicated on the type of disinfection strategy to be used with the system. Materials such as stainless steel, Teflon, PVDF and PEX are frequently preferred, because they are amenable to disinfection with ozone and hot water. According to Sato (2004), the careful construction and management of a piping system, the setting and management of filters, and avoidance of contamination of the dialysate port connectors (i.e. use of alternative connectors, which have more hygienic designs) are important in avoiding secondary contamination that is generated after the RO unit process and are integral to maintaining ultrapure dialysate quality.

Flow velocity appears to have little impact on biofilm formation. High flow rates may alter biofilm characteristics and growth rate, but do not prevent the attachment of bacteria to pipe surfaces (Patterson, et al., 1991; Meltzer, 1993; Soini, et al., 2002). While the relative thickness of the biofilm varies somewhat with the flow velocity, the actual number of bacteria in the biofilm is similar (just more or less densely arranged). These observations can be explained, at least in part, by the existence of a "boundary" layer adjacent to the wall of a pipe where the actual velocity is near zero. This boundary layer exists even in high velocity or turbulent situations and offers an ideal environment for biofilm establishment. The thickness of the boundary layer was calculated by Pittner and Bertler (1988) for various flow velocities and pipe sizes. Their calculations suggest that the shear forces within the boundary layer are much less than those required to dislodge adherent bacteria.

The use of fittings and piping with low surface roughness are often considered desirable. However, while smoother surfaces delay the initial buildup of attached bacteria, smoothness does not appear to significantly affect the final amount of biofilm that will attach to a surface (Meltzer, 1993). Van Haecke, et al., (1990) compared the rate of attachment of *Pseudomonas aeruginosa* to 304 and 316-L stainless steel with various roughness values from 120-grit, 320-grit, 400-grit, and electro-polished. They found that for a given surface area, the maximum number of bacteria adhering was independent of the stainless steel type or the surface roughness. Pedersen (1990) compared biofilm development on stainless steel and PVC surfaces exposed to flowing municipal drinking water and reported no difference in the amount of cells on the hydrophilic electro-polished stainless steel and the hydrophobic PVC. Measurable adhesion, even to the electropolished surfaces, was evident within 30 seconds of exposure.



The system should be designed to facilitate reduction or elimination of bacterial load and biofilm through established methods, such as daily or frequent disinfection, application of continuous ultraviolet irradiation with endotoxin filtration, and/or periodic replacement of the treated water supply line. As many routine procedures as possible should be automated and validated. Connections that do not trap contaminants and/or are designed for easy cleaning should be used. Even with these measures, biofilms can occur and the operators of the system should have established and effective strategies to maintain microbiological control of the system. Because bicarbonate concentrate provides a favorable environment for bacterial proliferation (Ebben, et al., 1987), maintaining microbiological control of central bicarbonate concentrate preparation and distribution systems can be particularly difficult. These problems are greatly reduced by the use of on-line concentrate generators. With these systems, concentrate is provided as a container of powder that is attached to an individual dialysis machine. The powder is then converted into a concentrated solution by the dialysis machine and used to prepare the final dialysate; there is no storage of liquid bicarbonate concentrate and no distribution system to be maintained.

### 4.3 Disinfection method

There are several methods currently used to control bacterial proliferation in water systems and hemodialysis machines. ANSI/AAMI/ISO 26722:2009, *Water treatment equipment for hemodialysis applications and related therapies*, lists various chemical germicides, hot water, and ozone as methods for water system disinfection. Chemical germicides and cleaning agents include acetic acid, chlorine dioxide, citric acid, formaldehyde, glutaraldehyde, hydrogen peroxide, peracetic acid, and sodium hypochlorite (bleach). For hemodialysis machines, any of these methods can be used if approved by the manufacturer of the machine. For ultrapure fluid generation, where the focus is reduction of biofilm formation, only certain methods are appropriate. This is because very few chemical sterilants can penetrate biofilm. Holmes, et al. (2004) reported that heat disinfection alone killed viable biofilm bacteria, but did not remove all the biomass components, including endotoxin. The combination of pre-treatment with citric acid followed by heat disinfection was the most effective in eliminating all biofilm components from the hydraulic circuit of their *in vitro* model. Similar results were reported by Cappelli and colleagues (2003). Depending on system design, one or more methods may have to be used. Use of chemicals is generally considered environmentally unfriendly. This is for two reasons. Chemical handling is an additional step that users must perform and the chemicals involved are not always safe to handle. Also, any chemicals used need to be removed from the system to an acceptable residual level prior to treatment, requiring rinsing the system with large quantities of purified water. If chemicals are used to remove calcium and magnesium from the biofilm before disinfection, citric acid and acetic acid are the most desirable agents for two reasons. One, they are commonly used and handled by most users and, two, they form physiologically safe residual citrate or acetates (if any acid is left after washing) when used with bicarbonate dialysate. Sodium hypochlorite appears to be the most effective disinfectant against biofilm (Marion-Ferey, et al., 2003). An alternative approach to disinfection is to use a disposable piping system. That approach can be practical in small-scale systems, such as the systems used for home hemodialysis and portable dialysis, and can circumvent many of the problems associated with biofilm formation in permanent piping systems.

#### 4.3.1 Hot water disinfection

If the system is designed to handle 70 °C to 90 °C hot water, heat disinfection can be the most suitable method for controlling bacterial contamination of fluid distribution systems. This is because it can be used daily and raises few environmental concerns. Heat and hot water reach all the areas where bacteria can proliferate, and are capable of penetrating biofilms not only by direct contact but by heat convection as well. When high temperature is maintained in the flow path for a specified length of time, all vegetative bacteria are killed. Continuous circulation of heated water during hot water disinfection is required to achieve the time and temperature exposure necessary for this purpose.

The system needs to be carefully designed to withstand up to 90 °C daily exposure. High temperature exposure can greatly impact the performance of RO membranes. Heat-disinfectable RO membranes can lose 50 % of their output after the initial heat disinfection cycle. As a consequence RO units containing heat-disinfectable membranes might need to be oversized to consistently provide the desired water flow rate if hot water disinfection is to be used. The membrane manufacturer's instructions should be consulted regarding the compatibility of the membrane with heat disinfection, the recommended heat disinfection cycle time and temperature, and any expected loss of performance after heat disinfection. Daily exposure of bacteria- and endotoxin filters to high temperature can reduce their useful life and might result in the need for more frequent replacement.

#### 4.3.2 Ozonation

The use of ozone in water treatment systems has been described in detail by Dey and Thomas (2003). Ozone was first used for disinfection of water in the early 1900s. Ozone can achieve sterilization and significantly reduce levels of total organic carbon (TOC). Ozone kills microorganisms by oxidation and disintegration of cellular membranes. The speed of bacterial kill by ozone has been shown to be 3,125 times faster than chlorine. For both vegetative bacteria and viruses, 90 % to 99 % of organisms are inactivated within 10 to 20 seconds at ozone dosage of 0.3 ppm and greater. This means contact time for ozone disinfection is of little or no consequence. What is important is to maintain the required dose in water to the farthest point in the flow path. This is even more critical if there are dead zones. The quality of water used to carry ozone plays an important role. If water has TOC or other organic

contaminants, they will react with the ozone and reduce the effective ozone dose. Ozone can effectively destroy biofilm. As in hot water disinfection, material selection for systems to be disinfected with ozone is very important to avoid short- and long-term degradation. Ozone, being a powerful oxidizer, can attack many plastics even at low concentration after repeated exposures. If ozone is generated from air, air impurities can carry over to water and dialysate if they are not removed. By-products of the reaction of ozone with TOC, bacteria, and other contaminants may also need to be removed from the water distribution system prior to its use for dialysis treatments.

Unlike hot water disinfection, which requires only a high power heater, ozonation requires an external ozone generator or an in-line cell and electronics that control the output of ozone. There is also a significant issue with the odor of ozone and with its toxicity. As ozone is difficult to dissolve in water, it can rapidly diffuse into the air. OSHA has established requirements for the allowable level of ozone to which personnel can be exposed during an 8 hour period. This is termed "time weighted average" (TWA) exposure. For ozone, the TWA is 0.10 ppm (parts per million) for 8 hours per day exposure. Ozone can be produced from water by an electrochemical method and by proton exchange membranes, and from air or oxygen by coronal discharge. Ozone concentrations of 20 to 100 ppb are recommended for disinfection. The dosage is dependent on the TOC and microbiological load of the system and whether or not a mature biofilm is present. The concentration of ozone generated from air or pure oxygen is very low and transfer efficiency into water is even lower, thus affecting the dose. Also, due to extremely low solubility of ozone in water, the design of the ozone diffuser is an important consideration. Generally only 2 % to 4 % of gas contains ozone and 3 to 10 minutes of contact time is required to dissolve the gas in water. An efficient contactor gets 90 % efficiency in transferring ozone to water. Ozone concentrations can be measured using ozone in water test strips or other acceptable methods for determining ozone in water.

Frequent disinfection is important if biofilm formation is to be minimized. Smeets, et al. (2003) compared the development of biofilm between a water treatment system based on a single reverse osmosis unit producing purified water and a water treatment system based on double reverse osmosis and electric deionization, which was continuously disinfected with ultraviolet light and treated with ozone once a week. In contrast to a standard water treatment system producing purified water, the use of a system producing highly purified water, which was also treated with regular disinfection procedures, led to a significant reduction in biofilm formation, bacterial growth, and endotoxin levels in a highly vulnerable part of a water treatment system.

#### **4.4 System maintenance**

The quality of the dialysate is ultimately determined by the quality of the feed water, the design and maintenance of the water treatment and distribution system, the method used to prepare bicarbonate concentrate, and the maintenance of the dialysis machine. Options for disinfection are discussed in 4.3.

System operation and performance requires appropriate maintenance, monitoring, scheduling of replacement of consumables used in the water treatment, and disinfection. Manufacturer's recommendations should be followed regarding regular maintenance, cleaning, and disinfection procedures of the equipment. The user is responsible for developing a plan for appropriate operation and maintenance.

The user's procedures for proper maintenance of a water treatment system should include the following:

- a plan for monitoring and disinfection that includes the type and frequency of maintenance required;
- action levels and maximum allowable levels for bacteria endotoxin and other monitored parameters;
- validated test methods;
- provision of appropriate training for all personnel involved, documentation of that training and periodic audits to assess consistency of performance by trained personnel;
- records, maintained to include date, time, name of the person performing maintenance, test results, etc.; and
- a defined procedure to reconcile deviations.

All data analysis, related corrective and preventive action (CAPA), disinfection processes, and risk assessments should be performed by qualified individuals.

Action levels for all appropriate parameters and maximum allowable levels need to be established before regular monitoring starts.

#### **4.4.1 System disinfection**

Disinfection is considered the primary mechanism for the inactivation/destruction of microorganisms in the water distribution system, bicarbonate concentrate preparation and distribution systems, and the dialysis machine including the incoming water line to ensure contamination of the water system is kept to a minimum.

#### **4.4.2 Filter maintenance**

Appropriate steps should be taken to ensure that filters are not blocked and to prevent their colonization with bacteria. These steps should include replacement of filters, periodic flushing and backwashing of filters, and disinfection.

Water softeners and mixed bed deionizers used for water treatment need to be regenerated to maintain their effectiveness. Softeners are regenerated in situ using a salt solution. Regeneration cycles are usually preprogrammed to start automatically based on time, volume of water treated, or hardness, as measured by an on-line hardness monitor. During regeneration cycles, by-pass circuits must be used to shunt the product water flow from the regenerating softener away from patients. Cation and anion mixed bed deionizers use strong acids or alkali to regenerate. For that reason, exchange tanks, which are regenerated off-site, are used.

#### **4.4.3 Chemical quality of water**

The ability of the water treatment system to produce water that meets applicable standards for chemical contaminants, such as those provided in ANSI/AAMI/ISO 13959:2009, should be tested on a regular basis. The operational plan for the water treatment system should include an established protocol for testing the performance of each component of the system. Records of the test results and equipment maintenance should be maintained.

### **5 Demonstrating compliance with recommendations for the microbiological quality of dialysate**

Over 200 species of bacteria have been cultured in water and dialysate from hemodialysis facilities, and many other species that cannot be cultured using standard laboratory media are also present (Gomlia, et al., 2005; Nystrand, R. 2008; Pass, et al., 1996; Arvanitidou, et al., 2000). Because endotoxin levels in dialysate reportedly do not correlate with viable bacterial counts (Ledebø and Nystrand 1999), requirements to test for both bacteria and endotoxin are included in all current water and dialysate standards.

As water treatment systems, distribution loops, storage tanks, dialysis machines, and bicarbonate concentrate can contribute to the bioburden exposure of the hemodialysis patient, it is important to monitor these systems to ensure effective control of bacteria and endotoxin. Monitoring serves to demonstrate effectiveness of the facility's disinfection program. The data should not be used to determine when a disinfection of the system should be performed, but rather to evaluate the effectiveness of the current disinfection schedule. The results of monitoring should be interpreted relative to the history of the system: whether the system has been recently compromised, undergone maintenance procedures, or undergone major component or configuration change since the last monitoring. Disinfection of the system should be done on a regular basis to limit biofilm formation and minimize microbial contamination.

#### **5.1 Monitoring bacterial levels**

Recommended culturing methods differ by standard, country and whether dialysate or water is being tested. The most widely accepted are those recommended in ISO 13959 and ISO 11663. They are meant for monitoring viable bacteria only.

NOTE Bacterial levels recommended in ANSI/AAMI/ISO 13959 and ANSI/AAMI/ISO 11663 are lower than those recommended in the previous US standards, RD62:2006 and RD52:2004. The lower levels in ANSI/AAMI/ISO 13959 and ANSI/AAMI/ISO 11663 had not yet been adopted as regulation by the Centers for Medicare and Medicaid Services at the time of publication of this TIR.

It is important to remember that the culturing conditions recommended in current standards may not detect certain organisms, such as mycobacteria (Bolan, et al., 1985; Lowry, et al., 1990), and that no matter what culturing technique is used, the analysis of fluid samples only yields information on planktonic organisms; organisms present in biofilm on the surfaces of pipes and vessels will not be detected. Biofilm is the primary colonial mechanism and the preferred growth pattern for the microorganisms usually found in water and dialysate systems. Fluid samples may yield relatively low counts of bacteria even though a very large biofilm population exists. Depending on how the sample is obtained, the change in flow characteristics due to the sampling event may dislodge some biofilm, but regardless of the sample method, it is unlikely that the recorded count closely represents the actual bacterial population. In systems that have fluctuating water flow, or periodic flushing, bacteria will be sloughed off during the flush. This results in random 'particle showers' of bacteria, which can explain day-to-day fluctuations seen in total bacteria count results.

Table 1 below summarizes the recommended culture media and methods, incubation duration, and temperatures for the various dialysis fluids based on the specific standard and type of fluid.

**Table 1 — Microbiological techniques for monitoring water and dialysate**

| Standard/ fluid type tested     | Media type                                                              | Culturing method                                           | Sample volume processed                                       | Incubation temperature/time |
|---------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|-----------------------------|
| Water (ISO 13959)               | Tryptone Glucose Extract Agar (TGEA), Reasoner's 2A (R2A) or equivalent | Spread plate, pour plate or membrane filtration techniques | Spread plate, 0.1-0.3 mL<br><br>Pour plate, 0.1-1mL           | 17-23 °C/7 days             |
| Standard Dialysate (ISO 11663)  | TGEA, R2A or equivalent                                                 | Spread plate, pour plate or membrane filtration techniques | Spread plate, 0.1-0.3 mL<br><br>Pour plate, 0.1-1mL           | 17-23 °C/7 days             |
| Ultrapure Dialysate (ISO 11663) | TGEA, R2A or equivalent                                                 | Membrane filtration                                        | 10 mL-1000 mL(1L) filtered through a 0.22 µm bacterial filter | 17-23 °C/7 days             |

\*None of these methods can provide an absolute measure of the number of organisms in a sample of water or dialysate. However, higher yields of total viable bacteria are obtained with longer incubation times, lower temperatures, and more nutrient-poor media.

NOTE The methodologies specified in Table 1 above may not detect non-tubercular mycobacteria such as those isolated in connection with outbreaks of infection in dialysis clinics (Bolan, et al., 1985; Lowry, et al., 1990) or yeast and fungi that have been reported as contaminants in water and dialysate used for hemodialysis (Klein, et al., 1990).

None of these testing methods is able to show the complete picture of bacterial contamination. The results will depend on the type of medium used, the conditions of incubation (temperature and time) as well as the type of organisms present at the time. The type of microbial degradation products that are present can also influence the results seen. Only living organisms can give rise to a colony on an agar plate. Many organisms will not be able to grow well or at all under the culture conditions used and thus will not be represented in the resultant plate count. As an alternative to conventional cultures, levels of both living and dead bacteria can be determined using epifluorescence microscopy, a rapid turn-around method based on fluorescent dyes (Yamaguchi, et al., 2007; Ogawa, et al., 2005; Shimakita, et al. 2007). In these assays, dialysate is subjected to membrane filtration and the bacteria retained on the membrane stained with 4',6'-diamidino-2-phenylindole (DAPI), which stains all bacteria, and carboxyfluorescein diacetate (CFDA), which stains live bacteria, or propidium iodide, which stains dead bacteria. The stained bacteria are visualized using fluorescence microscopy and counted using automated image analysis. Results can be obtained within 1 to 2 hours of collecting the dialysate sample, compared to the 2 to 7 days required for conventional culturing methods. While not used in the United States as yet, these assay methods are being applied to the analysis of dialysate in Japan. Another approach to quantifying bacteria in solutions uses fluorochromes and solid phase cytometry (Broadaway, et al., 2003; Lisle, et al., 2004). These methods are suitable for high throughput compared to conventional culture methods. To date, their use in the United States has been confined to the pharmaceutical industry and as a research tool.

Monitoring for bacterial contamination of ultrapure dialysate should utilize the membrane filtration method with a minimum sample volume filtered of 10 mL. A larger volume improves sensitivity of the assay, but does increase the risk of contamination in handling such a large sample both during sample collection and analysis. Contamination of the sample during analysis can be minimized by processing samples in a properly maintained biological safety cabinet. Compliance with the microbiological standard for substitution solution for on-line convective therapies cannot be demonstrated by culturing for viable bacteria. The sample volume needed to be processed to provide the necessary sensitivity would be impractical to collect and impractical to culture. Somewhere between 30,000,000 mL to 300,000,000 mL would be needed to detect 30 to 300 colonies, the number of colonies required to have a statistically valid count on an agar plate. This assumes that 100 % of the organisms are detectable by the given culture medium and conditions of incubation. Thus, compliance with the microbial standards for this type of dialysate can only be met currently by using a validated system for generating on-line ultrapure dialysate for infusion or substitution fluid and following the requirements and instructions of the manufacturer of the system and components (ISO 11663:2009).

Ideally, to maximize recovery, the original environmental conditions of the sample should be duplicated by the culture conditions. However this is typically impossible to do for all organisms. Under any set of environmental conditions, some organisms will dominate over others. In a biofilm for example, there are some organisms that are

dormant as they reside deep within the biofilm under anaerobic conditions, while others on the surface are freer to proliferate with sufficient oxygen being available. However, if a piece of the biofilm sloughs off from the surface of a pipe, tubing, or filter, the less dominant species may now be able to proliferate and the colony count and number of detectable organisms may change.

Because the water and dialysate environments are relatively nutrient poor, one can argue that a nutrient poor medium such as TGEA and incubation at room temperature or lower is most appropriate as specified by ISO. Several studies have shown that use of a nutrient-poor media such as Reasoner's R2A or tryptone glucose extract agar (TGEA) results in an increased recovery of bacteria from water (Ledebø and Nystrand, 1999; van der Linde, et al., 1999; Pass, et al., 1996; Reasoner and Geldreich, 1985). Under these conditions, microbial growth is slower and thus a longer incubation period is required (5 to 7 days) (Ledebø and Nystrand, 1999; Pass, et al., 1996; Reasoner and Geldreich, 1985). On the other hand, when the dialysate comes in contact with the patient, the temperature is typically 35 °C - 37 °C, and microorganisms surviving at this temperature might be considered to be putting the patient at most risk. Thus previous AAMI standards focused on shorter incubation times, a more nutrient rich medium (Tryptic Soy Agar-TSA), and an incubation temperature of 35 °C - 37 °C to mimic the conditions under which the dialysate is delivered to the patient. This reasoning may have had merit in the early days of dialysis when membrane ruptures were common and bacteria had direct access to the bloodstream. However, membrane ruptures are now extremely rare, and there are no reliable reports of bacteria or other microorganisms crossing intact dialyzer membranes even under the influence of backfiltration. Rather, the emphasis is on determining contamination by bacteria that proliferate in the fluid handling systems at room temperature and that contribute small pro-inflammatory substances to the water and dialysate.

A study by Ledebø and Nystrand (1999) showed up to a 2 log reduction in colony counts when dialysate samples were cultured on TSA at 37 °C versus on TGEA at 20 °C. Pass et al. (1996) made a similar observation under the same conditions both with TGEA, R2A and SMA (Standard Methods Agar). A longer incubation time of 7 days versus the 48 hours recommended in AAMI RD52 resulted in an increase in the number of colonies. Similar results were reported by van der Linde, et al. (1999). Thus, colony counts based on the AAMI standard almost certainly underestimate the resident bacterial population.

Current standards do not address monitoring for the levels of cytokine-inducing substances that could be derived from the total microbial population present in the dialysate other than by specifying limits and action levels for endotoxin. While endotoxin is a known mediator of cytokine activation, several investigators (Lonnemann, et al., 1992 and 2001) have shown that up to 50 % of the cytokine inducing substances in dialysate are not detectable by the LAL assay. Measurement of interleukin-1 production by isolated peripheral blood mononuclear cells provides a more global test that detects both endotoxin and non-endotoxin cytokine-inducing substances (Lonnemann, et al., 1992). This test is not practical for routine surveillance of dialysate quality because of the need for freshly isolated human blood cells. Recently, a version of this test was described in which the monocytic cell line, THP-1, was used instead of peripheral blood mononuclear cells (Glorieux, et al., 2009). Samples of dialysate are incubated with THP-1 cells for 24 hours and secreted interleukin-1 $\beta$  measured by ELISA.

Regardless of which dialysate quality recommendations are adopted, compliance is still an issue. In multiple studies conducted in the United States, Canada and Europe from 1990 to 1998, 7.4 % to 35.3 % of water samples and 11.7 % to 36.3 % of dialysate samples were out of compliance with the AAMI Standards for microbial levels and up to 44 % of samples contained more than 5 EU/mL endotoxin as measured by the LAL test (Klein, et al., 1990; Bambauer, et al., 1994; Laurence, et al., 1995; Arvanitidou, et al., 1998). These studies are all now at least 10 years old. In the interim, much more attention has been paid to fluid quality, particularly by the Centers for Medicare and Medicaid Services in the United States and more up-to-date studies are needed to establish current compliance with prevailing standards.

In all cases, the results of microbial monitoring should be interpreted relative to the monitoring history of the system, whether the system has been compromised, undergone maintenance procedures or a major component or configuration change since the last monitoring and routine disinfection was done. Frequency of disinfection should be in compliance with the applicable standards.

## 5.2 Monitoring for endotoxin levels

Endotoxin is the lipopolysaccharide-lipid A portion of the Gram-negative bacteria outer cell membrane. The *Limulus amoebocyte* lysate (LAL) test is the accepted method for endotoxin testing. However, other bacterial cell wall components, such as peptidoglycans and fragments such as muramyl-dipeptides and exotoxins cannot be detected by this assay, and 50 % of cytokine-inducing substances are not detected by the LAL assay (Lonnemann et al., 1992). While not detecting many bacterial products, the LAL assay is simple to perform and provides valuable data. It can indicate the potential risk of pyrogenic reactions and results can be obtained in a shorter timeframe than that needed to obtain results from bacterial cultures.

It was previously thought that endotoxin testing could substitute for bacterial culture testing, but several studies have shown no correlation between CFU levels and endotoxin levels (Klein, et al., 1990). Ledebø and Nystrand (1999)

reported a similar lack of correlation between endotoxin levels and either viable or total cell count (viable and non-viable measured microscopically with acridine orange staining). They postulated that this may have been due to different endotoxin activities by different bacterial strains, or larger aggregates or complexes having formed in dialysis fluid, making the Lipid A unavailable to react in the LAL assay. The presence of biofilm also contributes to the observed lack of correlation between endotoxin levels and bacterial counts. It is reasonable to expect some mathematical relationship between the two values, and in fact there is a correlation between the total population of bacteria (viable and residue of dead bacteria) and endotoxin levels subject to species variation and growth environment. However, the micellar nature of endotoxin tends to favor its free circulation while viable bacteria prefer the colony characteristics of the biofilm structure; thus, the correlation between the two becomes widely variable when only planktonic bacteria are sampled. It is not unusual to experience high endotoxin counts and relatively low observed bacteria counts. In such situations, it is prudent to recognize the underlying probability that there is a mature biofilm providing circulating endotoxin that can be easily sampled, while the active bacterial culture resides within the biofilm and is not readily accessible for sampling and culturing. The role of biofilm as a source of endotoxin is supported by the observation of Kulander, et al. (1993) that endotoxin levels increased with the length of the distribution system from the RO to the dialysis machines.

Two types of LAL assay can be used: a kinetic assay (colorimetric or turbidimetric) and the gel-clot assay. It is critical to have a validated test method with appropriate sensitivity. For ultrapure dialysate, the assay should be capable of measuring levels of endotoxin less than 0.03 EU/ml. The kinetic assay is generally performed by a qualified laboratory and provides quantitative results with a sensitivity of 0.005 EU/mL, or better, for water. The gel-clot method is not as sensitive, providing only a positive or negative result at specified levels of sensitivity. All forms of the LAL assay can be affected by the presence of interfering substances. These interfering substances can either inhibit the assay, giving rise to false negative results, or enhance the assay resulting in an over-estimation of the true concentration. Possible interfering substances in dialysate include divalent cations ( $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ), which can inhibit the assay, and glucose, which can contain (1 $\rightarrow$ 3)- $\beta$ -glucan, a substance known to test positive in the assay. Interference does not appear to be a problem with currently available turbidimetric assays. If necessary, however, the impact of interfering substances can be diminished by diluting the sample with sterile non-pyrogenic water and by using special buffers to eliminate the effects of (1 $\rightarrow$ 3)- $\beta$ -glucan. Bicarbonate concentrate is inhibitory to the LAL assay, and dilution with endotoxin-free/pyrogen-free water is required to obtain valid results. Current standards do not recommend testing of bicarbonate concentrate prepared at a dialysis facility for endotoxin, rather recommending that patient safety would be adequately safeguarded if the water used to prepare the concentrate and the final dialysate meet the bacterial and endotoxin limits.

### 5.3 Monitoring biofilm

There are a number of methods available for detection of biofilm, although most are impractical in a dialysis setting. Conventional methods are based on scraping or swabbing a defined area of the internal surface of a pipe or using a removable coupon or ring that can be sonicated to recover biofilm. The recovered material is then analyzed using conventional culturing methods. An example is the "Robbins device" (Kharazmi, et al., 1999), which consists of plugs inserted flush with the inner pipe wall so that they are exposed to the same flow conditions as the pipe. The plugs are removed at intervals for analysis. Newer methods that do not require recovery of biofilm and culturing include the use of fluorescent stains combined with automated spectrophotometric analysis (Jacobs, et al. 1996) or confocal laser scanning microscopy (Lawrence and Neu, 1999).

### 5.4 Recommended monitoring frequencies

A key concept in routinely producing ultrapure dialysate is that disinfection of all fluid handling systems should be performed on a schedule that prevents bacterial proliferation. Regular monitoring of the microbial quality of water and dialysate is used to verify the adequacy of the disinfection schedule. Thus, the frequency of monitoring at a given facility should be based on that facility's disinfection schedule. Although the frequency of monitoring may differ from facility to facility, some general guidelines can be given.

- For water storage and distribution systems, the frequency of monitoring should be based on data collected during the initial validation process and reassessed in light of the results of subsequent revalidations. Weekly monitoring is frequently adopted in the initial phase of operation while the system is undergoing performance validation. This frequency may then be adjusted based on the results of the validation process, but the interval between samples usually does not exceed one month. Less frequent monitoring might be possible under certain circumstances, such as when systems are disinfected daily. However, a decision to sample less frequently than once per month should be taken only when data obtained over an extended period of operation show consistent compliance with the appropriate standards.

NOTE Low bacterial counts obtained during the first month of operation of a new system should be treated with caution, because microbiological growth in a fluid system starts as surface growth (biofilm formation) and little or nothing might be seen in a fluid sample taken from a system during that time. In particular, low levels of bacteria during the first month of operation should not be used as a rationale for decreasing the

frequency of disinfection. On the other hand, high bacteria counts indicate a need to increase the frequency of disinfection and to examine the system for breaks in integrity that are allowing recontamination from external sources.

- For dialysis machines, samples should be taken from the line just before entry of the dialysate to the dialyzer, either directly from the tubing or from an in-line sampling port. Note that sampling ports, depending on their design, can be foci for bacterial growth, biofilm, and endotoxin. Therefore, sampling directly from the dialysis tubing proximal to the dialyzer is preferred.
- For dialysis machines, at least two machines should be sampled each sampling period to verify the effectiveness of the disinfection process. Sampling should be rotated to ensure that all machines are tested at least once per year. An unacceptable result for the one machine sample should lead to corrective actions involving all machines. Monthly monitoring is most frequently adopted.
- For water storage and distribution systems, the number of samples and positions of sampling should be based on the size and complexity of the system. In general, samples should be taken from the last outlet of the distribution loop and outlets supplying reuse equipment and concentrate mixing tanks.
- For water treatment systems, samples should be drawn after the last purification device in the system or in accordance with the system manufacturer's instructions for use.
- Because acid concentrate is not conducive to bacterial growth, monitoring these systems for bacteria and endotoxin is not necessary. Also, because it is difficult to perform cultures and endotoxin assays on samples with high concentrations of salts, routine monitoring of bicarbonate concentrate is not necessary.
- If test results are not in compliance with the requirements of the applicable standard, additional testing from an expanded number of sampling sites may be helpful in troubleshooting the problem.
- It is not necessary to take samples of ultrapure dialysate if its production path within the dialysis machine is fitted with bacteria- and endotoxin-retentive filters validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless required by the manufacturer's instructions for use of the filter. However, it might be necessary to sample the dialysate entering such a bacteria- and endotoxin-retentive filter, depending on the manufacturer's instructions for use of the filter; for example, when the instructions for use specify the quality of the fluid entering the filter.
- Samples should always be collected before disinfection. If repeat samples need to be taken, such as in the event of an action level being exceeded and disinfection has already been initiated, the system should be flushed completely and tested for residual disinfectant (if possible) prior to collection of repeat samples. In general, resampling should not occur sooner than 24 hours after disinfection except in those systems disinfected daily, where resampling should occur as close as is practicable to the next disinfection.
- If there is a clinical indication of a pyrogenic reaction or septicemia, additional sampling is in order.
- Applicable standards should be consulted for sampling instructions and recommendations regarding sample volume, storage, handling, and maximum time lapse requirements to properly maintain samples prior to analysis. This will help ensure scientifically valid results.
- It is not possible to monitor compliance with the bacterial quality requirements for substitution solution using presently available culturing methods.

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# **Cardiovascular implants and extracorporeal systems — Hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators**

Approved 26 July 2010 by  
**Association for the Advancement of Medical Instrumentation**

Approved 3 August 2010 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies requirements for hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators for use in humans.

**Keywords:** biological safety, filtration rate, inlet and outlet ports, labeling, mechanical integrity, nonpyrogenicity, performance characteristics, sieving coefficient, sterility, test methods

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1–57020–390–3



# Contents

Page

|                                                         |     |
|---------------------------------------------------------|-----|
| Glossary of equivalent standards .....                  | iv  |
| Committee representation .....                          | vi  |
| Background of ANSI/AAMI adoption of ISO 8637:2010 ..... | vii |
| Foreword .....                                          | vii |
| Introduction .....                                      | ix  |
| 1 Scope.....                                            | 1   |
| 2 Normative references .....                            | 1   |
| 3 Terms and definitions.....                            | 2   |
| 4 Requirements .....                                    | 4   |
| 4.1 Biological safety.....                              | 4   |
| 4.2 Sterility .....                                     | 4   |
| 4.3 Nonpyrogenicity.....                                | 5   |
| 4.4 Mechanical characteristics .....                    | 5   |
| 4.5 Performance characteristics.....                    | 7   |
| 4.6 Expiry date.....                                    | 8   |
| 5 Test methods.....                                     | 8   |
| 5.1 General.....                                        | 8   |
| 5.2 Biological safety.....                              | 9   |
| 5.3 Sterility .....                                     | 9   |
| 5.4 Nonpyrogenicity.....                                | 9   |
| 5.5 Mechanical characteristics .....                    | 9   |
| 5.6 Performance characteristics.....                    | 10  |
| 5.7 Expiry date.....                                    | 16  |
| 6 Labeling .....                                        | 16  |
| 6.1 Labeling on the device .....                        | 16  |
| 6.2 Labeling on the unit containers.....                | 16  |
| 6.3 Labeling on the outer containers .....              | 17  |
| 6.4 Accompanying documentation .....                    | 17  |
| Bibliography .....                                      | 20  |

## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation. The code in the US column, “(R)20xx” indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

| International designation                          | U.S. designation                                                                                            | Equivalency                                                     |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| IEC 60601-1:2005<br>Technical Corrigendum 1 and 2  | ANSI/AAMI ES60601-1:2005 and ANSI/AAMI<br>ES60601-1:2005/A2:2010<br>ANSI/AAMI ES60601-1:2005/C1:2009 (amdt) | Major technical variations<br>C1 Identical to Corrigendum 1 & 2 |
| IEC 60601-1-2:2007                                 | ANSI/AAMI/IEC 60601-1-2:2007                                                                                | Identical                                                       |
| IEC 60601-2-2:2009                                 | ANSI/AAMI/IEC 60601-2-2:2009                                                                                | Identical                                                       |
| IEC 60601-2-4:2002                                 | ANSI/AAMI DF80:2003/(R)2010                                                                                 | Major technical variations                                      |
| IEC 60601-2-19:2009                                | ANSI/AAMI/IEC 60601-2-19:2009                                                                               | Identical                                                       |
| IEC 60601-2-20:2009                                | ANSI/AAMI/IEC 60601-2-20:2009                                                                               | Identical                                                       |
| IEC 60601-2-21:2009                                | ANSI/AAMI/IEC 60601-2-21:2009                                                                               | Identical                                                       |
| IEC 60601-2-24:1998                                | ANSI/AAMI ID26:2004/(R)2009                                                                                 | Major technical variations                                      |
| IEC 60601-2-47:2001                                | ANSI/AAMI EC38:2007                                                                                         | Major technical variations                                      |
| IEC 60601-2-50:2009                                | ANSI/AAMI/IEC 60601-2-50:2009                                                                               | Identical                                                       |
| IEC 80601-2-30:2009 and Technical<br>Corrigendum 1 | ANSI/AAMI/IEC 80601-2-30:2009 and<br>ANSI/AAMI/IEC 80601-2-30:2009/ C1:2009<br>(amdt) – consolidated text   | Identical (with inclusion)<br>C1 Identical to Corrigendum 1     |
| IEC 80601-2-58:2008                                | ANSI/AAMI/IEC 80601-2-58:2008                                                                               | Identical                                                       |
| IEC/TR 60878:2009                                  | ANSI/AAMI/IEC TIR60878:2003                                                                                 | Identical                                                       |
| IEC/TR 62296:2009                                  | ANSI/AAMI/IEC TIR62296:2009                                                                                 | Identical                                                       |
| IEC 62304:2006                                     | ANSI/AAMI/IEC 62304:2006                                                                                    | Identical                                                       |
| IEC/TR 62348:2006                                  | ANSI/AAMI/IEC TIR62348:2006                                                                                 | Identical                                                       |
| IEC/TR 62354:2009                                  | ANSI/AAMI/IEC TIR62354:2009                                                                                 | Identical                                                       |
| IEC/TR 80002-1:2009                                | ANSI/IEC/TR 80002-1:2009                                                                                    | Identical                                                       |
| ISO 5840:2005                                      | ANSI/AAMI/ISO 5840:2005/(R)2010                                                                             | Identical                                                       |
| ISO 7198:1998                                      | ANSI/AAMI/ISO 7198:1998/2001/(R)2010                                                                        | Identical                                                       |
| ISO 7199:2009                                      | ANSI/AAMI/ISO 7199:2009                                                                                     | Identical                                                       |
| ISO 8637:2010                                      | ANSI/AAMI/ISO 8637:2010                                                                                     | Identical                                                       |
| ISO 8638:2010                                      | ANSI/AAMI/ISO 8638:2010                                                                                     | Identical                                                       |
| ISO 10993-1:2009                                   | ANSI/AAMI/ISO 10993-1:2009                                                                                  | Identical                                                       |
| ISO 10993-2:2006                                   | ANSI/AAMI/ISO 10993-2:2006                                                                                  | Identical                                                       |
| ISO 10993-3:2003                                   | ANSI/AAMI/ISO 10993-3:2003/(R)2009                                                                          | Identical                                                       |
| ISO 10993-4:2002 and<br>Amendment 1:2006           | ANSI/AAMI/ISO 10993-4:2002/(R)2009 and<br>Amendment 1:2006/(R)2009                                          | Identical                                                       |
| ISO 10993-5:2009                                   | ANSI/AAMI/ISO 10993-5:2009                                                                                  | Identical                                                       |
| ISO 10993-6:2007                                   | ANSI/AAMI/ISO 10993-6:2007                                                                                  | Identical                                                       |
| ISO 10993-7:2008                                   | ANSI/AAMI/ISO 10993-7:2008                                                                                  | Identical                                                       |
| ISO 10993-9:2009                                   | ANSI/AAMI/ISO 10993-9:2009                                                                                  | Identical                                                       |
| ISO 10993-10:2002 and<br>Amendment 1:2006          | ANSI/AAMI BE78:2002/(R)2008<br>ANSI/AAMI BE78:2002/A1:2006/(R)2008                                          | Minor technical variations<br>Identical                         |
| ISO 10993-11:2006                                  | ANSI/AAMI/ISO 10993-11:2006                                                                                 | Identical                                                       |
| ISO 10993-12:2007                                  | ANSI/AAMI/ISO 10993-12:2007                                                                                 | Identical                                                       |
| ISO 10993-13:1998                                  | ANSI/AAMI/ISO 10993-13:1999/(R)2004                                                                         | Identical                                                       |
| ISO 10993-14:2001                                  | ANSI/AAMI/ISO 10993-14:2001/(R)2006                                                                         | Identical                                                       |
| ISO 10993-15:2000                                  | ANSI/AAMI/ISO 10993-15:2000/(R)2006                                                                         | Identical                                                       |
| ISO 10993-16:2010                                  | ANSI/AAMI/ISO 10993-16:2010                                                                                 | Identical                                                       |
| ISO 10993-17:2002                                  | ANSI/AAMI/ISO 10993-17:2002/(R)2008                                                                         | Identical                                                       |
| ISO 10993-18:2005                                  | ANSI/AAMI BE83:2006                                                                                         | Major technical variations                                      |
| ISO/TS 10993-19:2006                               | ANSI/AAMI/ISO TIR10993-19:2006                                                                              | Identical                                                       |

| International designation                       | U.S. designation                                       | Equivalency                 |
|-------------------------------------------------|--------------------------------------------------------|-----------------------------|
| ISO/TS 10993-20:2006                            | ANSI/AAMI/ISO TIR10993-20:2006                         | Identical                   |
| ISO 11135-1:2007                                | ANSI/AAMI/ISO 11135-1:2007                             | Identical                   |
| ISO/TS 11135-2:2008                             | ANSI/AAMI/ISO TIR11135-2:2008                          | Identical                   |
| ISO 11137-1:2006                                | ANSI/AAMI/ISO 11137-1:2006/(R)2010                     | Identical                   |
| ISO 11137-2:2006 (2006-08-01 corrected version) | ANSI/AAMI/ISO 11137-2:2006                             | Identical                   |
| ISO 11137-3:2006                                | ANSI/AAMI/ISO 11137-3:2006/(R)2010                     | Identical                   |
| ISO 11138-1: 2006                               | ANSI/AAMI/ISO 11138-1:2006/(R)2010                     | Identical                   |
| ISO 11138-2: 2006                               | ANSI/AAMI/ISO 11138-2:2006/(R)2010                     | Identical                   |
| ISO 11138-3: 2006                               | ANSI/AAMI/ISO 11138-3:2006/(R)2010                     | Identical                   |
| ISO 11138-4: 2006                               | ANSI/AAMI/ISO 11138-4:2006/(R)2010                     | Identical                   |
| ISO 11138-5: 2006                               | ANSI/AAMI/ISO 11138-5:2006/(R)2010                     | Identical                   |
| ISO/TS 11139:2006                               | ANSI/AAMI/ISO 11139:2006                               | Identical                   |
| ISO 11140-1:2005                                | ANSI/AAMI/ISO 11140-1:2005/(R)2010                     | Identical                   |
| ISO 11140-3:2007                                | ANSI/AAMI/ISO 11140-3:2007                             | Identical                   |
| ISO 11140-4:2007                                | ANSI/AAMI/ISO 11140-4:2007                             | Identical                   |
| ISO 11140-5:2007                                | ANSI/AAMI/ISO 11140-5:2007                             | Identical                   |
| ISO 11607-1:2006                                | ANSI/AAMI/ISO 11607-1:2006                             | Identical                   |
| ISO 11607-2:2006                                | ANSI/AAMI/ISO 11607-2:2006                             | Identical                   |
| ISO 11737-1: 2006                               | ANSI/AAMI/ISO 11737-1:2006                             | Identical                   |
| ISO 11737-2:2009                                | ANSI/AAMI/ISO 11737-2:2009                             | Identical                   |
| ISO 13408-1:2008                                | ANSI/AAMI/ISO 13408-1:2008                             | Identical                   |
| ISO 13408-2:2003                                | ANSI/AAMI/ISO 13408-2:2003                             | Identical                   |
| ISO 13408-3:2006                                | ANSI/AAMI/ISO 13408-3:2006                             | Identical                   |
| ISO 13408-4:2005                                | ANSI/AAMI/ISO 13408-4:2005                             | Identical                   |
| ISO 13408-5:2006                                | ANSI/AAMI/ISO 13408-5:2006                             | Identical                   |
| ISO 13408-6:2006                                | ANSI/AAMI/ISO 13408-6:2006                             | Identical                   |
| ISO 13485:2003                                  | ANSI/AAMI/ISO 13485:2003/(R)2009                       | Identical                   |
| ISO 14155-1:2003                                | ANSI/AAMI/ISO 14155-1:2003/(R)2008                     | Identical                   |
| ISO 14155-2:2003                                | ANSI/AAMI/ISO 14155-2:2003/(R)2008                     | Identical                   |
| ISO 14160:1998                                  | ANSI/AAMI/ISO 14160:1998/(R)2008                       | Identical                   |
| ISO 14161:2009                                  | ANSI/AAMI/ISO 14161:2009                               | Identical                   |
| ISO 14708-3:2008                                | ANSI/AAMI/ISO 14708-3:2008                             | Identical                   |
| ISO 14708-4:2008                                | ANSI/AAMI/ISO 14708-4:2008                             | Identical                   |
| ISO 14708-5:2010                                | ANSI/AAMI /ISO 14708-5:2010                            | Identical                   |
| ISO 14937:2009                                  | ANSI/AAMI/ISO 14937:2009                               | Identical                   |
| ISO/TR 14969:2004                               | ANSI/AAMI/ISO TIR14969:2004                            | Identical                   |
| ISO 14971:2007                                  | ANSI/AAMI/ISO 14971:2007                               | Identical                   |
| ISO 15223-1:2007 and A1:2008                    | ANSI/AAMI/ISO 15223-1:2007 and A1:2008                 | Identical                   |
| ISO 15223-2:2010                                | ANSI/AAMI/ISO 15223-2:2010                             | Identical                   |
| ISO 15225:2010                                  | ANSI/AAMI/ISO 15225:2010                               | Identical                   |
| ISO 15674:2009                                  | ANSI/AAMI/ISO 15674:2009                               | Identical                   |
| ISO 15675:2009                                  | ANSI/AAMI/ISO 15675:2009                               | Identical                   |
| ISO 15882:2008                                  | ANSI/AAMI/ISO 15882:2008                               | Identical                   |
| ISO 15883-1:2006                                | ANSI/AAMI ST15883-1:2009                               | Major technical variations  |
| ISO/TR 16142:2006                               | ANSI/AAMI/ISO TIR16142:2005                            | Identical                   |
| ISO 17664:2004                                  | ANSI/AAMI ST81:2004                                    | Major technical variations  |
| ISO 17665-1:2006                                | ANSI/AAMI/ISO 17665-1:2006                             | Identical (with inclusions) |
| ISO/TS 17665-2:2009                             | ANSI/AAMI/ISO TIR17665-2:2009                          | Identical                   |
| ISO 18472:2006                                  | ANSI/AAMI/ISO 18472:2006                               | Identical                   |
| ISO/TS 19218:2005                               | ANSI/AAMI/ISO 19218:2005                               | Identical                   |
| ISO 22442-1:2007                                | ANSI/AAMI/ISO 22442-1:2007                             | Identical                   |
| ISO 22442-2:2007                                | ANSI/AAMI/ISO 22442-2:2007                             | Identical                   |
| ISO 22442-3:2007                                | ANSI/AAMI/ISO 22442-3:2007                             | Identical                   |
| ISO 25539-1:2003 and A1:2005                    | ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009 | Identical                   |
| ISO 25539-2:2008                                | ANSI/AAMI/ISO 25539-2:2008                             | Identical                   |
| ISO 27186:2010                                  | ANSI/AAMI/ISO 27186:2010                               | Identical                   |
| ISO 81060-1:2007                                | ANSI/AAMI/ISO 81060-1:2007                             | Identical                   |
| ISO 81060-2:2009                                | ANSI/AAMI/ISO 81060-2:2009                             | Identical                   |

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Renal Disease and Detoxification Committee

The adoption of ISO 8637:2010 as an American National Standard was initiated by the AAMI Renal Disease and Detoxification Committee. The AAMI Renal Disease and Detoxification Committee also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Renal Disease and Detoxification Committee (U.S. Sub-TAG for ISO/TC 150/SC 2/WG 5) played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

*Cochairs:*           Conor Curtin  
                          Richard A. Ward, PhD

*Members:*           G Steven Acres, MD, Carolina Regional Nephrology Associates  
                          Larry Alexander, Florian Services  
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                          James Weldon Baker, AmeriWater  
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                          Conor Curtin, Fresenius Medical Care North America  
                          Jim Curtis, Home Dialysis Plus LTD  
                          R. Barry Deeter, RN MSN, University of Utah Dialysis Program  
                          Robert Dudek, Siemens Water Technologies Corporation  
                          Gema Gonzalez, FDA/CDRH  
                          Elizabeth Howard, Davita Inc..  
                          Bertrand L. Jaber, MD, Caritas St Elizabeths Medical Center  
                          Byron L. Jacobs, CBET, Sanford USD Medical Center  
                          David C. Katz, El Camino Hospital  
                          Fei M. Law, CaridianBCT Sterilization Services Inc.  
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                          Jo Ann Maltais, PhD, Maltais Consulting  
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                          Michael Webb, NxStage Medical Inc

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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

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## Background of ANSI/AAMI adoption of ISO 8637:2010

As indicated in the foreword to the main body of this document (page viii), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for minimum safety and performance requirements for hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators used in blood purification therapies.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the requirements provided in this document.

The U.S. adoption of ANSI/AAMI/ISO 8637:2010 was approved by the American National Standards Institute (ANSI) as a revision of ANSI/AAMI RD16:2007, *Cardiovascular implants and artificial organs-Hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators* on 3 August 2010. The AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) developed ANSI/AAMI RD16:2007 and initiated the U.S. adoption of ISO 8637:2010.

Major differences between ANSI/AAMI RD16:2007 and ANSI/AAMI/ISO 8637:2010 include the addition of alternative test solutions for use in determining clearances and sieving coefficients; the addition of  $\beta_2$ -microglobulin as an alternative solute to myoglobin in the determination of sieving coefficients; and changes to the hematocrit and protein concentration of test solutions used to determine the filtration rate of hemoconcentrators.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited. “May” is used to indicate that a course of action is permissible within the limits of the recommended practice. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Dr. Suite 301, Arlington, VA 22203-1633.

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NOTE—Beginning with the foreword on page viii, this American National Standard is identical to ISO 8637:2010.

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## Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 8637 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO 8637:2004), which has been technically revised.

## Introduction

This International Standard is concerned with devices intended for hemodialysis, hemodiafiltration, hemofiltration and hemoconcentration in humans. The requirements specified in this International Standard will help to ensure safety and satisfactory function.

It was not found practicable to specify materials of construction. This International Standard therefore requires only that materials have been tested and that the methods and results are made available upon request. There is no intention to specify, or to set limits on, the performance characteristics of the devices because such restrictions are unnecessary for the qualified user and would limit the alternatives available when choosing a device for a specific application.

The dimensions of the blood ports and the dialysis fluid or filtrate ports have been specified to ensure compatibility of the device with the extracorporeal blood circuit specified in ISO 8638. The design and dimensions have been selected in order to minimize the risk of leakage of blood and the ingress of air.

This International Standard reflects the consensus of physicians, manufacturers and other interested parties for devices that are approved for clinical use. Conformance with this International Standard is voluntary and it does not supersede any national regulation.





# Cardiovascular implants and extracorporeal systems — Hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators

## 1 Scope

This International Standard specifies requirements for hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators, hereinafter collectively referred to as “the device”, for use in humans.

This International Standard is not applicable to:

- extracorporeal blood circuits;
- plasmafilters;
- hemoperfusion devices;
- vascular access devices;
- blood pumps;
- pressure monitors for the extracorporeal blood circuit;
- air detection devices;
- systems to prepare, maintain or monitor dialysis fluid;
- systems used to perform hemodialysis, hemodiafiltration, hemofiltration or hemoconcentration;
- reprocessing procedures and equipment.

NOTE Requirements for the extracorporeal blood circuit for hemodialyzers, hemodiafilters and hemofilters are specified in ISO 8638.

## 2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 594-2, *Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 2: Lock fittings*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

### 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

#### 3.1

##### **blood compartment**

part of a hemodialyzer (3.12), hemodiafilter (3.10), hemofilter (3.14) or hemoconcentrator (3.9) through which blood is intended to pass

NOTE For hollow-fiber devices, the blood compartment includes the volume of the hollow fibers plus the headers.

#### 3.2

##### **clearance**

volume of a solution from which a solute is completely removed per unit time

#### 3.3

##### **convection**

transport of solutes across a semipermeable membrane, along with filtered fluid, caused by a pressure gradient or pressure differential across the membrane

#### 3.4

##### **dialysis fluid**

aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during hemodialysis (3.13) or hemodiafiltration (3.11)

NOTE 1 The term “dialysis fluid” is used throughout this International Standard to mean the fluid (made from dialysis water and concentrates) which is delivered to the hemodialyzer or hemodiafilter by the dialysis fluid delivery system. Such phrases as “dialysate”, “dialysis solution” or “dialysing fluid” can be used in place of dialysis fluid.

NOTE 2 The dialysis fluid entering the hemodialyzer or hemodiafilter is referred to as “fresh dialysis fluid”, while the fluid leaving the hemodialyzer or hemodiafilter is referred to as “spent dialysis fluid”.

NOTE 3 Dialysis fluid does not include pre-packaged parenteral fluids used in some renal replacement therapies, such as hemodiafiltration and hemofiltration.

#### 3.5

##### **dialysis fluid compartment**

part of a hemodialyzer (3.12) or hemodiafilter (3.10) through which dialysis fluid (3.4) is intended to pass

#### 3.6

##### **diffusion**

transport of solutes across a semipermeable membrane, caused by a concentration gradient

### **3.7**

#### **filtrate**

fluid removed from the blood across the semipermeable membrane into the dialysis fluid or filtrate compartment of a hemodialyzer (3.12), hemodiafilter (3.10), hemofilter (3.14) or hemoconcentrator (3.9), due to a pressure gradient (including the contributions of both hydrostatic and oncotic pressures) across the semipermeable membrane

### **3.8**

#### **hemoconcentration**

process whereby plasma water and electrolytes are removed from diluted blood across a semipermeable membrane

### **3.9**

#### **hemoconcentrator**

device intended to perform hemoconcentration (3.8)

### **3.10**

#### **hemodiafilter**

device intended to perform hemodiafiltration (3.11)

### **3.11**

#### **hemodiafiltration**

process whereby solute imbalances in a patient's blood are corrected by means of simultaneous convection and diffusion across a semipermeable membrane, and by replacement with an appropriate physiological fluid

NOTE Normally, the process also includes a net fluid removal.

### **3.12**

#### **hemodialyzer**

device intended to perform hemodialysis (3.13)

### **3.13**

#### **hemodialysis**

process whereby solute imbalances in a patient's blood are corrected, mainly by diffusion across a semipermeable membrane

NOTE Normally, the process also includes a net fluid removal.

### **3.14**

#### **hemofilter**

device intended to perform hemofiltration (3.15)

### **3.15**

#### **hemofiltration**

process whereby solute imbalances in a patient's blood are corrected, mainly by convection across a semipermeable membrane and replacement with an appropriate physiological fluid

NOTE Normally, the process also includes a net fluid removal.

### **3.16**

#### **labeling**

written, printed, graphic or electronic matter that:

— is affixed to a medical device or any of its containers or wrappers

or

— accompanies a medical device and which is related to identification, technical description and use of that medical device, but excluding shipping documents

### **3.17**

#### **sieving coefficient**

ratio of a solute concentration in the filtrate to the simultaneous concentration of the same solute in the plasma

### **3.18**

#### **transmembrane pressure**

TPM

$P_{TM}$

mean pressure exerted across a semipermeable membrane

NOTE For practical reasons, the mean TMP is generally expressed as either:

— the difference between arithmetic means of inlet and outlet pressures of the blood and dialysis fluid compartments of a hemodialyzer or a hemodiafilter

or

— the difference between the arithmetic mean of the inlet and outlet pressures of the blood compartment and the filtrate pressure of a hemofilter or a hemoconcentrator.

### **3.19**

#### **ultrafiltration coefficient**

permeability of membrane to water, generally expressed in milliliters per hour per millimeter of mercury

## **4 Requirements**

### **4.1 Biological safety**

Parts of the device that are intended to come into direct or indirect contact with blood shall be evaluated for freedom from biological hazards, in accordance with 5.2. If the device is labeled for reuse, testing shall be performed after reprocessing following the manufacturer's instructions for use.

Attention is drawn to the need to establish whether national regulations or national standards governing toxicology and biocompatibility testing exist in the country in which the device is produced and, if applicable, in the countries in which the device is to be marketed.

### **4.2 Sterility**

The blood pathway of the device shall be sterile. Compliance shall be verified in accordance with 5.3.

### **4.3 Nonpyrogenicity**

The blood pathway of the device shall be non-pyrogenic. Compliance shall be verified in accordance with 5.4.

### **4.4 Mechanical characteristics**

#### **4.4.1 Structural integrity**

The device shall be capable of withstanding a positive pressure of  $1.5 \times$  the manufacturer's recommended maximum pressure and a negative pressure not exceeding 700 mmHg (93.3 kPa below atmospheric pressure) or the highest obtainable negative pressure if at high elevation, when tested according to 5.5.1.

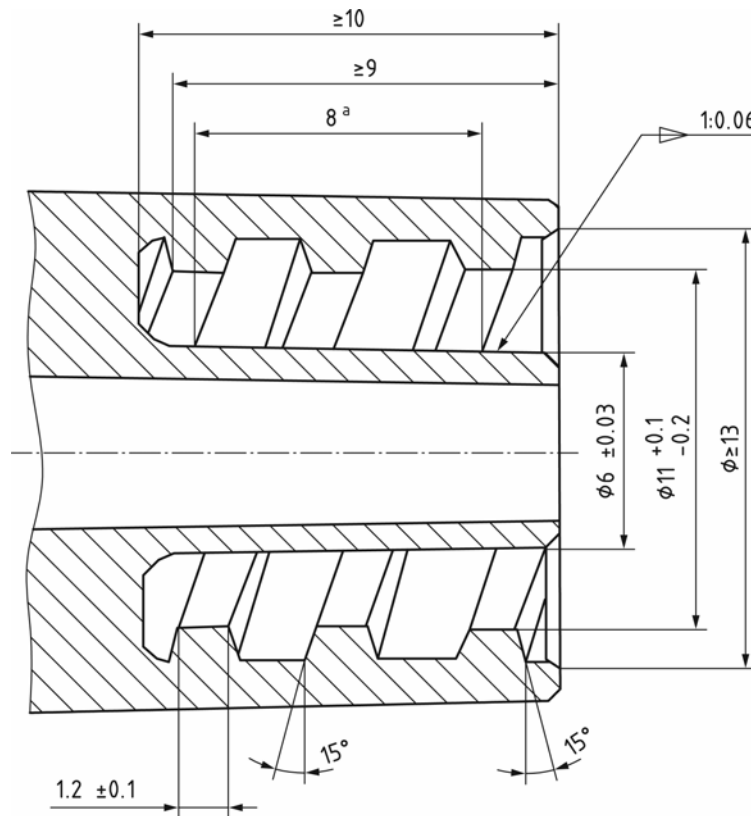
NOTE This requirement refers to the external case integrity of the device.

#### **4.4.2 Blood compartment integrity**

When exposing the blood compartment to a validated test procedure performed at  $1.5 \times$  the manufacturer's maximum recommended transmembrane pressure, the blood compartment shall not leak. Compliance with this requirement shall be verified in accordance with 5.5.2.

#### **4.4.3 Hemodialyzer, hemodiafilter and hemofilter blood compartment ports**

Except where the hemodialyzer, hemodiafilter or hemofilter and the extracorporeal blood circuit are designed as an integral system, the dimensions of the blood ports shall be as given in Figure 1. Compliance with this requirement shall be verified in accordance with 5.5.3.



<sup>a</sup> Double thread.

**Figure 1 — Main fitting dimensions of blood inlet and outlet ports**

#### 4.4.4 Hemodialyzer and hemodiafilter dialysis fluid compartment ports

Except where the hemodialyzer or hemodiafilter and the dialysis fluid circuit are designed as an integral system, the dimensions of the dialysis fluid compartment ports shall be as given in Figure 2. Compliance with this requirement shall be verified in accordance with 5.5.4.

#### 4.4.5 Hemofilter filtrate ports

Except where the hemofilter and the filtrate circuit are designed as an integral system, the filtrate ports of hemofilters shall comply either with Figure 2 or with the requirements of the Luer lock fitting of ISO 594-2. Compliance with this requirement shall be verified in accordance with 5.5.5.

#### 4.4.6 Hemoconcentrator blood and filtrate ports

The blood and filtrate ports of hemoconcentrators shall allow for a secure connection to the tubing which is to be used with the device. Compliance with this requirement shall be verified in accordance with 5.5.6.

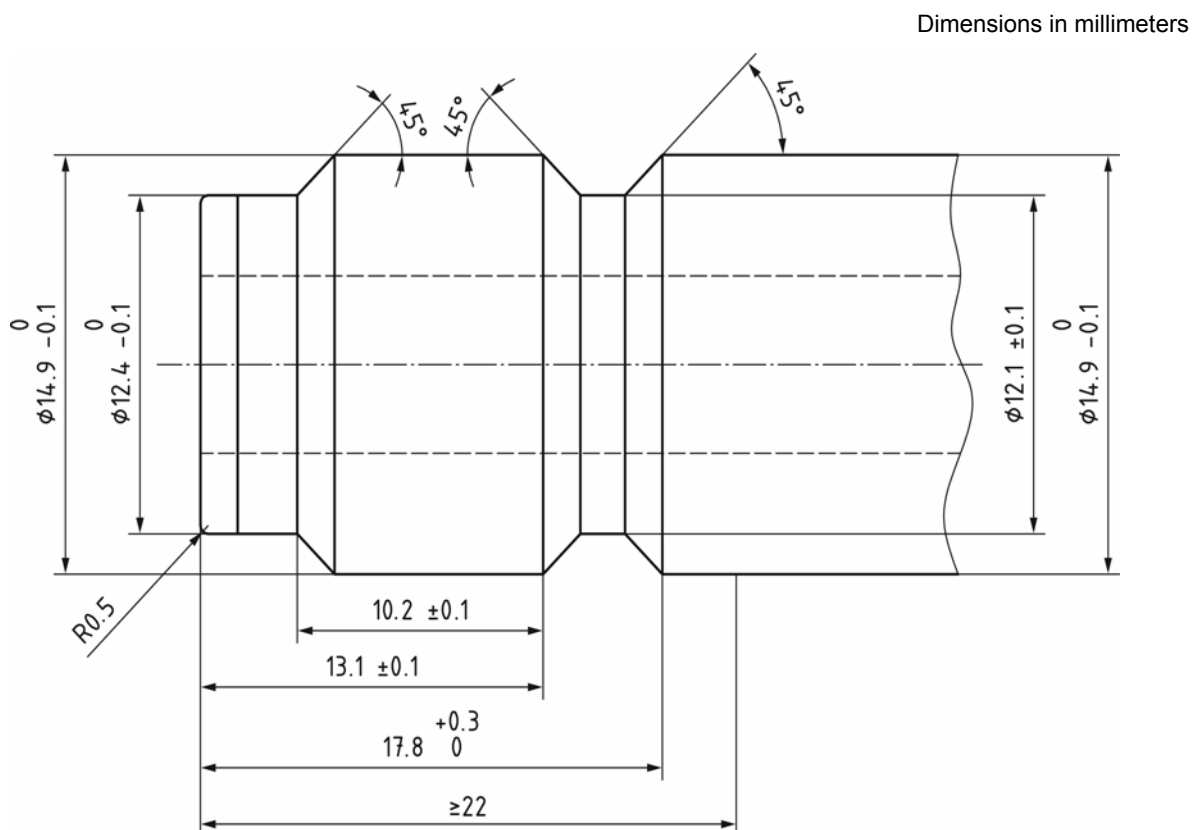


**Figure 2 — Main fitting dimensions of dialysis fluid inlet and outlet ports**

## **4.5 Performance characteristics**

### **4.5.1 Clearance of hemodialyzers and hemodiafilters**

The clearance of urea, creatinine, phosphate and vitamin B<sub>12</sub> shall be determined in accordance with 5.6.1. Blood and dialysis fluid flow rates shall cover the manufacturer's specified range.

NOTE As a supplement,  $K_0A$  results can be included.

### **4.5.2 Sieving coefficient of hemodiafilters, hemofilters and hemoconcentrators**

The sieving coefficient for albumin, inulin and myoglobin or  $\beta_2$ -microglobulin shall be determined in accordance with 5.6.2.

### **4.5.3 Ultrafiltration coefficient**

The ultrafiltration coefficient shall be determined in accordance with 5.6.3. Testing shall be conducted over the manufacturer's specified range of transmembrane pressures and blood flow rates.

#### 4.5.4 Volume of the blood compartment

The volume of the blood compartment shall be determined in accordance with 5.6.4 over the specified range of transmembrane pressures.

NOTE If the blood compartment is noncompliant, it is acceptable to determine the volume at one transmembrane pressure.

#### 4.5.5 Pressure drop of the blood compartment

The pressure drop of the blood compartment shall be determined in accordance with 5.6.5.

### 4.6 Expiry date

The biological safety, sterility and mechanical integrity of the device shall be proven after storage for a period corresponding to the expiry date. Compliance shall be in accordance with 5.7.

## 5 Test methods

### 5.1 General

The performance characteristics specified in 4.5 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that might alter its performance. If labeled for multiple uses, devices shall be tested for clearances and ultrafiltration coefficient after reprocessing according to the manufacturer's instructions to characterize the effects of the recommended cleaning agent and germicide on membrane performance.

The sample of devices shall be drawn at random from the manufacturer's production and shall have passed all applicable quality control steps, as well as sterilization, if applicable. They shall be prepared according to the manufacturer's recommendations as though they are to be used for a clinical procedure.

Measurements shall be made *in vitro* at  $(37 \pm 1)^\circ\text{C}$ . When the relationship between variables is non-linear, sufficient determinations shall be made to permit interpolation between the data points. The techniques of measurement given in this International Standard are reference tests. Other test methods may be used, provided they have been validated and shown to be precise and reproducible.

The test systems shown do not indicate all the necessary details of practicable test apparatus. The design and construction of actual test systems and the establishment of actual test systems shall also address the many factors contributing to measurement error, including, but not limited to, pressure measurement errors due to static head effects and dynamic pressure drops; parameter stabilization time; uncontrolled temperature variations at the non-constant flow rates; pH; degradation of test substances due to heat, light and time; degassing of test fluids; trapped air; and system contamination by foreign material, algae and bacteria.

NOTE Clause 5 contains tests that are of a type-testing nature, such as the ones described in 5.5.1, 5.5.3, 5.5.4, 5.6.1, 5.6.2, 5.6.3 and 5.6.4, which are carried out prior to marketing of a new device or when changes are made to the device or its manufacturing processes. Others are of a quality control nature, such as the ones described in 5.3, 5.4 and 5.5.2, which are repeated on a regular basis in accordance with quality management system requirements.



## Bibliography

- [1] ISO 7000, *Graphical symbols for use on equipment — Index and synopsis*
- [2] ISO 8638, *Cardiovascular implants and extracorporeal systems — Extracorporeal blood circuit for hemodialyzers, hemodiafilters and hemofilters*
- [3] ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*
- [4] ISO/TS 11135-2, *Sterilization of health care products — Ethylene oxide — Part 2: Guidance on the application of ISO 11135-1*
- [5] ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*
- [6] ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*
- [7] ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*
- [8] ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*
- [9] ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labeling and information to be supplied — Part 1: General requirements*
- [10] ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labeling, and information to be supplied — Part 2: Symbol development, selection and validation*
- [11] ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*
- [12] ISO 17665-2, *Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1*

## **5.2 Biological safety**

The biological safety of hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators that are intended to come into direct or indirect contact with the patient's blood shall be evaluated on samples of each new type of device prior to its marketing, or after any change in the materials of construction of that type of device, or after any change in the method of sterilization. If labeled for multiple use, testing shall demonstrate the safety of the device before first use and after reprocessing according to the manufacturer's instructions. Testing shall be carried out in accordance with ISO 10993-1, ISO 10993-4, ISO 10993-7 or ISO 10993-11, as relevant.

## **5.3 Sterility**

Compliance with 4.2 shall be verified by inspection of the records to show that the device has been exposed to a validated sterilization process.

## **5.4 Nonpyrogenicity**

Compliance with 4.3 shall be verified in accordance with ISO 10993-11.

## **5.5 Mechanical characteristics**

### **5.5.1 Structural integrity**

#### **5.5.1.1 General**

The requirements of 4.4.1 shall be verified by the following test methods.

#### **5.5.1.2 Positive-pressure test**

Completely fill the device with degassed water at  $(37 \pm 1)^\circ\text{C}$ . Seal all ports except the port to which pressure is applied. Apply a positive pressure  $1.5 \times$  the manufacturer's recommended maximum pressure and seal the apparatus. After 10 min, record the pressure and visually examine the device for leaks.

#### **5.5.1.3 Negative pressure test**

Completely fill the device with degassed water at  $(37 \pm 1)^\circ\text{C}$ . Seal all ports except the port to which pressure is applied. Put the device under sub-atmospheric pressure,  $1.5 \times$  the manufacturer's recommended maximum pressure, unless that sub-atmospheric pressure exceeds 700 mmHg or is not specified; in that case, apply a sub-atmospheric pressure of 700 mmHg (93.3 kPa) and seal the apparatus. After 10 min, record the pressure and visually examine the device for leaks.

### **5.5.2 Blood compartment integrity**

Compliance shall be determined by review of the validation records for the test procedure.

### **5.5.3 Hemodialyzer, hemodiafilter and hemofilter blood compartment ports**

Compliance with 4.4.3 shall be determined by inspection. See Figure 1 and Figure 3.

### 5.5.4 Hemodialyzer and hemodiafilter dialysis fluid compartment ports

Compliance with 4.4.4 shall be determined by inspection. See Figure 2.

### 5.5.5 Hemofilter filtrate ports

Compliance with 4.4.5 shall be determined by inspection and shall meet the requirements of Figure 2 or the requirements of ISO 594-2.

### 5.5.6 Hemoconcentrator blood and filtrate ports

Compliance with 4.4.6 shall be determined by inspection and shall not separate under an axial force of 15 N.

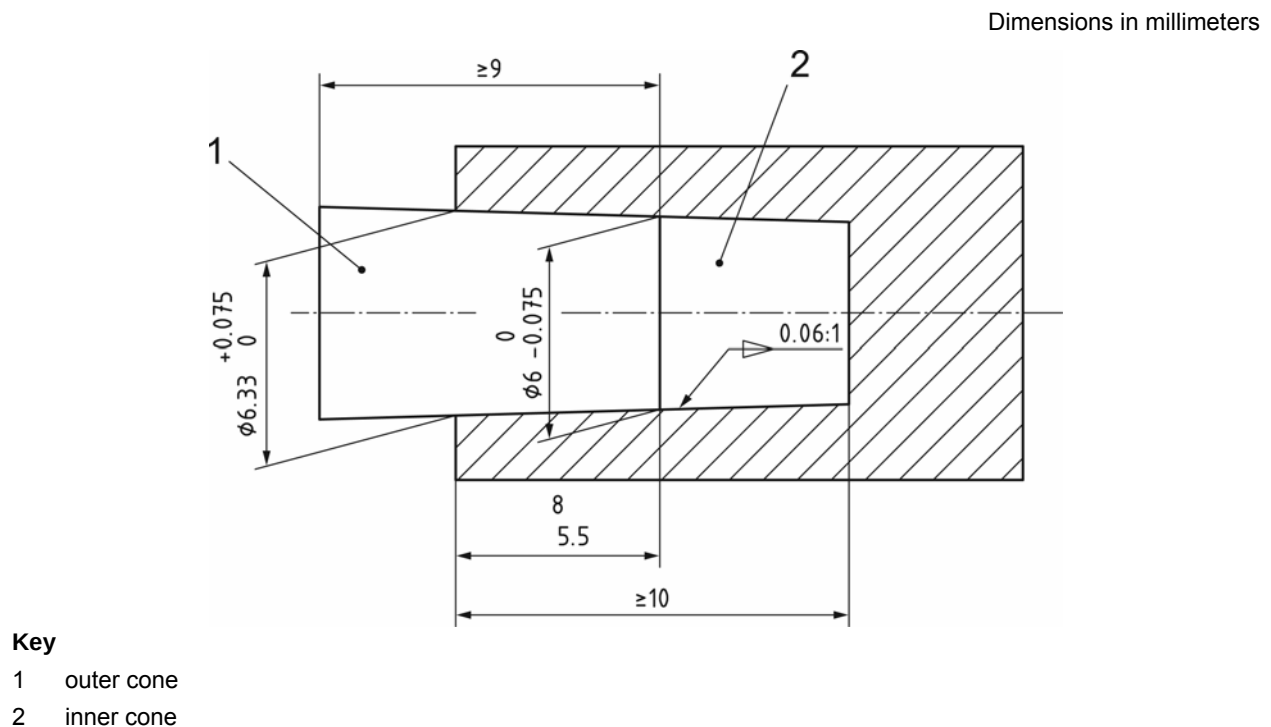


**Figure 3 — Gauge for measuring length of engagement of the male cone of blood inlet and outlet ports**

## 5.6 Performance characteristics

### 5.6.1 Clearance

#### 5.6.1.1 General

Compliance with 4.5.1 shall be determined as stated below.

#### 5.6.1.2 Test solutions

Perfuse the blood compartment with dialysis fluid, saline, phosphate-buffered saline or water containing one or more of the test substances listed in Table 1.

Perfuse the dialysis fluid compartment of hemodialyzers and hemodiafilters with dialysis fluid, saline, phosphate-buffered saline or water.

NOTE The solutions used to perfuse the blood and dialysis fluid compartments should be of similar ionic strength.

**Table 1 — Reference concentrations of test solutions**

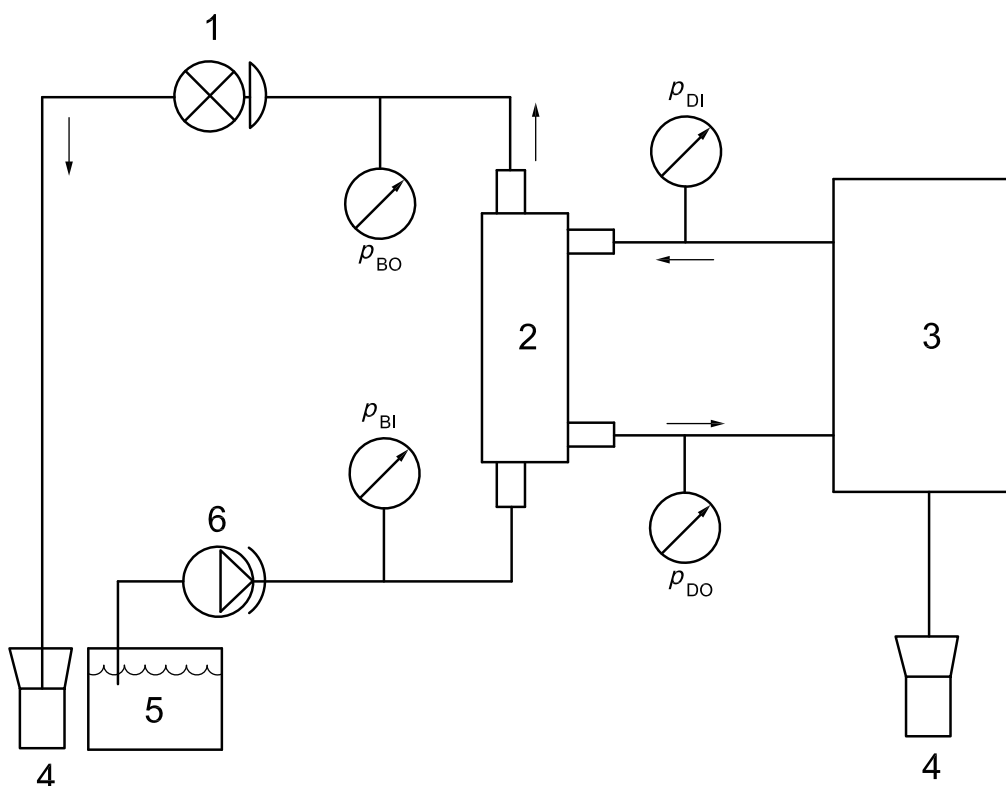
| Solute                                                                                                                                      | Molar concentration                  |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Urea, mmol/l                                                                                                                                | 15 to 35                             |
| Creatinine, $\mu\text{mol/l}$                                                                                                               | 500 to 1,000                         |
| Phosphate, mmol/l                                                                                                                           | 1 to 5, adjusted to pH $7.4 \pm 0.1$ |
| Vitamin B <sub>12</sub> , $\mu\text{mol/l}$                                                                                                 | 15 to 40                             |
| NOTE The concentrations of the solutes listed will vary based on the test procedure. The listed solutes are only given as a starting point. |                                      |

### 5.6.1.3 Clearance test procedure

Set up the test circuit as shown in Figure 4. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the hemodialyzer or hemodiafilter. Collect test samples after steady state has been reached, over the specified range of blood and dialysis fluid flow rates. The ultrafiltration rate shall be stated for each condition. Analyze samples and calculate clearance in accordance with Equation (1).

NOTE 1 Although Figure 4 shows flow entering the blood compartment at the bottom of the hemodialyzer or hemodiafilter, the test can also be performed with flow entering the blood compartment at the top of the hemodialyzer or hemodiafilter, provided the flows through the blood and dialysis fluid compartments remain counter-current. The test can also be performed with the hemodialyzer or hemodiafilter in the horizontal position, provided that configuration has been shown to produce equivalent results to those obtained with the hemodialyzer or hemodiafilter in the vertical position.

NOTE 2 A practical method of confirming the reliability of the measurement is to monitor the mass balance error.



#### Key

- 1 pressure control
- 2 hemodialyzer or hemodiafilter
- 3 dialysis fluid supply system with ultrafiltration controller
- 4 waste
- 5 test solution reservoir
- 6 blood pump
- $p_{BI}$  blood pressure, in
- $p_{BO}$  blood pressure, out
- $p_{DI}$  dialysis fluid pressure, in
- $p_{DO}$  dialysis fluid pressure, out

**Figure 4 — Diagram of open-loop system for measuring clearance of hemodialyzer or hemodiafilter**

#### 5.6.1.4 Equation for calculating clearance

The clearance for hemodialysis and hemodiafiltration,  $K$ , is calculated using Equation (1).

$$K = \left( \frac{c_{BI} - c_{BO}}{c_{BI}} \right) q_{BI} + \frac{c_{BO}}{c_{BI}} q_F \quad (1)$$

In the equation, it is necessary to use the same units of measurement for  $c_{BI}$  and  $c_{BO}$ .

where

- $c_{BI}$  is the concentration of solute on the blood inlet side of the hemodialyzer or hemodiafilter;
- $c_{BO}$  is the concentration of solute on the blood outlet side of the hemodialyzer or hemodiafilter;
- $q_{BI}$  is the blood flow rate at the inlet of the device;
- $q_F$  is the filtrate flow rate (ultrafiltration rate).

## 5.6.2 Sieving coefficient of hemodiafilters, hemofilters and hemoconcentrators

### 5.6.2.1 General

Compliance with 4.5.2 shall be determined in accordance with the test described below.

### 5.6.2.2 Test solutions

The test fluid shall be anticoagulated bovine plasma with a protein content of  $(60 \pm 5)$  g/l or anticoagulated whole blood with a hematocrit of  $(32 \pm 3)$  % and a plasma protein content of  $(60 \pm 5)$  g/l.

Perfuse the blood compartment with a test fluid containing one or more of the substances listed in 4.5.2.

### 5.6.2.3 Test procedure

Set up the test circuit as shown in Figure 5. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the hemodiafilter, hemofilter or hemoconcentrator. Adjust the ultrafiltration rate to cover the manufacturer's specified range. Collect paired test samples of blood and filtrate fluid flows. Calculate sieving coefficient in accordance with Equation (2).

**NOTE** Although Figure 5 shows flow entering the blood compartment at the bottom of the hemodiafilter, hemofilter or hemoconcentrator, the test can also be performed with flow entering the blood compartment at the top of the hemodiafilter, hemofilter or hemoconcentrator. The test can also be performed with the hemodiafilter, hemofilter or hemoconcentrator in the horizontal position, provided that configuration has been shown to produce equivalent results to those obtained with the hemodiafilter, hemofilter or hemoconcentrator in the vertical position.

### 5.6.2.4 Equation for sieving coefficient

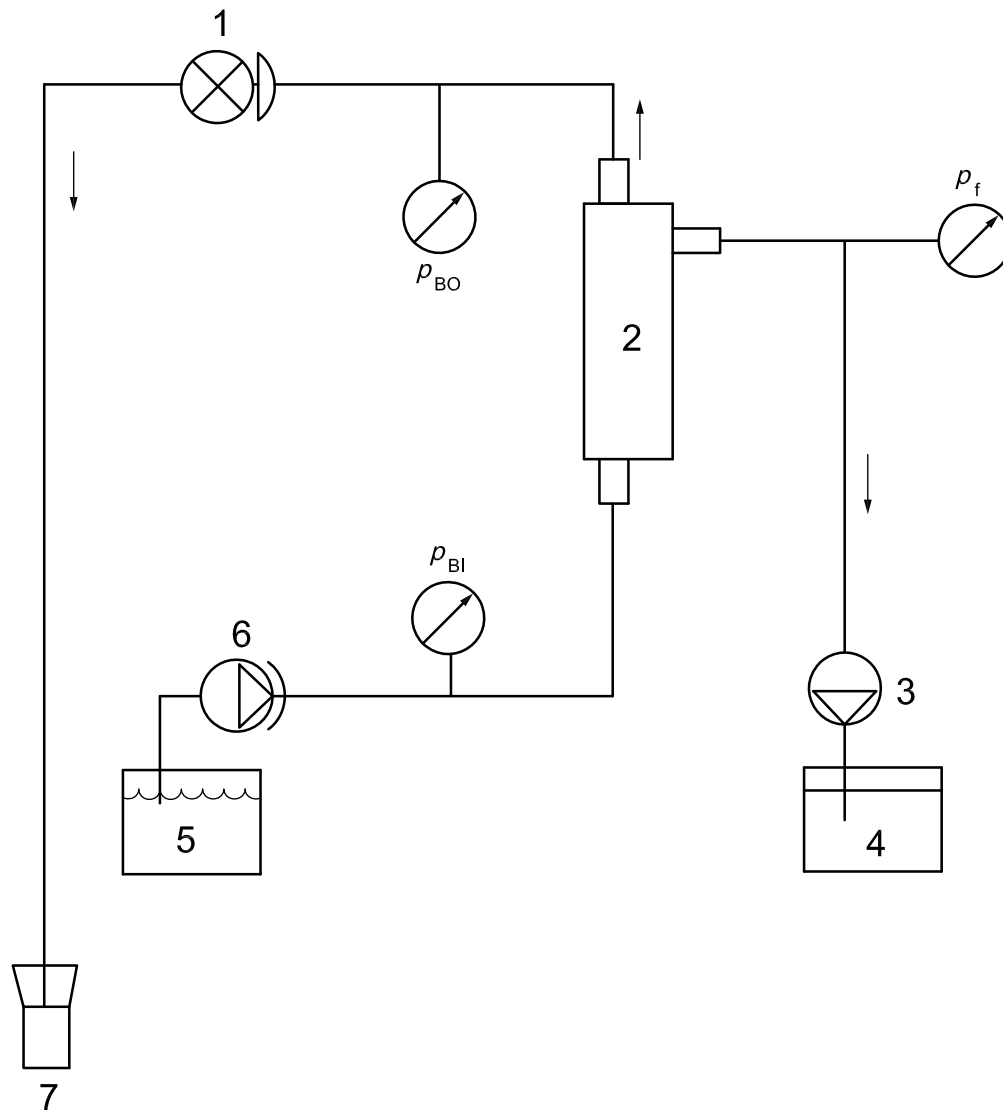
The sieving coefficient,  $S$ , is calculated using Equation (2).

$$S = \frac{2C_F}{(C_{BI} + C_{BO})} \quad (2)$$

where

- $S$  is the sieving coefficient;
- $C_{BI}$  is the concentration of solute on the blood inlet side of the hemodiafilter, hemofilter or hemoconcentrator;
- $C_{BO}$  is the concentration of solute on the blood outlet side of the hemodiafilter, hemofilter or hemoconcentrator;
- $C_F$  is the concentration of the solute on the filtrate side of the hemodiafilter, hemofilter or hemoconcentrator.

In Equation (2) it is necessary to use the same units of concentration for  $C_{BI}$ ,  $C_{BO}$  and  $C_F$ .



#### Key

- |   |                                                             |          |                     |
|---|-------------------------------------------------------------|----------|---------------------|
| 1 | pressure control                                            | 6        | blood pump          |
| 2 | hemodialyzer, hemodiafilter, hemofilter or hemoconcentrator | 7        | waste               |
| 3 | filtrate pump                                               | $p_{BO}$ | blood pressure, out |
| 4 | filtrate                                                    | $p_{BI}$ | blood pressure, in  |
| 5 | test solution reservoir                                     | $p_f$    | filtrate pressure   |

**Figure 5 — Diagram of system for measuring ultrafiltration or sieving coefficients of a hemodialyzer, hemodiafilter, hemofilter or hemoconcentrator**

### **5.6.3 Ultrafiltration coefficient**

#### **5.6.3.1 Test solution**

The test solution for hemodialyzers, hemodiafilters and hemofilters shall be anticoagulated bovine or human blood, with a hematocrit of  $(32 \pm 3) \%$  and a protein content of  $(60 \pm 5) \text{ g/l}$ . For hemoconcentrators, a test solution of anticoagulated bovine or human blood, with a hematocrit of  $(25 \pm 3) \%$  and a protein content of  $(50 \pm 5) \text{ g/l}$  may be used.

No fluid is to perfuse the dialysis fluid or filtrate compartment.

#### **5.6.3.2 Test procedure**

Set up the test circuit as shown in Figure 5. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the hemodiafilter, hemofilter or hemoconcentrator. Measure the ultrafiltration flow rate over the manufacturer's specified range. Calculate the ultrafiltration coefficient as the slope of the regression line between filtration flow rate and transmembrane pressure, taking oncotic pressure into account.

**NOTE** The filtration flow rate is not a linear function of transmembrane pressure above some value of transmembrane pressure. Beyond that point, the filtration flow rate tends to reach a constant value, representing the maximum filtration flow rate for the device.

### **5.6.4 Volume of the blood compartment**

For hollow-fiber devices, the cell volume can be calculated by utilizing the dimensions of the device and the number of fibers in the bundle. If the membrane is known to significantly change dimensions after wetting, the following alternative method should be used.

Alternately, fill the blood compartment with a fluid that is easily removable but that will not pass through the membrane. Measure the volume of the fluid needed to fill the blood compartment. Perform measurements over the specified range of transmembrane pressures. If the blood compartment is noncompliant, the measurement at a single pressure is acceptable.

### **5.6.5 Pressure drop of the blood compartment**

#### **5.6.5.1 General**

Compliance with 4.5.5 shall be determined in accordance with the test described below.

#### **5.6.5.2 Test fluids**

Fill the blood compartment with a test solution of anticoagulated bovine blood, with a hematocrit of  $(32 \pm 3) \%$  and a protein content of  $(60 \pm 5) \text{ g/l}$  or a fluid of similar viscosity, such as aqueous glycerin solution or a xanthan gum/glycerin solution.

Fill the dialysis fluid or filtrate compartment with normal dialysis fluid or saline.

#### **5.6.5.3 Test procedure**

Establish blood flow rate. Read the inlet and outlet pressures of the blood compartment. Determine the pressure drop. Repeat over the manufacturer's specified range of blood flow rates.



For plate dialyzers, it is also necessary to establish dialysis fluid flow rates and measure pressures and blood flow rates.

## **5.7 Expiry date**

Compliance with 4.6 can be met by accelerated or real time testing for biological safety, sterility and mechanical integrity of the device after storage for a period corresponding to the expiry date.

# **6 Labeling**

## **6.1 Labeling on the device**

The device shall be labeled with at least the following information:

- a) the manufacturer's name;
- b) the proprietary device name;
- c) the manufacturer's identifying code for the device;
- d) the lot number;
- e) the direction of blood flow and dialysis fluid flow, if applicable;
- f) the maximum transmembrane pressure;
- g) the expiry date, stated as mm/yyyy or yyyy/mm;
- h) the method of sterilization;
- i) a statement of single use, if appropriate.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

## **6.2 Labeling on the unit containers**

At least the following information shall be visible on or through the unit container:

- a) the manufacturer's name and address;
- b) the proprietary device name;
- c) the manufacturer's identifying code for the device;
- d) the lot number;
- e) a statement of sterility and nonpyrogenicity; there are three possibilities:
  - 1) that the entire contents of the package are sterile;
  - 2) that the fluid pathways (blood and dialysis fluid) are sterile;
  - 3) that only the blood pathway is sterile;

- f) the method of sterilization;
- g) the expiry date, stated as mm/yyyy or yyyy/mm;
- h) a statement of single use or multiple use;
- i) the statement, "Read the instructions before use";
- j) if applicable, a statement that an ultrafiltration control machine is required.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

### **6.3 Labeling on the outer containers**

At least the following information shall appear on the outer container:

- a) the manufacturer's name and address;
- b) the name and address of the distributor, if different from the information given under a), if applicable and in accordance with national requirements;
- c) the proprietary device name, description of contents and number of devices contained within the outer container;
- d) the manufacturer's identifying code for the device;
- e) the lot number;
- f) a statement of sterility and nonpyrogenicity;
- g) instructions and warnings regarding handling and storage;
- h) the expiry date, stated as mm/yyyy or yyyy/mm.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

### **6.4 Accompanying documentation**

At least the following information shall be supplied with each outer container:

- a) the manufacturer's name and address;
- b) the proprietary device name;
- c) directions for use:
  - 1) a statement to follow the machine manufacturer's instructions (if provided) for the orientation of the device in the support;
  - 2) the positioning of the extracorporeal circuit connection and, if appropriate, the positioning of the dialysis fluid tubing connections;
  - 3) the recommended priming, rinsing and termination of hemodialysis, hemodiafiltration, hemofiltration or hemoconcentration procedures;

- 4) the direction of blood flow, if applicable;
  - 5) a typical circuit diagram;
  - 6) the need for anticoagulation and a statement to follow the physician's prescription;
  - 7) details of any ancillary equipment required;
- d) cautions and warnings:
- 1) pressure limitations, if any;
  - 2) dialysis fluid flow rate limitations, if any (applicable only to hemodialyzers and hemodiafilters);
  - 3) blood flow rate limitations, if any;
  - 4) instructions to rinse the device as recommended before use;
  - 5) the need for any special equipment;
  - 6) a list of known adverse reactions;
  - 7) a list of general and specific contra-indications, such as "Not recommended for pediatric use" and "Do not use on non-de-aerated dialysis fluid delivery systems";
  - 8) appropriate warnings and contra-indications of diminished performance if the device is used below certain flow rates, below a certain pressure or in particular orientations (horizontal, vertical, etc.);
- e) the manufacturer's identifying code (catalogue number) for the device;
- f) a statement of sterility and nonpyrogenicity, and the method of sterilization;
- g) a statement of single use or multiple use; if labeled for multiple use, a statement where data supporting multiple use may be obtained (if required by national or regional regulations, the data supporting reuse shall be included in the package insert);
- h) performance data for the device shall be included or referred to. Performance data for the device shall include membrane surface area, clearances, sieving coefficient (if the device is intended for convective therapies), ultrafiltration coefficient ( $k_{UF}$ ), information on the relationship between ultrafiltration rate and transmembrane pressure if the device is intended for convective therapies, blood side pressure drop and blood compartment volume for the device;
- NOTE Performance data should include or make reference to:
- a statement, if appropriate, that *in vitro* results are likely to differ from *in vivo* results, with an estimate of the magnitude of the difference, if known;
  - a statement, if appropriate, that the performance might change with the duration of observation;
  - the test methods used for determination of performance characteristics.
- i) instruction for reprocessing of the hemodialyzer, if so labeled, shall include but not be limited to:
- 1) instructions for header and o-ring disassembly, cleaning and assembly, if applicable;
  - 2) recommended cleaning and reprocessing agents and processes;

- 3) a method for determining chemical residuals before use;
  - 4) instructions on performance tests needed prior to reuse of the hemodialyzer;
  - 5) a warning against the use of any agent or process known to adversely affect the hemodialyzer;
  - 6) if labeled for reuse, a statement that the hemodialyzer shall only be reused on the same patient;
  - 7) a statement, if applicable, of the effect of hemodialyzer reuse on the performance of the hemodialyzer;
- j) the generic name and, if applicable, the brand name of the membrane;

NOTE The generic name of the membrane should include the complete chemical name of the membrane material.

- k) a general description of the device; this information should include special features such as filtration rates requiring special controllers or adverse effects of bubbles in the dialysis fluid;
- l) the connectors recommended for the dialysis fluid ports or filtration port;
- m) if blood compartment connectors are not as in Figure 1 and Figure 3, specify the type of blood tubing connectors that are compatible with the device;
- n) the generic names of materials of construction of the device intended for direct or indirect contact with blood.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

# **Cardiovascular implants and extracorporeal systems** **— *Extracorporeal blood circuit for hemodialyzers,*** ***hemodiafilters and hemofilters***

Approved 26 July 2010 by  
**Association for the Advancement of Medical Instrumentation**

Approved 3 August 2010 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies requirements for the single-use extracorporeal blood circuit and (integral and non-integral) transducer protectors which are intended for use in hemodialysis, hemodiafiltration and hemofiltration.

**Keywords:** biological safety, connectors, labeling, mechanical integrity, nonpyrogenicity, sample port, pump segment, sterility, transducer protectors

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1–57020–391-1

# Contents

Page

|                                                         |      |
|---------------------------------------------------------|------|
| Glossary of equivalent standards .....                  | iv   |
| Committee representation .....                          | vi   |
| Background of ANSI/AAMI adoption of ISO 8638:2010 ..... | vii  |
| Foreword .....                                          | viii |
| Introduction .....                                      | ix   |
| 1 Scope.....                                            | 1    |
| 2 Normative references .....                            | 1    |
| 3 Terms and definitions.....                            | 2    |
| 4 Requirements .....                                    | 3    |
| 4.1 Biological safety.....                              | 3    |
| 4.2 Sterility .....                                     | 3    |
| 4.3 Nonpyrogenicity.....                                | 3    |
| 4.4 Mechanical characteristics .....                    | 3    |
| 4.5 Expiry date.....                                    | 5    |
| 4.6 Tubing compliance .....                             | 6    |
| 5 Test methods.....                                     | 6    |
| 5.1 General.....                                        | 6    |
| 5.2 Biological safety.....                              | 6    |
| 5.3 Sterility .....                                     | 6    |
| 5.4 Nonpyrogenicity.....                                | 6    |
| 5.5 Mechanical characteristics .....                    | 7    |
| 5.6 Expiry date.....                                    | 11   |
| 5.7 Tubing compliance .....                             | 11   |
| 6 Labeling .....                                        | 11   |
| 6.1 Labeling on the device .....                        | 11   |
| 6.2 Labeling on the unit container.....                 | 11   |
| 6.3 Labeling on the outer container .....               | 12   |
| 6.4 Accompanying documentation .....                    | 12   |
| Bibliography .....                                      | 14   |

## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation. The code in the US column, “(R)20xx” indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

| International designation                          | U.S. designation                                                                                            | Equivalency                                                     |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| IEC 60601-1:2005<br>Technical Corrigendum 1 and 2  | ANSI/AAMI ES60601-1:2005 and ANSI/AAMI<br>ES60601-1:2005/A2:2010<br>ANSI/AAMI ES60601-1:2005/C1:2009 (amdt) | Major technical variations<br>C1 Identical to Corrigendum 1 & 2 |
| IEC 60601-1-2:2007                                 | ANSI/AAMI/IEC 60601-1-2:2007                                                                                | Identical                                                       |
| IEC 60601-2-2:2009                                 | ANSI/AAMI/IEC 60601-2-2:2009                                                                                | Identical                                                       |
| IEC 60601-2-4:2002                                 | ANSI/AAMI DF80:2003/(R)2010                                                                                 | Major technical variations                                      |
| IEC 60601-2-19:2009                                | ANSI/AAMI/IEC 60601-2-19:2009                                                                               | Identical                                                       |
| IEC 60601-2-20:2009                                | ANSI/AAMI/IEC 60601-2-20:2009                                                                               | Identical                                                       |
| IEC 60601-2-21:2009                                | ANSI/AAMI/IEC 60601-2-21:2009                                                                               | Identical                                                       |
| IEC 60601-2-24:1998                                | ANSI/AAMI ID26:2004/(R)2009                                                                                 | Major technical variations                                      |
| IEC 60601-2-47:2001                                | ANSI/AAMI EC38:2007                                                                                         | Major technical variations                                      |
| IEC 60601-2-50:2009                                | ANSI/AAMI/IEC 60601-2-50:2009                                                                               | Identical                                                       |
| IEC 80601-2-30:2009 and Technical<br>Corrigendum 1 | ANSI/AAMI/IEC 80601-2-30:2009 and<br>ANSI/AAMI/IEC 80601-2-30:2009/ C1:2009<br>(amdt) – consolidated text   | Identical (with inclusion)<br>C1 Identical to Corrigendum 1     |
| IEC 80601-2-58:2008                                | ANSI/AAMI/IEC 80601-2-58:2008                                                                               | Identical                                                       |
| IEC/TR 60878:2009                                  | ANSI/AAMI/IEC TIR60878:2003                                                                                 | Identical                                                       |
| IEC/TR 62296:2009                                  | ANSI/AAMI/IEC TIR62296:2009                                                                                 | Identical                                                       |
| IEC 62304:2006                                     | ANSI/AAMI/IEC 62304:2006                                                                                    | Identical                                                       |
| IEC/TR 62348:2006                                  | ANSI/AAMI/IEC TIR62348:2006                                                                                 | Identical                                                       |
| IEC/TR 62354:2009                                  | ANSI/AAMI/IEC TIR62354:2009                                                                                 | Identical                                                       |
| IEC/TR 80002-1:2009                                | ANSI/IEC/TR 80002-1:2009                                                                                    | Identical                                                       |
| ISO 5840:2005                                      | ANSI/AAMI/ISO 5840:2005/(R)2010                                                                             | Identical                                                       |
| ISO 7198:1998                                      | ANSI/AAMI/ISO 7198:1998/2001/(R)2010                                                                        | Identical                                                       |
| ISO 7199:2009                                      | ANSI/AAMI/ISO 7199:2009                                                                                     | Identical                                                       |
| ISO 8637:2010                                      | ANSI/AAMI/ISO 8637:2010                                                                                     | Identical                                                       |
| ISO 8638:2010                                      | ANSI/AAMI/ISO 8638:2010                                                                                     | Identical                                                       |
| ISO 10993-1:2009                                   | ANSI/AAMI/ISO 10993-1:2009                                                                                  | Identical                                                       |
| ISO 10993-2:2006                                   | ANSI/AAMI/ISO 10993-2:2006                                                                                  | Identical                                                       |
| ISO 10993-3:2003                                   | ANSI/AAMI/ISO 10993-3:2003/(R)2009                                                                          | Identical                                                       |
| ISO 10993-4:2002 and<br>Amendment 1:2006           | ANSI/AAMI/ISO 10993-4:2002/(R)2009 and<br>Amendment 1:2006/(R)2009                                          | Identical                                                       |
| ISO 10993-5:2009                                   | ANSI/AAMI/ISO 10993-5:2009                                                                                  | Identical                                                       |
| ISO 10993-6:2007                                   | ANSI/AAMI/ISO 10993-6:2007                                                                                  | Identical                                                       |
| ISO 10993-7:2008                                   | ANSI/AAMI/ISO 10993-7:2008                                                                                  | Identical                                                       |
| ISO 10993-9:2009                                   | ANSI/AAMI/ISO 10993-9:2009                                                                                  | Identical                                                       |
| ISO 10993-10:2002 and<br>Amendment 1:2006          | ANSI/AAMI BE78:2002/(R)2008<br>ANSI/AAMI BE78:2002/A1:2006/(R)2008                                          | Minor technical variations<br>Identical                         |
| ISO 10993-11:2006                                  | ANSI/AAMI/ISO 10993-11:2006                                                                                 | Identical                                                       |
| ISO 10993-12:2007                                  | ANSI/AAMI/ISO 10993-12:2007                                                                                 | Identical                                                       |
| ISO 10993-13:1998                                  | ANSI/AAMI/ISO 10993-13:1999/(R)2004                                                                         | Identical                                                       |
| ISO 10993-14:2001                                  | ANSI/AAMI/ISO 10993-14:2001/(R)2006                                                                         | Identical                                                       |
| ISO 10993-15:2000                                  | ANSI/AAMI/ISO 10993-15:2000/(R)2006                                                                         | Identical                                                       |
| ISO 10993-16:2010                                  | ANSI/AAMI/ISO 10993-16:2010                                                                                 | Identical                                                       |
| ISO 10993-17:2002                                  | ANSI/AAMI/ISO 10993-17:2002/(R)2008                                                                         | Identical                                                       |
| ISO 10993-18:2005                                  | ANSI/AAMI BE83:2006                                                                                         | Major technical variations                                      |
| ISO/TS 10993-19:2006                               | ANSI/AAMI/ISO TIR10993-19:2006                                                                              | Identical                                                       |
| ISO/TS 10993-20:2006                               | ANSI/AAMI/ISO TIR10993-20:2006                                                                              | Identical                                                       |



| International designation                       | U.S. designation                                       | Equivalency                 |
|-------------------------------------------------|--------------------------------------------------------|-----------------------------|
| ISO 11135-1:2007                                | ANSI/AAMI/ISO 11135-1:2007                             | Identical                   |
| ISO/TS 11135-2:2008                             | ANSI/AAMI/ISO TIR11135-2:2008                          | Identical                   |
| ISO 11137-1:2006                                | ANSI/AAMI/ISO 11137-1:2006/(R)2010                     | Identical                   |
| ISO 11137-2:2006 (2006-08-01 corrected version) | ANSI/AAMI/ISO 11137-2:2006                             | Identical                   |
| ISO 11137-3:2006                                | ANSI/AAMI/ISO 11137-3:2006/(R)2010                     | Identical                   |
| ISO 11138-1: 2006                               | ANSI/AAMI/ISO 11138-1:2006/(R)2010                     | Identical                   |
| ISO 11138-2: 2006                               | ANSI/AAMI/ISO 11138-2:2006/(R)2010                     | Identical                   |
| ISO 11138-3: 2006                               | ANSI/AAMI/ISO 11138-3:2006/(R)2010                     | Identical                   |
| ISO 11138-4: 2006                               | ANSI/AAMI/ISO 11138-4:2006/(R)2010                     | Identical                   |
| ISO 11138-5: 2006                               | ANSI/AAMI/ISO 11138-5:2006/(R)2010                     | Identical                   |
| ISO/TS 11139:2006                               | ANSI/AAMI/ISO 11139:2006                               | Identical                   |
| ISO 11140-1:2005                                | ANSI/AAMI/ISO 11140-1:2005/(R)2010                     | Identical                   |
| ISO 11140-3:2007                                | ANSI/AAMI/ISO 11140-3:2007                             | Identical                   |
| ISO 11140-4:2007                                | ANSI/AAMI/ISO 11140-4:2007                             | Identical                   |
| ISO 11140-5:2007                                | ANSI/AAMI/ISO 11140-5:2007                             | Identical                   |
| ISO 11607-1:2006                                | ANSI/AAMI/ISO 11607-1:2006                             | Identical                   |
| ISO 11607-2:2006                                | ANSI/AAMI/ISO 11607-2:2006                             | Identical                   |
| ISO 11737-1: 2006                               | ANSI/AAMI/ISO 11737-1:2006                             | Identical                   |
| ISO 11737-2:2009                                | ANSI/AAMI/ISO 11737-2:2009                             | Identical                   |
| ISO 13408-1:2008                                | ANSI/AAMI/ISO 13408-1:2008                             | Identical                   |
| ISO 13408-2:2003                                | ANSI/AAMI/ISO 13408-2:2003                             | Identical                   |
| ISO 13408-3:2006                                | ANSI/AAMI/ISO 13408-3:2006                             | Identical                   |
| ISO 13408-4:2005                                | ANSI/AAMI/ISO 13408-4:2005                             | Identical                   |
| ISO 13408-5:2006                                | ANSI/AAMI/ISO 13408-5:2006                             | Identical                   |
| ISO 13408-6:2006                                | ANSI/AAMI/ISO 13408-6:2006                             | Identical                   |
| ISO 13485:2003                                  | ANSI/AAMI/ISO 13485:2003/(R)2009                       | Identical                   |
| ISO 14155-1:2003                                | ANSI/AAMI/ISO 14155-1:2003/(R)2008                     | Identical                   |
| ISO 14155-2:2003                                | ANSI/AAMI/ISO 14155-2:2003/(R)2008                     | Identical                   |
| ISO 14160:1998                                  | ANSI/AAMI/ISO 14160:1998/(R)2008                       | Identical                   |
| ISO 14161:2009                                  | ANSI/AAMI/ISO 14161:2009                               | Identical                   |
| ISO 14708-3:2008                                | ANSI/AAMI/ISO 14708-3:2008                             | Identical                   |
| ISO 14708-4:2008                                | ANSI/AAMI/ISO 14708-4:2008                             | Identical                   |
| ISO 14708-5:2010                                | ANSI/AAMI /ISO 14708-5:2010                            | Identical                   |
| ISO 14937:2009                                  | ANSI/AAMI/ISO 14937:2009                               | Identical                   |
| ISO/TR 14969:2004                               | ANSI/AAMI/ISO TIR14969:2004                            | Identical                   |
| ISO 14971:2007                                  | ANSI/AAMI/ISO 14971:2007                               | Identical                   |
| ISO 15223-1:2007 and A1:2008                    | ANSI/AAMI/ISO 15223-1:2007 and A1:2008                 | Identical                   |
| ISO 15223-2:2010                                | ANSI/AAMI/ISO 15223-2:2010                             | Identical                   |
| ISO 15225:2010                                  | ANSI/AAMI/ISO 15225:2010                               | Identical                   |
| ISO 15674:2009                                  | ANSI/AAMI/ISO 15674:2009                               | Identical                   |
| ISO 15675:2009                                  | ANSI/AAMI/ISO 15675:2009                               | Identical                   |
| ISO 15882:2008                                  | ANSI/AAMI/ISO 15882:2008                               | Identical                   |
| ISO 15883-1:2006                                | ANSI/AAMI ST15883-1:2009                               | Major technical variations  |
| ISO/TR 16142:2006                               | ANSI/AAMI/ISO TIR16142:2005                            | Identical                   |
| ISO 17664:2004                                  | ANSI/AAMI ST81:2004                                    | Major technical variations  |
| ISO 17665-1:2006                                | ANSI/AAMI/ISO 17665-1:2006                             | Identical (with inclusions) |
| ISO/TS 17665-2:2009                             | ANSI/AAMI/ISO TIR17665-2:2009                          | Identical                   |
| ISO 18472:2006                                  | ANSI/AAMI/ISO 18472:2006                               | Identical                   |
| ISO/TS 19218:2005                               | ANSI/AAMI/ISO 19218:2005                               | Identical                   |
| ISO 22442-1:2007                                | ANSI/AAMI/ISO 22442-1:2007                             | Identical                   |
| ISO 22442-2:2007                                | ANSI/AAMI/ISO 22442-2:2007                             | Identical                   |
| ISO 22442-3:2007                                | ANSI/AAMI/ISO 22442-3:2007                             | Identical                   |
| ISO 25539-1:2003 and A1:2005                    | ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009 | Identical                   |
| ISO 25539-2:2008                                | ANSI/AAMI/ISO 25539-2:2008                             | Identical                   |
| ISO 27186:2010                                  | ANSI/AAMI/ISO 27186:2010                               | Identical                   |
| ISO 81060-1:2007                                | ANSI/AAMI/ISO 81060-1:2007                             | Identical                   |
| ISO 81060-2:2009                                | ANSI/AAMI/ISO 81060-2:2009                             | Identical                   |

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Renal Disease and Detoxification Committee

The adoption of ISO 8638:2010 as an American National Standard was initiated by the AAMI Renal Disease and Detoxification Committee. The AAMI Renal Disease and Detoxification Committee also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Renal Disease and Detoxification Committee (U.S. Sub-TAG for ISO/TC 150/SC 2/WG 5) played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

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                          Richard A. Ward, PhD

*Members:*           G Steven Acres, MD, Carolina Regional Nephrology Associates  
                          Larry Alexander, Florian Services  
                          Matthew J. Arduino, DrPH, US Centers for Disease Control and Prevention  
                          James Weldon Baker, AmeriWater  
                          Robert Berube, Church & Dwight Co Inc.  
                          Arnold Boehnlein, Baxter Healthcare Corporation  
                          Karla S. Byrne, Rockwell Medical Inc.  
                          Wayne Carlson, Minntech Corporation  
                          Danilo B. Concepcion, CHT CCHT CBNT, St Joseph Hospital Renal Center  
                          Conor Curtin, Fresenius Medical Care North America  
                          Jim Curtis, Home Dialysis Plus LTD  
                          R. Barry Deeter, RN MSN, University of Utah Dialysis Program  
                          Robert Dudek, Siemens Water Technologies Corporation  
                          Gema Gonzalez, FDA/CDRH  
                          Elizabeth Howard, Davita Inc..  
                          Bertrand L. Jaber, MD, Caritas St Elizabeths Medical Center  
                          Byron L. Jacobs, CBET, Sanford USD Medical Center  
                          David C. Katz, El Camino Hospital  
                          Fei M. Law, CaridianBCT Sterilization Services Inc.  
                          Nathan W. Levin, MD, Renal Research Institute LLC  
                          Jo Ann Maltais, PhD, Maltais Consulting  
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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

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## Background of ANSI/AAMI adoption of ISO 8638:2010

As indicated in the foreword to the main body of this document (page viii), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 150, Subcommittee 2, *Cardiovascular implants and extracorporeal systems*, to fill a need for minimum safety and performance requirements for single-use extracorporeal blood circuits and (integral and non-integral) transducer protectors intended for use in hemodialysis, hemodiafiltration and hemofiltration.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 150/SC 2, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 150/SC 2 supports the requirements provided in this document.

The U.S. adoption of ANSI/AAMI/ISO 8638:2010 was approved by the American National Standards Institute (ANSI) as a revision of ANSI/AAMI RD17:2007, *Cardiovascular implants and artificial organs-Hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators* on 3 August 2010. The AAMI Renal Disease and Detoxification Committee (U.S. sub-TAG for ISO/TC 150/SC 2/WG 5, Renal replacement, detoxification and apheresis) developed ANSI/AAMI RD17:2007 and initiated the U.S. adoption of ISO 8638:2010.

Major differences between ANSI/AAMI RD17:2007 and ANSI/AAMI/ISO 8638:2010 include the addition of alternative methods for testing the structural integrity of an extracorporeal blood circuit.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited. “May” is used to indicate that a course of action is permissible within the limits of the recommended practice. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Dr. Suite 301, Arlington, VA 22203-1633.

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NOTE—Beginning with the foreword on page viii, this American National Standard is identical to ISO 8638:2010.

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## Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 8638 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO 8638:2004), which has been technically revised.

## Introduction

This International Standard is concerned with the extracorporeal blood circuit manufactured for single use and intended for use in conjunction with hemodialyzers, hemodiafilters and hemofilters. The requirements specified in this International Standard for the extracorporeal blood circuit will help to ensure safety and satisfactory function.

It was not found practicable to specify materials of construction. This International Standard therefore requires only that materials have been tested and that the methods and results are made available upon request.

The dimensions of the connectors intended for connecting the extracorporeal blood circuit to a hemodialyzer, hemodiafilter or hemofilter have been specified to ensure compatibility with these devices, as specified in ISO 8637. The design and dimensions have been selected in order to minimize the risk of leakage of blood and ingress of air. Connectors with either fixed or loose locking shells are permitted.

This International Standard reflects the consensus of physicians, manufacturers and other interested parties for devices that are approved for clinical use. Conformance with this International Standard is voluntary and it is not intended to supersede any national regulation.



# Cardiovascular implants and extracorporeal systems — Extracorporeal blood circuit for hemodialyzers, hemodiafilters and hemofilters

## 1 Scope

This International Standard specifies requirements for hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators (hereafter referred to as “the device”) and (integral and non-integral) transducer protectors which are intended for use in hemodialysis, hemodiafiltration and hemofiltration.

This International Standard does not apply to:

- hemodialyzers, hemodiafilters or hemofilters;
- plasmafilters;
- hemoperfusion devices;
- vascular access devices;
- blood pumps;
- pressure monitors for the extracorporeal blood circuit;
- air detection devices;
- systems to prepare, maintain or monitor dialysis fluid;
- systems or equipment intended to perform hemodialysis, hemodiafiltration, hemofiltration or hemoconcentration.

NOTE Requirements for hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators are specified in ISO 8637.

## 2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 594-2, *Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 2: Lock fittings*

ISO 7864, *Sterile hypodermic needles for single use*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

### 3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

#### 3.1

##### **air capture chamber**

component intended to capture air and which can provide compliance to the blood circuit or allow pressure to be monitored

NOTE Air capture chambers are also known as drip chambers, bubble traps or venous and arterial blood chambers.

#### 3.2

##### **extracorporeal blood circuit**

blood tubing and integral accessory tubing, including fluid and infusion tubing, for attaching the extracorporeal blood circuit to pressure monitors and integral components

EXAMPLES (Of integral components.) Air-capture chambers and transducer protectors.

#### 3.3

##### **fluid pathway**

internal surfaces of the extracorporeal blood circuit

#### 3.4

##### **labeling**

written, printed, graphic or electronic matter that:

— is affixed to a medical device or any of its containers or wrappers

or

— accompanies a medical device and which is related to identification, technical description and use of that medical device, but excluding shipping documents

#### 3.5

##### **pump segment**

portion of the extracorporeal blood circuit (3.2) that is acted upon by the blood pump

#### 3.6

##### **transducer protector**

##### **pressure-transmitting sterile barrier**

component of the extracorporeal blood circuit (3.2) that is intended to provide an interconnection between the extracorporeal blood circuit and the hemodialysis machine while allowing the pressure within the extracorporeal blood circuit to be measured by the machine



## **4 Requirements**

### **4.1 Biological safety**

Parts of the device that are intended to come into direct or indirect contact with blood shall be evaluated for freedom from biological hazards, in accordance with 5.2.

**NOTE** Attention is drawn to the need to establish whether national regulations or national standards governing toxicology and biocompatibility testing exist in the country in which the device is produced and, if applicable, in the countries in which the device is to be marketed.

### **4.2 Sterility**

All fluid contacting surfaces of the device, and the mating surfaces of all connectors integral to the device, shall be sterile. Compliance shall be verified in accordance with 5.3.

### **4.3 Nonpyrogenicity**

The blood pathway of the device shall be non-pyrogenic. Compliance shall be verified in accordance with 5.4.

### **4.4 Mechanical characteristics**

#### **4.4.1 Structural integrity**

The device shall be capable of withstanding a positive pressure of  $1.5 \times$  the manufacturer's recommended maximum pressure and a negative pressure not exceeding 700 mmHg (93.3 kPa below atmospheric pressure) or the highest obtainable negative pressure if at high elevation, when tested in accordance with 5.5.1.

#### **4.4.2 Connectors to hemodialyzer, hemodiafilter or hemofilter**

**4.4.2.1** Except where the hemodialyzer, hemodiafilter or hemofilter and the extracorporeal blood circuit are designed as an integral system, the dimensions of the connectors for the hemodialyzer, hemodiafilter or hemofilter shall be as given in Figure 1. Compliance shall be verified in accordance with 5.5.2.

**4.4.2.2** Connectors made of semi-rigid materials shall meet the performance requirements of ISO 594-2.

#### **4.4.3 Connectors to vascular access device**

Except where the extracorporeal blood circuit and the vascular access device are an integral system, the dimensions of the connectors intended for connection to vascular access devices shall be a male 6 % (Luer) taper lock fitting (see ISO 594-2). Connectors made of semi-rigid materials shall meet the performance requirements of ISO 594-2 taper lock fittings. Compliance shall be verified in accordance with 5.5.3.

#### **4.4.4 Connectors to ancillary components**

All parts of the extracorporeal blood circuit intended for use with non-integral ancillary components, such as heparin lines, pressure-transducer lines, medication-administration lines and level-adjustment lines,

shall terminate in fittings that meet the performance requirements of ISO 594-2 taper lock fittings. Compliance shall be verified in accordance with 5.5.4.

#### 4.4.5 Color coding

The arterial patient-connection end shall be color-coded red, and the venous patient-connection end shall be color-coded blue. The coding shall be prominently displayed within 100 mm of the end of the tubing. Compliance with this requirement shall be verified in accordance with 5.5.5.

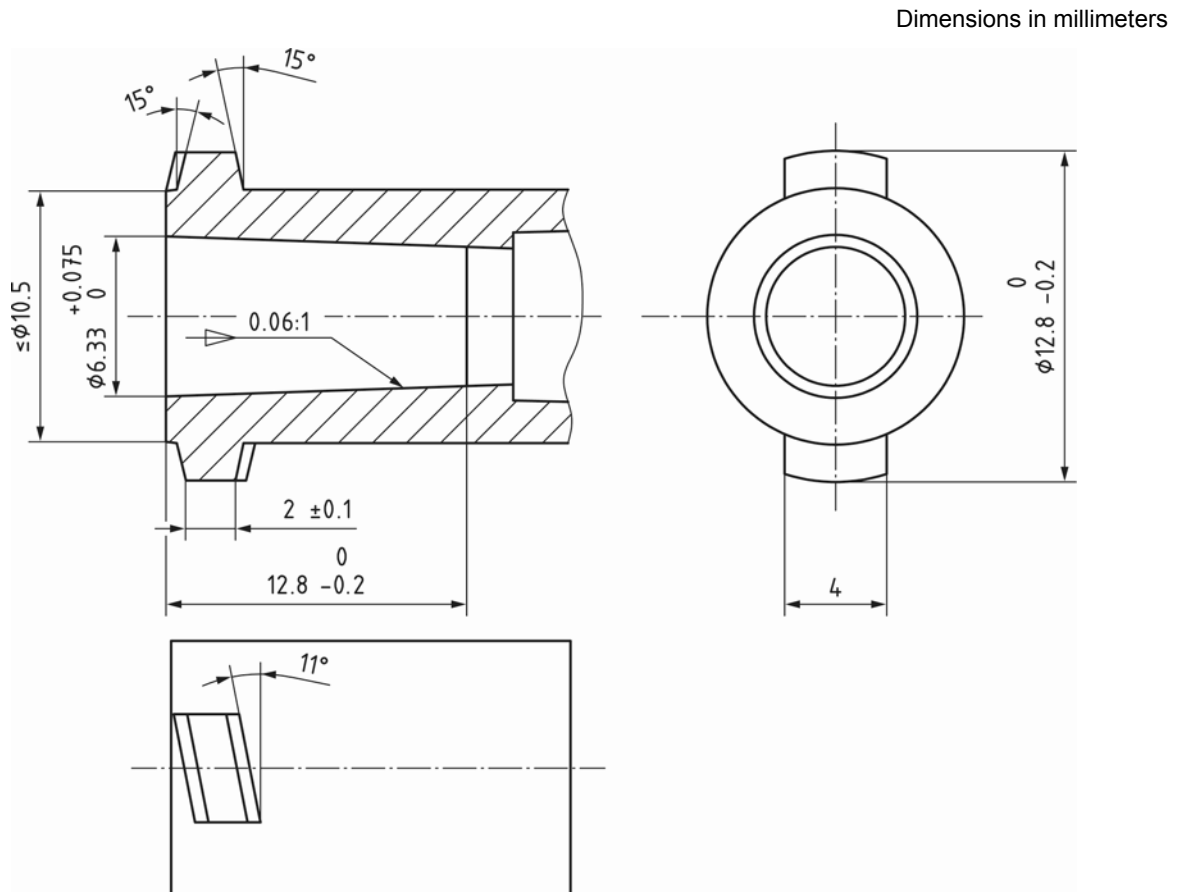


**Figure 1 — Main fitting dimensions of extracorporeal blood circuit connector to blood ports of hemodialyzer, hemodiafilter or hemofilter**

#### 4.4.6 Access ports

##### 4.4.6.1 Needle access ports

Needle access ports shall not leak when tested in accordance with 5.5.6.1. The access ports shall be designed so as to minimize the risk of the needle piercing the tube completely and causing injury.

##### 4.4.6.2 Needleless access ports

Needleless access ports shall not leak when tested in accordance with 5.5.6.2.

#### **4.4.7 Blood pathway volume**

The range of the blood pathway volume of the extracorporeal blood circuits shall be specified by the manufacturer. Compliance with this requirement shall be verified in accordance with 5.5.7.

NOTE The blood pathway volume is also known as the priming volume.

#### **4.4.8 Air-capture chamber fill level**

The recommended fill level of the air-capture chamber should be marked on the air-capture chamber if that level is required for proper operation of some monitoring system. Compliance with this requirement shall be verified in accordance with 5.5.8.

#### **4.4.9 Transducer protectors**

##### **4.4.9.1 Integral transducer protectors**

Extracorporeal blood circuits supplied with integral transducer protectors shall be capable of preventing cross-contamination. The transducer protector shall be capable of maintaining a secure and leak-free connection to the hemodialysis machine when subjected to pressures of  $1.5 \times$  the manufacturer's recommended maximum pressure for the device. The machine side of the transducer protector shall be transparent (clear) to allow for visual inspection of blood contamination during use. Compliance with this requirement shall be in accordance with 5.5.9.

##### **4.4.9.2 Non-integral transducer protectors**

If not supplied as an integral component of the extracorporeal blood circuit, connectors shall be provided to allow the use of a transducer protector to prevent cross contamination. The transducer protector shall be capable of maintaining a secure and leak-free connection to the hemodialysis machine when subjected to pressures of  $1.5 \times$  the manufacturer's recommended maximum pressure for the device. The machine side of the transducer protector shall be transparent (clear) to allow for visual inspection of blood contamination during use. Compliance with this requirement shall be in accordance with 5.5.9.

#### **4.4.10 Blood pathway flow dynamics**

Extracorporeal blood pathways shall be designed to minimize harmful effects to the blood components. Compliance with this requirement shall be verified in accordance with 5.5.10.

#### **4.4.11 Pump segment performance**

The performance characteristics of the pump segment shall be evaluated over the range of inlet pressures (normally 0 mmHg to -250 mmHg).

Compliance with this requirement shall be verified in accordance with 5.5.11.

### **4.5 Expiry date**

If the expiry date is given, it shall be validated. Accelerated stability studies are acceptable if real time data are not available. Compliance with this requirement shall be verified in accordance with 5.6.

## 4.6 Tubing compliance

The blood tubing shall be capable of being occlusively clamped by the venous line clamp of the dialysis delivery system(s) with which the extracorporeal blood circuit is intended to be used, as indicated in the labeling for the blood tubing. Compliance with this requirement shall be verified in accordance with 5.7.

## 5 Test methods

### 5.1 General

The performance characteristics specified in Clause 4 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that might alter its performance.

The sample of devices shall be drawn at random from the manufacturer's production and shall have passed all applicable quality control steps, as well as sterilization, if applicable. They shall be prepared according to the manufacturer's recommendations as though they are to be used for a clinical procedure.

Measurements shall be made *in vitro* at  $(37 \pm 1) ^\circ\text{C}$ . When the relationship between variables is non-linear, sufficient determinations shall be made to permit interpolation between the data points. The techniques of measurement are reference tests. Other test methods may be used, provided it can be shown that they are validated and of comparable precision and reproducibility.

The test systems shown do not indicate all the necessary details of practicable test apparatus. The design and construction of actual test systems and their establishment shall also address the many factors contributing to measurement error, including, but not limited to, pressure measurement errors due to static head effects and dynamic pressure drops; parameter stabilization time; uncontrolled temperature variations at non-constant flow rates; pH; degradation of test substances due to heat, light and time; degassing of test fluids; trapped air; and system contamination by foreign material, algae and bacteria.

### 5.2 Biological safety

The biological safety of devices that are intended to come into direct or indirect contact with the patient's blood shall be evaluated on samples of each new type of device prior to its marketing or after any change in the materials of construction of that type of device or after any change in the method of sterilization. Testing shall be carried out in accordance with ISO 10993-1, ISO 10993-4 or ISO 10993-7, as relevant.

### 5.3 Sterility

Compliance with 4.2 shall be verified by inspection of the device records that show that the device has been exposed to a validated sterilization process.

### 5.4 Nonpyrogenicity

Compliance with 4.3 shall be verified in accordance with ISO 10993-11.

## **5.5 Mechanical characteristics**

### **5.5.1 Structural integrity**

#### **5.5.1.1 Positive pressure**

Compliance with 4.4.1 (positive pressure) shall be determined by either of the following tests.

- a) Fill the device with water at  $(37 \pm 1)^\circ\text{C}$ . Cap all connections with applicable caps. Subject the device to a pressure of  $1.5 \times$  the manufacturer's recommended maximum pressure. Maintain pressure for a minimum of 10 min and inspect for visible signs of leakage.
- b) Cap all ports with applicable caps. Submerge the device in water at  $(37 \pm 1)^\circ\text{C}$ . Subject the lumen of the device to air pressure of  $1.5 \times$  the manufacturer's recommended maximum pressure. Maintain pressure for a minimum of 10 min and inspect the device for leakage of air bubbles.

#### **5.5.1.2 Negative pressure**

Compliance with 4.4.1 (negative pressure) shall be determined by either of the following tests.

- a) Cap all ports with applicable caps. Submerge the device in a water bath at  $(37 \pm 1)^\circ\text{C}$ . Subject the device to  $1.5 \times$  the manufacturer's recommended maximum negative pressure or 700 mmHg (93.3 kPa below atmospheric pressure) or the highest obtainable sub-atmospheric pressure if at high elevation. Maintain pressure for a minimum of 10 min and inspect the device for visual signs of leakage.
- b) Fill the device with water at  $(37 \pm 1)^\circ\text{C}$ . Cap all ports with applicable caps. Subject the lumen of the device to  $1.5 \times$  the manufacturer's recommended maximum negative pressure or 700 mmHg (93.3 kPa below atmospheric pressure) or the highest obtainable sub-atmospheric pressure if at high elevation. Maintain pressure for a minimum of 10 min and inspect the device for leakage of air bubbles.

### **5.5.2 Connectors to hemodialyzer, hemodiafilter or hemofilter**

Compliance with 4.4.2 shall be determined by inspection (see Figures 1, 2 and 3).

### **5.5.3 Connector to vascular access device**

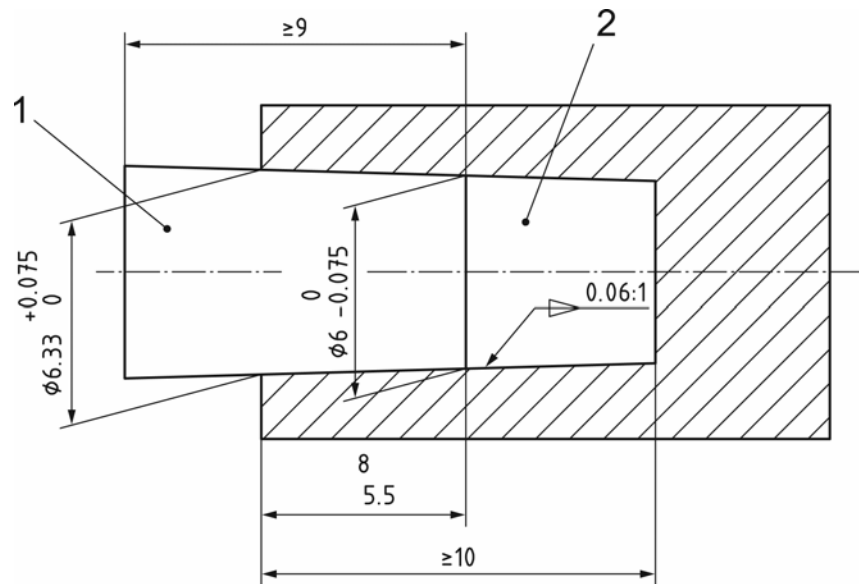
Compliance with 4.4.3 shall be determined by inspection (see ISO 594-2).

### **5.5.4 Connectors to ancillary components**

Compliance with 4.4.4 shall be determined by inspection (see ISO 594-2).

### **5.5.5 Color coding**

Compliance with 4.4.5 shall be determined by inspection.



**Key**

- 1 outer cone
- 2 inner cone

**Figure 2 — Gauge for 6 % taper fitting for length of engagement of the male cone of blood inlet and outlet ports**

## 5.5.6 Access ports

### 5.5.6.1 Needle access ports

Compliance with 4.4.6.1 shall be determined by the following procedure.

- Fill the portion of the extracorporeal blood circuit that contains the access port with water at  $(37 \pm 1) ^\circ\text{C}$  and apply a pressure  $1.5 \times$  the maximum stated by the manufacturer [see 6.4 f) 1)]. Puncture the access port with a hypodermic needle, as stated by the manufacturer or, if no details are given, of outside diameter 0.8 mm (21 gauge) and in accordance with ISO 7864. Insert and withdraw the needle five times through the access port. Maintain the pressure for 6 h and visually inspect the device for the emergence of water.
- Using the same circuit, completely fill the device with degassed water at  $(37 \pm 1) ^\circ\text{C}$ . Seal all ports except the port to which pressure is applied. Put the device under sub-atmospheric pressure,  $1.5 \times$  the manufacturer's recommended maximum negative pressure, unless that sub-atmospheric pressure exceeds 700 mmHg or is not specified; in that case, apply a sub-atmospheric pressure of 700 mmHg and seal the apparatus. Access the port in accordance with the manufacturer's instructions. Access the port an additional 10 times over a 10 min period. Maintain the pressure for 6 h and visually inspect the device for the leakage of air into the tubing. The water may be circulated through the device.

### 5.5.6.2 Needleless access ports

Compliance with 4.4.6.2 shall be determined by the following procedure.

- Fill the portion of the extracorporeal blood circuit that contains the access port with water at  $(37 \pm 1)^\circ\text{C}$  and apply a pressure  $1.5 \times$  the maximum stated by the manufacturer [see 6.4 f) 1)]. Access the port in accordance with the manufacturer's instructions. Access the port an additional 10 times over a 10 min period. Maintain the pressure for 6 h and visually inspect the device for the emergence of water.
- Using the same circuit, completely fill the device with degassed water at  $(37 \pm 1)^\circ\text{C}$ . Seal all ports except the port to which pressure is applied. Put the device under sub-atmospheric pressure,  $1.5 \times$  the manufacturer's recommended pressure, unless that sub-atmospheric pressure exceeds 700 mmHg or is not specified; in that case, apply a sub-atmospheric pressure of 700 mmHg and seal the apparatus. Access the port in accordance with the manufacturer's instructions. Access the port an additional 10 times over a 10 min period. Maintain the pressure for 6 h and visually inspect the device for the leakage of air into the tubing. The water may be circulated through the device.

### 5.5.7 Blood pathway volume

Compliance with the 4.4.7 shall be verified by filling the blood pathway of the device with water and measuring the volume of the water needed to fill this pathway. The air-capture chambers shall be filled to their normal operating level.

### 5.5.8 Air-capture chamber fill level

Compliance with this marking shall be by visual inspection of the existence of a marking giving the normal operating level.

### 5.5.9 Transducer protectors

Compliance with 4.4.9.1 and 4.4.9.2 shall be verified by testing to withstand  $1.5 \times$  the maximum pressure specified by the manufacturer according to the following.

With the machine side open, fill the extracorporeal blood circuit side with water, pressurize the extracorporeal side to  $1.5 \times$  the manufacturer's recommended maximum pressure and hold for 1 h; examine for signs of leakage. Leakage shall not occur at the Luer connector, at the housing welds or through the membrane.

Visually inspect the device component to ensure compliance with the connection requirements of 4.4.4.

Visually inspect the transducer for transparency of the machine side.

### 5.5.10 Blood pathway flow dynamics

Compliance with 4.4.10 shall be verified by review of the manufacturing risk management file for the device.

### 5.5.11 Pump segment performance

Compliance with 4.4.11 can be determined by evaluating the flow rate changes over time with a negative inlet pressure between 0 mmHg and -250 mmHg. The testing shall be performed over the range of blood flows recommended by the manufacturer with back-pressures. The results shall be used to give the recommendations in 6.4 f) 3).

Dimensions in millimeters

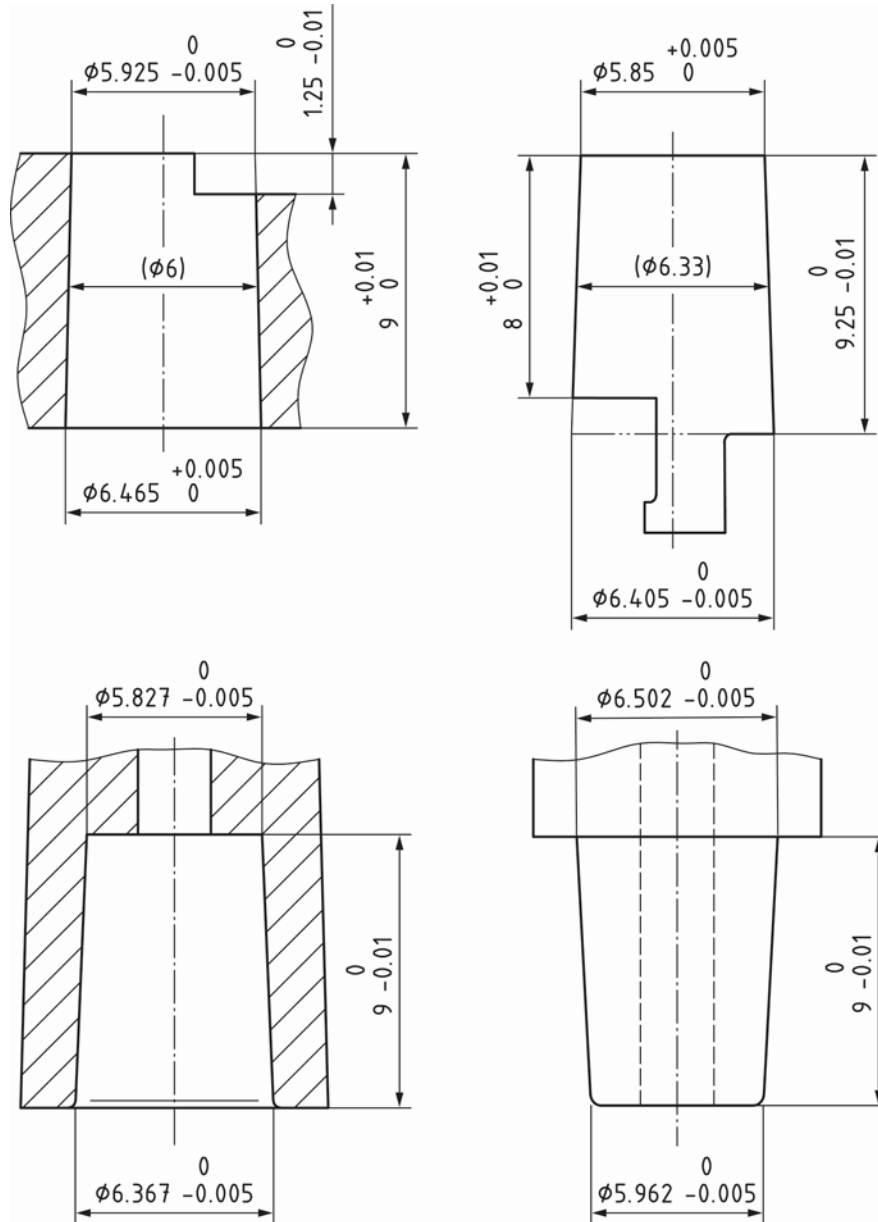


**Figure 3 — Test device used for ISO blood port connectors**



## 5.6 Expiry date

Compliance with 4.5 can be met by accelerated or real time testing of the device for biological safety, sterility and mechanical integrity after storage for a period corresponding to the expiry date.

## 5.7 Tubing compliance

Compliance with 4.6 can be verified by placing the tubing in the dialysis machine clamp for which the product will be labeled, and activating the clamp. The circuit shall then be pressurized to  $1.5 \times$  the manufacturer's recommended maximum pressure and observed for leakage past the clamp for 20 min. No leakage shall occur.

# 6 Labeling

## 6.1 Labeling on the device

The device shall be labeled with at least the following information:

- a) red and blue markings at patient connection ends;
- b) air-capture chamber level markings, if appropriate.

NOTE In all cases, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

## 6.2 Labeling on the unit container

At least the following information shall be visible on or through the unit container:

- a) the manufacturer's name and address;
- b) the proprietary device name;
- c) the manufacturer's identifying code for the device;
- d) the lot number;
- e) a statement of sterility and nonpyrogenicity, and whether the entire contents of the container or the fluid pathways only are sterile;
- f) the expiry date, stated as mm/yyyy or yyyy/mm;
- g) a statement of single use;
- h) the statement, "Read the instructions before use";
- i) the method of sterilization;
- j) if not provided as an integral part of the set, a statement stating, "Caution, a transducer protector must be installed on each pressure monitoring line prior to patient use";
- k) the length and internal diameter of the pump segment.

NOTE In all cases, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

### 6.3 Labeling on the outer container

At least the following information shall appear on the outer container:

- a) the manufacturer's name and address;
- b) the name and address of the distributor, if different from the information given under a), if applicable and in accordance with national requirements;
- c) the proprietary device name, description of contents and number of devices contained in the outer container;
- d) the manufacturer's identifying code for the device;
- e) the lot number;
- f) a statement of sterility and nonpyrogenicity;
- g) the expiry date, stated as mm/yyyy or yyyy/mm;
- h) instructions and warnings regarding handling and storage.

NOTE In all cases, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

### 6.4 Accompanying documentation

At least the following information shall be supplied with each outer container:

- a) the manufacturer's name and address;
- b) the proprietary device name;
- c) the manufacturer's identifying code for the device;
- d) a statement of sterility and nonpyrogenicity and method of sterilization;
- e) a statement of single use;
- f) cautions and warnings, including, but not limited to, the following:
  - 1) maximum pressures (both positive and negative) and applicable blood flow limitations, such as the maximum blood flow rate;
  - 2) a statement that the device is compatible with the relevant components of the equipment for which it is intended;
  - 3) a statement that the actual blood flow rate might differ from the blood flow rate indicated by the machine and that the difference might change with time, if applicable;
  - 4) a warning not to kink the tubing;
  - 5) a statement concerning the potential for air infusion and a recommendation to use an air detector;

- 6) a warning that locking connectors might separate if either the male or female part is exposed to a lubricant, for example, by transfer of lubricant from a lubricated needleless valve;
- 7) a warning that the air detector will not detect air introduced by a syringe through an access port distal to the air detector, if applicable;
- g) instructions on how to prepare the extracorporeal blood circuit before use;
- h) an explanation of the color coding that is used to identify the arterial and venous lines;
- i) if transducer protectors are an integral part of the device, specifications of the transducer protectors and instructions for using them and replacing them if wetted by saline or if blood shall be included;
- j) details of ancillary equipment required;
- k) a general description of the extracorporeal blood circuit;
- l) details of the orientation of the connectors to the hemodialyzer or hemodiafilter in relation to the dialysis fluid lines;
- m) if monitor lines are included, an instruction that devices to prevent contamination of monitors by blood shall be used, unless these devices are part of the extracorporeal blood circuit;
- n) a list of disinfectants for external application (e.g. when sampling blood) that are compatible with the components of the extracorporeal blood circuit and a warning that the compatibility of other disinfectants with the components of the extracorporeal blood circuit shall be determined prior to clinical use;
- o) the recommended procedure for terminating the operational procedure, if applicable;
- p) typical fluid circuit diagrams;
- q) a statement that the generic names of materials that directly or indirectly contact the blood pathway are available to the user upon request;
- r) the machine or machines for which the extracorporeal blood circuit is intended;
- s) the largest needle recommended by the manufacturer for accessing the access ports;
- t) volume of the blood pathway and blood circuit.

NOTE In all cases, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

## Bibliography

- [1] ISO 7000, *Graphical symbols for use on equipment — Index and synopsis*
- [2] ISO 8637, *Cardiovascular implants and extracorporeal systems — Hemodialyzers, hemodiafilters, hemofilters and hemoconcentrators*
- [3] ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*
- [4] ISO/TS 11135-2, *Sterilization of health care products — Ethylene oxide — Part 2: Guidance on the application of ISO 11135-1*
- [5] ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*
- [6] ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*
- [7] ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*
- [8] ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*
- [9] ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labeling and information to be supplied — Part 1: General requirements*
- [10] ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labeling, and information to be supplied — Part 2: Symbol development, selection and validation*
- [11] ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*
- [12] ISO 17665-2, *Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1*

# Reprocessing of hemodialyzers

Developed by  
**Association for the Advancement of Medical Instrumentation**

Approved 8 May 2008 by  
**American National Standards Institute, Inc.**

**Abstract:** This recommended practice is addressed to the physician responsible for reprocessing hemodialyzers. It covers personnel and patient considerations, records, equipment, physical plant and environmental safety, reprocessing material, patient identification and hemodialyzer labeling, reprocessing and storage procedures, disposition of rejected dialyzers, preparation for subsequent use, patient monitoring, and quality assurance and quality control. This document does not endorse either single use or reuse of dialyzers.

**Keywords:** blood, dialysis, labeling, medical equipment, packaging, personnel, records, reprocessing, reuse, test

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*Published by*

Association for the Advancement of Medical Instrumentation  
1110 N. Glebe Road, Suite 220  
Arlington, VA 22201-4795  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

**ISBN 1-57020-313-x**

# Contents

|                                                                       | Page     |
|-----------------------------------------------------------------------|----------|
| Glossary of equivalent standards .....                                | viii     |
| Committee representation .....                                        | vii      |
| Foreword .....                                                        | viii     |
| Introduction: Need for this AAMI recommended practice .....           | ix       |
| <b>1</b> Scope .....                                                  | <b>1</b> |
| <b>1.1</b> Inclusions .....                                           | <b>1</b> |
| <b>1.2</b> Exclusions .....                                           | <b>1</b> |
| <b>2</b> Normative references .....                                   | <b>1</b> |
| <b>3</b> Definitions .....                                            | <b>2</b> |
| <b>4</b> Records .....                                                | <b>4</b> |
| <b>4.1</b> Dialyzer reprocessing manual .....                         | <b>4</b> |
| <b>4.2</b> Reprocessing record .....                                  | <b>5</b> |
| <b>4.3</b> Equipment maintenance record .....                         | <b>5</b> |
| <b>4.4</b> Personnel health monitoring records .....                  | <b>5</b> |
| <b>4.5</b> Complaint investigation record .....                       | <b>5</b> |
| <b>4.6</b> Quality assurance and quality control record .....         | <b>5</b> |
| <b>5</b> Personnel qualifications and training .....                  | <b>5</b> |
| <b>5.1</b> Qualifications .....                                       | <b>5</b> |
| <b>5.2</b> Training .....                                             | <b>5</b> |
| <b>5.2.1</b> Curriculum .....                                         | <b>5</b> |
| <b>5.2.2</b> Documentation .....                                      | <b>6</b> |
| <b>6</b> Patient considerations .....                                 | <b>6</b> |
| <b>6.1</b> Medical issues .....                                       | <b>6</b> |
| <b>6.2</b> Patient education .....                                    | <b>6</b> |
| <b>7</b> Equipment .....                                              | <b>6</b> |
| <b>7.1</b> Water systems .....                                        | <b>6</b> |
| <b>7.2</b> Reprocessing systems .....                                 | <b>6</b> |
| <b>7.2.1</b> Utility requirements .....                               | <b>6</b> |
| <b>7.2.2</b> Process control testing .....                            | <b>6</b> |
| <b>7.2.3</b> Maintenance .....                                        | <b>7</b> |
| <b>7.2.4</b> Repairs .....                                            | <b>7</b> |
| <b>8</b> Physical plant and environmental safety considerations ..... | <b>7</b> |
| <b>8.1</b> Reprocessing area and ventilation .....                    | <b>7</b> |
| <b>8.2</b> Storage area .....                                         | <b>7</b> |
| <b>8.3</b> Laboratory area .....                                      | <b>8</b> |
| <b>8.4</b> Personnel protection .....                                 | <b>8</b> |
| <b>8.5</b> Environmental safety .....                                 | <b>8</b> |
| <b>9</b> Reprocessing supplies .....                                  | <b>8</b> |
| <b>9.1</b> Specifications and testing .....                           | <b>8</b> |
| <b>9.2</b> Inventory control .....                                    | <b>9</b> |
| <b>10</b> Hemodialyzer labeling .....                                 | <b>8</b> |
| <b>10.1</b> Time of labeling .....                                    | <b>8</b> |
| <b>10.2</b> Label composition .....                                   | <b>8</b> |
| <b>10.3</b> Information recorded .....                                | <b>8</b> |

|                           |                                                                                                          |           |
|---------------------------|----------------------------------------------------------------------------------------------------------|-----------|
| <b>11</b>                 | <b>Reprocessing .....</b>                                                                                | <b>9</b>  |
| 11.1                      | Transportation and handling.....                                                                         | 9         |
| 11.2                      | Rinsing and cleaning.....                                                                                | 9         |
| 11.2.1                    | Dialyzer precleaning .....                                                                               | 9         |
| 11.2.2                    | Initiation of cleaning .....                                                                             | 9         |
| 11.2.3                    | Water quality for cleaning .....                                                                         | 9         |
| 11.2.4                    | Cleaning agents .....                                                                                    | 9         |
| 11.3                      | Performance measurements.....                                                                            | 9         |
| 11.3.1                    | Performance test after each use .....                                                                    | 10        |
| 11.3.2                    | Ultrafiltration.....                                                                                     | 10        |
| 11.3.3                    | Blood path integrity test .....                                                                          | 10        |
| 11.4                      | Germicide.....                                                                                           | 10        |
| 11.4.1                    | Interior (blood/dialysate compartment).....                                                              | 10        |
| 11.4.2                    | Exterior .....                                                                                           | 11        |
| 11.5                      | Inspection.....                                                                                          | 11        |
| 11.6                      | Disposition of rejected dialyzers.....                                                                   | 12        |
| 11.7                      | Storage .....                                                                                            | 12        |
| <b>12</b>                 | <b>Preparation for dialysis and testing for chemical germicides and potentially toxic residues .....</b> | <b>12</b> |
| 12.1                      | Visual inspection .....                                                                                  | 12        |
| 12.2                      | Verification of patient identification .....                                                             | 12        |
| 12.3                      | Verification of germicidal contact.....                                                                  | 12        |
| 12.3.1                    | Presence test of each hemodialyzer .....                                                                 | 12        |
| 12.3.2                    | Process control and sampling .....                                                                       | 12        |
| 12.4                      | Priming the dialyzer and rinsing the germicide .....                                                     | 13        |
| 12.4.1                    | Testing for residual germicide.....                                                                      | 13        |
| 12.5                      | Written procedure for tests for germicide or other residues.....                                         | 13        |
| <b>13</b>                 | <b>Monitoring .....</b>                                                                                  | <b>13</b> |
| 13.1                      | Dialysis.....                                                                                            | 13        |
| 13.2                      | Symptoms .....                                                                                           | 14        |
| 13.2.1                    | Fever and chills.....                                                                                    | 14        |
| 13.2.2                    | Other symptoms.....                                                                                      | 14        |
| 13.2.3                    | Recording .....                                                                                          | 14        |
| 13.3                      | Dialyzer failures.....                                                                                   | 14        |
| 13.4                      | Clinical results .....                                                                                   | 14        |
| <b>14</b>                 | <b>Quality assurance .....</b>                                                                           | <b>14</b> |
| 14.1                      | Records.....                                                                                             | 15        |
| 14.2                      | Schedule of quality assurance activities.....                                                            | 15        |
| 14.3                      | Patient considerations .....                                                                             | 15        |
| 14.4                      | Equipment .....                                                                                          | 15        |
| 14.5                      | Physical plant and environmental safety considerations .....                                             | 15        |
| 14.6                      | Reprocessing supplies .....                                                                              | 15        |
| 14.7                      | Hemodialyzer labeling .....                                                                              | 16        |
| 14.8                      | Reprocessing .....                                                                                       | 16        |
| 14.9                      | Preparation for dialysis.....                                                                            | 16        |
| <b>Annexes</b>            |                                                                                                          |           |
| <b>A</b>                  | <b>Rationale for the development and provisions of this recommended practice.....</b>                    | <b>17</b> |
| <b>B</b>                  | <b>Systems diagram for reprocessing dialyzers.....</b>                                                   | <b>30</b> |
| <b>C</b>                  | <b>Self-assessment of compliance with recommendations for hemodialyzer reprocessing.....</b>             | <b>31</b> |
| <b>Bibliography .....</b> |                                                                                                          | <b>53</b> |
| <b>Tables</b>             |                                                                                                          |           |
| <b>1</b>                  | <b>OSHA environmental exposure limits (29 CFR 1910, 1 July 1998), except as indicated .....</b>          | <b>7</b>  |
| <b>2</b>                  | <b>Quality assurance audit schedule .....</b>                                                            | <b>15</b> |



## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

| International designation                | U.S. designation                                                   | Equivalency                             |
|------------------------------------------|--------------------------------------------------------------------|-----------------------------------------|
| IEC 60601-1:2005                         | ANSI/AAMI ES60601-1:2005                                           | Major technical variations              |
| IEC 60601-1-2:2007                       | ANSI/AAMI/IEC 60601-1-2:2007                                       | Identical                               |
| IEC 60601-2-2:2006                       | ANSI/AAMI/IEC 60601-2-2:2006                                       | Identical                               |
| IEC 60601-2-4:2002                       | ANSI/AAMI DF80:2003                                                | Major technical variations              |
| IEC 60601-2-19:1990 and Amendment 1:1996 | ANSI/AAMI II36:2004                                                | Major technical variations              |
| IEC 60601-2-20:1990 and Amendment 1:1996 | ANSI/AAMI II51:2004                                                | Major technical variations              |
| IEC 60601-2-21:1994 and Amendment 1:1996 | ANSI/AAMI/IEC 60601-2-21 and Amendment 1:2000 (consolidated texts) | Identical                               |
| IEC 60601-2-24:1998                      | ANSI/AAMI ID26:2004                                                | Major technical variations              |
| IEC 60601-2-47:2001                      | ANSI/AAMI EC38:2007                                                | Major technical variations              |
| IEC 60601-2-50:2001                      | ANSI/AAMI/IEC 60601-2-50:2006                                      | Identical                               |
| IEC/TR 60878:2003                        | ANSI/AAMI/IEC TIR60878:2003                                        | Identical                               |
| IEC/TR 62296:2003                        | ANSI/AAMI/IEC TIR62296:2003                                        | Identical                               |
| IEC 62304:2006                           | ANSI/AAMI/IEC 62304:2006                                           | Identical                               |
| IEC/TR 62348:2006                        | ANSI/AAMI/IEC TIR62348:2006                                        | Identical                               |
| ISO 5840:2005                            | ANSI/AAMI/ISO 5840:2005                                            | Identical                               |
| ISO 7198:1998                            | ANSI/AAMI/ISO 7198:1998/2001/(R)2004                               | Identical                               |
| ISO 7199:1996                            | ANSI/AAMI/ISO 7199:1996/(R)2002                                    | Identical                               |
| ISO 8637:2004                            | ANSI/AAMI RD16:2007                                                | Major technical variations              |
| ISO 8638:2004                            | ANSI/AAMI RD17:2007                                                | Major technical variations              |
| ISO 10993-1:2003                         | ANSI/AAMI/ISO 10993-1:2003                                         | Identical                               |
| ISO 10993-2:2006                         | ANSI/AAMI/ISO 10993-2:2006                                         | Identical                               |
| ISO 10993-3:2003                         | ANSI/AAMI/ISO 10993-3:2003                                         | Identical                               |
| ISO 10993-4:2002 and Amendment 1:2006    | ANSI/AAMI/ISO 10993-4:2002 and Amendment 1:2006                    | Identical                               |
| ISO 10993-5:1999                         | ANSI/AAMI/ISO 10993-5:1999                                         | Identical                               |
| ISO 10993-6:2007                         | ANSI/AAMI/ISO 10993-6:2007                                         | Identical                               |
| ISO 10993-7:1995                         | ANSI/AAMI/ISO 10993-7:1995/(R)2001                                 | Identical                               |
| ISO 10993-9:1999                         | ANSI/AAMI/ISO 10993-9:1999/(R)2005                                 | Identical                               |
| ISO 10993-10:2002 and Amendment 1:2006   | ANSI/AAMI BE78:2002<br>ANSI/AAMI BE78:2002/A1:2006                 | Minor technical variations<br>Identical |
| ISO 10993-11:2006                        | ANSI/AAMI/ISO 10993-11:2006                                        | Identical                               |
| ISO 10993-12:2007                        | ANSI/AAMI/ISO 10993-12:2007                                        | Identical                               |
| ISO 10993-13:1998                        | ANSI/AAMI/ISO 10993-13:1999/(R)2004                                | Identical                               |
| ISO 10993-14:2001                        | ANSI/AAMI/ISO 10993-14:2001/(R)2006                                | Identical                               |
| ISO 10993-15:2000                        | ANSI/AAMI/ISO 10993-15:2000/(R)2006                                | Identical                               |
| ISO 10993-16:1997                        | ANSI/AAMI/ISO 10993-16:1997/(R)2003                                | Identical                               |

| <b>International designation</b>                | <b>U.S. designation</b>                              | <b>Equivalency</b>         |
|-------------------------------------------------|------------------------------------------------------|----------------------------|
| ISO 10993-17:2002                               | ANSI/AAMI/ISO 10993-17:2002                          | Identical                  |
| ISO 10993-18:2005                               | ANSI/AAMI BE83:2006                                  | Major technical variations |
| ISO/TS 10993-19:2006                            | ANSI/AAMI/ISO TIR10993-19:2006                       | Identical                  |
| ISO/TS 10993-20:2006                            | ANSI/AAMI/ISO TIR10993-20:2006                       | Identical                  |
| ISO 11135-1:2007                                | ANSI/AAMI/ISO 11135-1:2007                           | Identical                  |
| ISO 11137-1:2006                                | ANSI/AAMI/ISO 11137-1:2006                           | Identical                  |
| ISO 11137-2:2006 (2006-08-01 corrected version) | ANSI/AAMI/ISO 11137-2:2006                           | Identical                  |
| ISO 11137-3:2006                                | ANSI/AAMI/ISO 11137-3:2006                           | Identical                  |
| ISO 11138-1: 2006                               | ANSI/AAMI/ISO 11138-1:2006                           | Identical                  |
| ISO 11138-2: 2006                               | ANSI/AAMI/ISO 11138-2:2006                           | Identical                  |
| ISO 11138-3: 2006                               | ANSI/AAMI/ISO 11138-3:2006                           | Identical                  |
| ISO 11138-4: 2006                               | ANSI/AAMI/ISO 11138-4:2006                           | Identical                  |
| ISO 11138-5: 2006                               | ANSI/AAMI/ISO 11138-5:2006                           | Identical                  |
| ISO/TS 11139:2006                               | ANSI/AAMI/ISO 11139:2006                             | Identical                  |
| ISO 11140-1:2005                                | ANSI/AAMI/ISO 11140-1:2005                           | Identical                  |
| ISO 11140-3:2007                                | ANSI/AAMI/ISO 11140-3:2007                           | Identical                  |
| ISO 11140-4:2007                                | ANSI/AAMI/ISO 11140-4:2007                           | Identical                  |
| ISO 11140-5:2007                                | ANSI/AAMI/ISO 11140-5:2007                           | Identical                  |
| ISO 11607-1:2006                                | ANSI/AAMI/ISO 11607-1:2006                           | Identical                  |
| ISO 11607-2:2006                                | ANSI/AAMI/ISO 11607-2:2006                           | Identical                  |
| ISO 11737-1: 2006                               | ANSI/AAMI/ISO 11737-1:2006                           | Identical                  |
| ISO 11737-2:1998                                | ANSI/AAMI/ISO 11737-2:1998                           | Identical                  |
| ISO 11737-3:2004                                | ANSI/AAMI/ISO 11737-3:2004                           | Identical                  |
| ISO 13485:2003                                  | ANSI/AAMI/ISO 13485:2003                             | Identical                  |
| ISO 14155-1:2003                                | ANSI/AAMI/ISO 14155-1:2003                           | Identical                  |
| ISO 14155-2:2003                                | ANSI/AAMI/ISO 14155-2:2003                           | Identical                  |
| ISO 14160:1998                                  | ANSI/AAMI/ISO 14160:1998                             | Identical                  |
| ISO 14161:2000                                  | ANSI/AAMI/ISO 14161:2000                             | Identical                  |
| ISO 14937:2000                                  | ANSI/AAMI/ISO 14937:2000                             | Identical                  |
| ISO/TR 14969:2004                               | ANSI/AAMI/ISO TIR14969:2004                          | Identical                  |
| ISO 14971:2007                                  | ANSI/AAMI/ISO 14971:2007                             | Identical                  |
| ISO 15223-1:2007                                | ANSI/AAMI/ISO 15223-1:2007                           | Identical                  |
| ISO 15225:2000 and A1:2004                      | ANSI/AAMI/ISO 15225:2000/(R)2006 and A1:2004/(R)2006 | Identical                  |
| ISO 15674:2001                                  | ANSI/AAMI/ISO 15674:2001                             | Identical                  |
| ISO 15675:2001                                  | ANSI/AAMI/ISO 15675:2001                             | Identical                  |
| ISO 15882:2003                                  | ANSI/AAMI/ISO 15882:2003                             | Identical                  |
| ISO/TR 16142:2006                               | ANSI/AAMI/ISO TIR16142:2005                          | Identical                  |
| ISO 17664:2004                                  | ANSI/AAMI ST81:2004                                  | Major technical variations |
| ISO 17665-1:2006                                | ANSI/AAMI/ISO 17665-1:2006                           | Identical                  |
| ISO 18472:2006                                  | ANSI/AAMI/ISO 18472:2006                             | Identical                  |
| ISO/TS 19218:2005                               | ANSI/AAMI/ISO 19218:2005                             | Identical                  |
| ISO 22442-1:2007                                | ANSI/AAMI/ISO 22442-1:2007                           | Identical                  |
| ISO 22442-2:2007                                | ANSI/AAMI/ISO 22442-2:2007                           | Identical                  |
| ISO 22442-3:2007                                | ANSI/AAMI/ISO 22442-3:2007                           | Identical                  |
| ISO 25539-1:2003 and A1:2005                    | ANSI/AAMI/ISO 25539-1:2003 and A1:2005               | Identical                  |
| ISO 81060-1:2007                                | ANSI/AAMI/ISO 81060-1:2007                           | Identical                  |

## Committee representation

### Association for the Advancement of Medical Instrumentation

#### Renal Disease and Detoxification Committee

This recommended practice was developed by the AAMI Renal Disease and Detoxification Committee. Committee approval of the recommended practice does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

|                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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NOTE—Participation by federal agency representatives in the development of this recommended practice does not constitute endorsement by the federal government or any of its agencies.

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## Foreword

This recommended practice was developed by the AAMI Renal Disease and Detoxification Committee. The committee's objectives are to acknowledge the widespread practice of hemodialyzer reprocessing, without endorsement or criticism; to indicate risks associated with hemodialyzer reprocessing; and to provide recommendations for optimal hemodialyzer reprocessing, as a service to patients, physicians, and facilities.

This recommended practice reflects the conscientious efforts of health care professionals, patients, and medical device manufacturers to develop recommendations for optimal hemodialyzer reprocessing procedures. These recommendations are not meant to be construed as universally applicable in all circumstances. This document is intended to guide physicians in charge of hemodialyzer reprocessing, particularly the directors of dialysis facilities, in initiating a new hemodialyzer reprocessing program or evaluating an existing program against present day technology and accepted practices.

This recommended practice should be considered flexible and dynamic. As technology advances and new data are brought forward, this recommended practice will be reviewed and, if necessary, revised. The term "should" as used in this recommended practice reflects the committee's intent to define goals, not requirements. The term "shall" as used here denotes quality recommendations and procedures that are required by applicable standards. The term "must" is used only to describe unavoidable situations, including those mandated by government regulation.

The use of phrases such as "have been shown," "an established procedure," "demonstrated success," or others of similar words signifies that the basis for the process may be found in a manufacturer's labeling, medical or scientific literature, standards or publications from authoritative agencies, or clearly documented, scientifically sound studies performed locally.

These guidelines were developed by professionals and are not designed for regulatory applications but have been put into service as such.

The concepts incorporated in this recommended practice should not be considered inflexible or static. The recommendations presented here should be reviewed and updated periodically to assimilate technological developments.

The rationale for this recommended practice (annex A) not only contains explanations of the need for the provisions of the recommended practice, but also gives proposed revisions that were not included in this recommended practice and the reasons for those exclusions. The reader is encouraged to review the rationale for each section carefully to better understand the recommended practice itself and the state of the art in reprocessing hemodialyzers.

AAMI standards and guidelines are based on the national consensus of physicians, engineers, other health care professionals, government representatives, patients, and industry. This consensus has traditionally focused on technology design, performance, and testing—areas in which the AAMI membership has considerable knowledge and experience. During the development of this document, several interest groups requested detailed requirements for informed patient consent with respect to the reuse of hemodialyzers. It is unclear whether informed patient consent requirements can or should be developed by a consensus of the groups mentioned. It may be more appropriate for informed patient consent requirements to be developed by physicians, patients, and their representatives. This document does not go as far as the patients' representatives requested on that subject, although it does go further than previous documents of this type. The extent to which AAMI or any standards organization should develop informed patient consent requirements can be determined as this guideline is evaluated during its use.

Suggestions for improving this recommended practice are invited. Comments and suggested revisions should be sent to AAMI, Attn: Standards Department, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

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NOTE—This foreword does not contain provisions of the American National Standard ANSI/AAMI RD47:2008, *Reprocessing of hemodialyzers*, but it does provide important information about the development and intended use of the document.

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## Introduction: Need for this AAMI recommended practice

In June 1980, the Bureau of Medical Devices of the U.S. Food and Drug Administration (FDA), now the Center for Devices and Radiological Health, transmitted to AAMI the final report of an FDA-sponsored study, "An Investigation of the Risks and Hazards Associated with Hemodialysis Devices," that was undertaken to recommend ways of controlling these risks and hazards. This information was compiled to assist the medical community and to provide data to support the development of recommended practices.

Beginning in 1980, the reported incidence of hemodialyzer reuse rose dramatically, from an estimated 16 % of patients in 1980 to an estimated 82 % of clinics in 1997. This increase was attributable, in part, to the increasing pressure of federal measures to contain the costs of health care implemented by the prospective reimbursement regulations initiated on 1 August 1983. The percentage of centers practicing reuse declined after 1997 to 63 % in 2002 (Finelli, et al., 2005), and in 2005, it was estimated that 61 % of patients were being treated with single-use dialyzers (Lacson and Lazarus, 2006).

Although good results have been demonstrated by the practitioner experienced in hemodialyzer reprocessing, the widespread application of this technique in the absence of detailed consensus guidelines has created greater opportunities for the nonexpert practitioner to use inadequate methods. Moreover, cost saving by any procedure that adds risks to the patient if improperly done may cause some patients and health care professionals to suspect that the welfare of the patient may not be the primary concern. These fears may be justified, because merely claiming that reuse is safe, without defining details of the process, allows unsafe procedures to appear under the guise of acceptable medical practice. Thus, failure to ensure that reuse is done safely for all patients causes the brush of mistrust to paint all practitioners alike, when, in fact, the multiple use of hemodialyzers may actually improve the quality of care and access to dialysis. Those who are expert in reprocessing hemodialyzers can, therefore, perform a valuable service by developing guidelines for the less experienced practitioner that will achieve the high quality of care that health care professionals want for their patients. This recommended practice has been written to respond to the concern of patients, health care professionals, and manufacturers that dialyzer reprocessing be conducted safely and effectively.

It was against this background that AAMI convened a consensus-development conference in May 1983 to examine the issues surrounding reuse of hemodialyzers and to discuss the position of the medical and scientific community on the subject. One recommendation emerging from this conference, in which representatives from many medical and scientific societies participated, was that approval by consensus of a nationally developed recommended practice for the reprocessing of hemodialyzers was desirable and necessary for patient safety and continued clinical efficacy. Another recommendation was that the guidelines be developed under the auspices of AAMI because AAMI could coordinate the development of a national consensus. AAMI subsequently established the Hemodialyzer Reuse Subcommittee of the Renal Disease and Detoxification Committee. The subcommittee's membership includes representatives of manufacturers, patients, health care organizations, government agencies, and health care professionals.

In November 1984, an AAMI technology assessment conference was held on the subject of hemodialyzer reuse. The conference attendees reviewed the fourth draft of the recommended practice being written by the AAMI subcommittee. Presentations were also made about the results of a survey of hemodialyzer reprocessing in the United States, water for reprocessing, germicides, statistical analysis, methods of performance testing, reprocessing machines, the perspective of patients, the viewpoint of manufacturers, reprocessing in the home, and the FDA's position on the reprocessing of medical devices. Future revisions of the recommended practice incorporated information gleaned from the conference and comments from other interested parties. In October 1987, the Centers for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration, adopted the recommended practice as part of their regulations governing Medicare reimbursement. Because the guideline was not constructed as a regulation, many questions arose as surveyors attempted to enforce compliance. The AAMI Hemodialyzer Reuse Subcommittee issued an interpretive guideline in 1991 that clarified the issue of dialyzer performance verification, the most common source of misunderstanding in the previous version. When the reuse document was reviewed in 1993, the interpretation was incorporated. Subsequently, the CMS adopted the 1993 revisions in a manner similar to their adoption of the 1987 version. Dialyzer manufacturers are now expected to follow the FDA guidance document titled "Guidance for Hemodialyzer Reuse Labeling" (6 October 1995). This guidance requires a manufacturer to label its dialyzers for either single use or multiple use. In cases of labeling a dialyzer for reuse, the FDA guidance document requires that the manufacturer perform certain bench testing using simulated reuse and then perform a limited clinical trial to support the bench results. Those data are submitted to the FDA and reviewed as part of the 510(k) Premarket Notification for the reusable dialyzer.

In the early 1990s, a statistically significant association was reported between mortality and the use of low-flux dialyzers reprocessed with certain germicides in freestanding clinics (Held, et al., 1994; Feldman, et al., 1996). No cause-and-effect relationship was established in those studies, and potentially confounding variables, such as a

“center effect” and the adequacy of dialysis, were not evaluated. Indeed, the results of more recent studies (Collins, et al., 1998; Ebben, et al., 2000; Port, et al., 2001) suggest that factors other than the choice of germicide may have contributed to the differences in outcome.

# Reprocessing of hemodialyzers

## 1 Scope

This recommended practice describes the essential elements of good practice for reprocessing hemodialyzers to help ensure device safety and effectiveness. These practices embrace considerations of the device and the patient, as well as attention to equipment, facilities, cleaning and disinfection methods, labeling, preparation for multiple use, and quality control of the reuse process. This document does not endorse either single use or reuse of dialyzers.

Regardless of the labeling recommendations, prescription to reuse remains the sole responsibility of the patient's physicians. Therefore, this recommended practice is addressed to the physician responsible for the hemodialyzer reprocessing program. Users, however, should be aware that dialyzers intended for reuse must be labeled for reuse in accordance with the Food and Drug Administration (FDA) document "Guidance for Hemodialyzer Reuse Labeling" (6 October 1995).

The committee recognizes that reuse may affect such dialyzer characteristics as biocompatibility and clearance of larger molecules. Changes in dialyzer performance and biocompatibility vary with the materials of construction and the reuse method employed. Detailed analysis of these factors is beyond the scope of this document. Specific information on the effects of reuse on dialyzer performance and biocompatibility may be obtained from the dialyzer manufacturer and the scientific literature (Cheung, et al., 1999). This recommended practice does not address every risk or benefit that may be associated with reuse.

### 1.1 Inclusions

This recommended practice is directed to the physician in charge of hemodialyzer reprocessing by either the manual or the automated method. Subjects included within the scope of this recommended practice are recordkeeping, personnel considerations, patient considerations, equipment considerations, physical plant and environmental safety, reprocessing material considerations, patient identification and hemodialyzer labeling, reprocessing and storage procedures, disposition of rejected dialyzers, preparation for subsequent use, patient monitoring, quality assurance, and quality control.

### 1.2 Exclusions

This recommended practice does not cover the reprocessing of blood tubing sets, nor does it address labeling and performance requirements for single-use hemodialyzers.

## 2 Normative references

The following documents contain provisions that, through reference in this text, constitute provisions of this AAMI recommended practice. At the time of publication, the editions indicated were valid. All recommended practices are subject to revision, and parties to agreements that are based on this AAMI recommended practice are encouraged to investigate the possibility of applying the most recent editions of the documents listed below.

Association for the Advancement of Medical Instrumentation. *Water treatment equipment for hemodialysis applications*. ANSI/AAMI RD62:2006. Arlington (VA): AAMI, 2006.

Bolyard EA, Tablan OC, Williams WW, Pearson ML, Shapiro CN, Deitchman SD, and Hospital Infection Control Practices Advisory Committee. *Infection Control in Healthcare Personnel: Guideline for infection control in healthcare personnel*, 1998. *Infection Control and Hospital Epidemiology*, 19:407–463,1998. (available from [http://www.cdc.gov/ncidod/dhqp/gl\\_hcpersonnel.html](http://www.cdc.gov/ncidod/dhqp/gl_hcpersonnel.html))

Centers for Disease Control and Prevention. *Recommendations for preventing transmission of infections among hemodialysis patients*. *MMWR* 50, RR-5, 2001. (available from <http://www.cdc.gov/mmwr/PDF/rr/rr5005.pdf>)

Occupational Safety and Health Administration. Occupational Safety and Health Standards. Bloodborne pathogens. Code of Federal Regulations. Title 29, Volume 6, Chapter XVII, Part 1910.1030 Revised as of August 14, 2006 (available from [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10051](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10051))

Occupational Safety and Health Administration. Occupational Safety and Health Standards. Hazard communications. Code of Federal Regulations. Title 29, Volume 6, Chapter XVII, Part 1910.1200 Revised as of August 14, 2006 (available from [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10099](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10099))

Occupational Safety and Health Administration. Occupational Safety and Health Standards. Formaldehyde. Code of Federal Regulations. Title 29, Volume 6, Chapter XVII, Part 1910.1048 Revised as of August 14, 2006 (available from [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10075](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10075))

### 3 Definitions

For the purposes of this AAMI recommended practice, the following definitions apply.

**3.1 cleaning:** Flushing of a solution or solutions through the blood and dialysate compartments or the passage of fluid through the membrane (i.e., reverse ultrafiltration) to purge the dialyzer of blood and other substances.

**3.2 clearance:** Measure of net flux of a given solute across the hemodialyzer membrane that is expressed as the number of milliliters of blood completely cleared of a solute per unit of time. For the purpose of this recommended practice, clearance includes clearance because of ultrafiltration. (See also **clearance, open-loop system**.)

**3.3 clearance, open-loop system:** Clearance determined in a test system in which the solutions perfusing the hemodialyzer are discharged to drain after one passage through the hemodialyzer. The calculation for clearance by this method is as follows:

$$\text{Clearance (mL/min)} = \frac{(C_{Bi} - C_{Bo})Q_{Bi}}{C_{Bi}} + \frac{C_{Bo}Q_{UF}}{C_{Bi}}$$

where

$C_{Bi}$  = concentration of solute in the fluid entering the blood compartment,

$C_{Bo}$  = concentration of solute in the fluid leaving the blood compartment,

$Q_{Bi}$  = flow rate of fluid entering the blood compartment, and

$Q_{UF}$  = ultrafiltration rate.

**3.4 dialyzer:** See **hemodialyzer**.

**3.5 disinfection:** Destruction of pathogenic and other kinds of microorganisms by thermal or chemical means. Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but not necessarily all microbial forms. This definition of disinfection is equivalent to low-level disinfection in the Spaulding classification.

**3.6 endotoxin:** The major component of the outer cell wall of gram-negative bacteria. Endotoxins are lipopolysaccharides, consisting of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defenses, leading to an acute syndrome characterized by fever, shaking chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. Long-term exposure to low levels of endotoxin has been implicated in a chronic inflammatory response, which may contribute to some of the long-term complications seen in hemodialysis patients. However, the mechanisms of this process remain incompletely understood. (See also **pyrogen**.)

**3.7 fiber bundle volume (FBV):** Aggregate volume of patent hollow fibers contained within the blood compartment of a hollow-fiber dialyzer. Sometimes, incorrectly used interchangeably with total cell volume, which includes header volume.

**3.8 first-use syndrome:** Symptom complex characterized by chest tightness, back pain, dyspnea, angioedema or laryngeal edema, peripheral numbness and tingling, flushing of the skin, pruritis, and nausea and vomiting, occurring within minutes of the initiation of dialysis with a new dialyzer. Although usually mild in nature, the symptoms may, in extreme cases, progress to respiratory arrest and death. The etiology of first-use syndrome is not completely understood. However, the term is usually considered to include anaphylactoid reactions to residual ethylene oxide in ethylene oxide-sterilized dialyzers and anaphylactoid reactions resulting from the induction of bradykinin release by negatively charged AN69®<sup>1)</sup> membrane. The latter reactions are exacerbated by the presence of ACE inhibitors, which suppress bradykinin degradation. Anaphylactoid reactions, similar to first-use syndrome, have also been reported with reused dialyzers. The risk of these reactions is also increased when ACE inhibitors are present.

<sup>1)</sup>AN69® is a registered trademark of Hospal.



**3.9 formaldehyde:** Formaldehyde (CH<sub>2</sub>O) solution, USP (United States Pharmacopeia) (nominal concentration 37 % by weight (weight/weight [W/W]) or 40 % by volume (weight/volume [W/V])). Generally contains 8 % to 16 % methanol for stabilization. A dilution of 1 part of formaldehyde with 9 parts of water yields 4 % (W/V). Also called formalin. Concentrated formaldehyde stored under adverse conditions can polymerize to form paraformaldehyde, a white precipitate.

**3.10 germicide:** Agent that kills microorganisms.

**3.11 hazard:** Situation or condition that could be detrimental to patients or staff members.

**3.12 heat disinfection:** Physical method of disinfection used in reprocessing some dialyzer types.

**3.13 hemodialyzer:** Extracorporeal device that (a) changes the chemical composition of the blood by diffusive and convective transfer of substances between the blood and a solution of chemicals through a semipermeable membrane and that (b) functions within clinically acceptable rates of water and solute transport.

**3.14 high-level disinfection:** Process that kills all vegetative bacterial cells, *Mycobacterium tuberculosis* var. *bovis*, fungi, all small or nonlipid viruses, and (if the contact time is long enough) most bacterial endospores.

**3.15 labeling:** Display of written, printed, or graphic matter on a dialyzer, including all packaging and package inserts.

**3.16 lipopolysaccharide (LPS):** Major outer membrane component of gram-negative bacteria. Lipopolysaccharides are important antigenic factors and are endotoxins. The general structure is a heteropolysaccharide chain (core polysaccharide and O-specific chain) covalently bound to a glycolipid (lipid A). (See also **endotoxin**.)

**3.17 low-level disinfection:** Process or procedure that inactivates most vegetative bacteria, except for *Mycobacterium tuberculosis* var. *bovis* and some viruses. (See also **disinfection**.)

**3.18 material safety data sheets (MSDS):** Documents that identify, for any chemicals, the degree and type of any hazards and appropriate precautions. Manufacturers are required to provide these documents upon request.

**3.19 membrane:** Semipermeable material between the blood and dialysate compartments of a hemodialyzer.

**3.20 multiple use:** Use of a device for more than one procedure, after suitable reprocessing of the device.

**3.21 OSHA:** Occupational Safety and Health Administration.

**3.22 performance:** Solute and fluid mass transfer capabilities of a hemodialyzer.

**3.23 port, blood:** Opening into the blood compartment of a hemodialyzer.

**3.24 port, dialysate:** Opening into the dialysate compartment of a hemodialyzer.

**3.25 ppm:** Parts per million.

**3.26 preprocessed dialyzer:** Dialyzer subjected to reprocessing procedure before first use.

**3.27 pyrogen:** Fever-producing substance. Note that pyrogens are most often lipopolysaccharides of gram-negative bacterial origin. (See also **endotoxin**.)

**3.28 quality assurance (QA):** Verification that written policies and procedures have been developed and are being implemented.

**3.29 quality control (QC):** Determination that the materials, process tests, and performance of the final product meet the designated specifications.

**3.30 rebound:** Increase in germicide concentration after rinsing to a particular concentration.

**3.31 removal of germicide:** Passage of a solution through the blood and dialysate compartments of a hemodialyzer to purge it of the germicide.

**3.32 reprocessing number:** The number of times a dialyzer has been reprocessed.

NOTE—The reprocessing number is the number of times a dialyzer has been submitted to the clean–test–disinfect cycle. It may differ from the use number if a dialyzer is reprocessed more than once between actual treatments, as could occur if a dialyzer was prepared for a treatment, but not used.

**3.33 reverse ultrafiltration:** Passing of fluids through the membrane from the dialysate compartment to the blood compartment. This action is used to clean the membrane of blood products for the purpose of reuse.

**3.34 risk:** Event that is considered likely or possible and that is potentially hazardous but has not yet occurred or resulted in detrimental clinical consequences.

**3.35 standard precautions:** Synthesis of the major features of universal (blood and body fluid) precautions (designed to reduce the risk of transmission of bloodborne pathogens) and body substance isolation (designed to reduce the risk of transmission of pathogens from moist body substances). Standard precautions apply to (a) blood; (b) all body fluids, secretions, and excretions, except sweat, regardless of whether they contain visible blood; (c) nonintact skin; and (d) mucous membranes. Standard precautions are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in health care settings.

**3.36 sterile:** Free of all microbial life, including highly resistant bacterial spores.

**3.37 total cell volume (TCV):** Volume of an aqueous liquid to fully prime the blood compartment of a hollow-fiber hemodialyzer. This volume is the sum of the fiber bundle volume and the header volume.

**3.38 toxic substance:** Substance that, in sufficient amounts, causes harm to an exposed organism.

**3.39 transmembrane pressure (TMP):** Pressure exerted across the semipermeable membrane, from the blood to the dialysate side of the dialyzer, which can be expressed by the following equation:

$$TMP = (P_{Bi} + P_{Bo})/2 - (P_{Di} + P_{Do})/2 - P_{oncotic},$$

where

$P_{oncotic}$  = oncotic pressure created by plasma proteins,

$P_{Bi}$  = pressure at the arterial (inlet) port of a hemodialyzer blood compartment,

$P_{Bo}$  = pressure at the venous (outlet) port of a hemodialyzer blood compartment,

$P_{Di}$  = pressure at the inlet port of a hemodialyzer dialysate compartment, and

$P_{Do}$  = pressure at the outlet port of a hemodialyzer dialysate compartment.

**3.40 ultrafiltration (UF):** Transfer of fluid from the blood compartment to the dialysate compartment through the dialysis membrane as a result of a pressure gradient (transmembrane pressure) existing between the blood and dialysate compartments.

**3.41 use number:** Number of times a hemodialyzer has been used for dialysis treatments with a single patient.

NOTE—The use number is the number of actual treatments performed with a dialyzer. It may differ from the reprocessing number if a dialyzer is reprocessed more than once between treatments, as could occur if a dialyzer was prepared for a treatment but not used.

**3.43 validation or process validation:** Establishment of documented evidence providing a high degree of assurance that a given process will consistently yield a result meeting predetermined specifications and quality characteristics.

## 4 Records

All records described in this recommended practice shall meet the requirements for medical records, including completeness, legibility, and security. A place should be provided for the signature or other unique mark of identification of the person completing each step of the reprocessing procedure (i.e., the persons performing preventive maintenance procedures, the persons investigating complaints, and the persons conducting quality assurance and quality control activities). Maintaining these records is the responsibility of the medical director.

### 4.1 Dialyzer reprocessing manual

The dialyzer reprocessing manual should be a compilation of all specifications, policies, training materials, manuals, methodologies, and procedures that may be integrated into the dialysis facility's policy and procedures manual. The dialyzer reprocessing manual should also contain samples of forms and labels, if appropriate. The operational logs, manuals, and records may be kept separate from the dialyzer reprocessing manual. The manual should incorporate any special considerations specified by the dialyzer manufacturer.

## **4.2 Reprocessing record**

Records shall be kept that identify the new dialyzer, the date of each reprocessing step, the person performing the procedure, his or her signature or other identifying mark, and the results of tests of device performance and safety. This information should be recorded in a reprocessing log or the patient's chart, whichever is more convenient. Patients must be permitted to read records pertaining to the reprocessing and reuse of their own dialyzers.

## **4.3 Equipment maintenance record**

Records shall be maintained of the dates of preventive maintenance procedures and the results of scheduled testing to ensure the proper functioning of reprocessing, environmental control, safety, or other equipment.

## **4.4 Personnel health monitoring records**

A file must be kept of the results of personnel medical examinations that are required by OSHA or other regulatory agencies.

## **4.5 Complaint investigation record**

Records shall be kept of all complaints by patients and staff members about failures of preprocessed and reprocessed dialyzers or possible adverse reactions to any dialyzers; the results of a comprehensive investigation of these alleged problems; and, if appropriate, the corrective actions taken. The records should be reviewed periodically for trends of adverse reactions. Staff members should consider whether any adverse reactions need to be reported in compliance with the FDA's Medical Device User Reporting procedures.

## **4.6 Quality assurance and quality control record**

A record shall be kept of the date and results of QA and QC evaluations and the person or persons conducting the evaluations.

# **5 Personnel qualifications and training**

## **5.1 Qualifications**

Personnel shall possess adequate education, training, or experience to understand and perform procedures outlined by the individual dialysis facility relevant to the facility's multiple-use program. New personnel range in knowledge from those with no medical background who are fully trained by the facility to licensed practitioners with extensive medical background. Education should be geared to meet the needs of this wide range of personnel.

## **5.2 Training**

### **5.2.1 Curriculum**

The dialysis facility's physician or director shall establish a training course for the personnel performing hemodialyzer reprocessing. A written document should give details about the curriculum and, in particular, address the potential risks to patients and staff members of not following correct procedures. The curriculum should include at least the following information:

- a) the facility's specific reprocessing procedure, including a rationale for each step;
- b) basic documentation requirements of the program;
- c) the operation and maintenance of the facility's specific equipment for reprocessing hemodialyzers and, if appropriate, the dialysis systems and components;
- d) microbiology with respect to aseptic technique, the collection and handling of samples, and personnel safety precautions for infectious hazards;
- e) the risks and hazards of multiple use of hemodialyzers;
- f) the consequences of not performing tasks properly;
- g) the risks and hazards associated with toxic substances used in reprocessing hemodialyzers, proper handling of these substances, and procedures for handling spills and proper disposal of toxic substances;
- h) the use and location of protective eyewear, respirators, masks, and special clothing;
- i) emergency procedures as required by the facility; and

- j) the principles of dialysis, emphasizing the characteristics of the hemodialyzer and the effect of reuse on those characteristics.

### **5.2.2 Documentation**

Each person performing procedures for the multiple use of dialyzers should have successfully completed the dialysis facility's training course relevant to that person's task and demonstrated competence in the area covered by his or her training. Successful completion of training should be certified by the medical director or his or her designated representative and recorded in the trainee's personnel file along with verification of the trainee's having received the instruction. Retraining is necessary when new procedures are undertaken. Annual review of competence is required with appropriate retraining if deficiencies are found.

## **6 Patient considerations**

### **6.1 Medical issues**

An order to reprocess hemodialyzers shall be made by a physician knowledgeable about reprocessing and its medical and economic implications. Because the current human immunodeficiency virus (HIV), hepatitis B, or hepatitis C status of a patient cannot be known with certainty, all staff potentially exposed to the patient's blood shall observe standard precautions. Dialyzers should not be reprocessed from patients who have tested positive with hepatitis B surface antigens. Precautions for all infectious hazards should be emphasized and included in the reprocessing procedures. Written procedures should stipulate whether and how reprocessing will be done for patients who have shown sensitivity to materials used in the reprocessing of hemodialyzers.

### **6.2 Patient education**

The Centers for Medicare and Medicaid Services (CMS) *Conditions for Coverage of Suppliers of End-Stage Renal Disease (ESRD) Services* states that all patients in a dialysis facility will be fully informed regarding reuse of dialyzers. Printed material such as brochures describing the facility's services should contain a statement about dialyzer reprocessing if reuse is performed. National renal organizations may have additional materials available.

## **7 Equipment**

Each piece of equipment used for reprocessing shall be appropriately designed, constructed, and tested to perform its intended task. Types of reprocessing systems vary from sophisticated microprocessor-controlled systems to hand-operated valving systems. Satisfactory operation of manual and automated systems shall be ensured by appropriate functional tests. Strict QA and QC shall be maintained for any type of dialyzer reprocessing equipment. Additionally, complete documentation of system function, operating procedures, potential system failures, and dialyzer-reuse criteria shall be included in the dialyzer reprocessing manual, be known to the operator, and be available for review.

### **7.1 Water systems**

The system providing water for reprocessing shall meet all the requirements for pressure and flow rate for operating the reprocessing equipment under minimal and peak load conditions. Product water used for rinsing, cleaning, filling, and diluting the germicide shall be shown to comply with the chemical and microbiological quality requirements specified in the current version of ANSI/AAMI RD62, *Water treatment equipment for hemodialysis applications*. Water bacteriology monitoring shall be carried out where the dialyzer is connected to the reuse system or as close as possible to that point.

### **7.2 Reprocessing systems**

#### **7.2.1 Utility requirements**

The quality, pressure, flow rate, and temperature of the water used for reprocessing should be specified in the dialyzer reprocessing manual, established before the initiation of a reprocessing program, and maintained thereafter. The manufacturer's or designer's recommendations for the water supply should be followed. Provision should also be made for adequate drains, ventilation, and electrical power.

#### **7.2.2 Process control testing**

**7.2.2.1** Dialyzer test methods (11.3) shall be established before clinical use of the reprocessed dialyzers. Verification of tests should be repeated after each significant change in the reprocessing system. For automated systems, adherence to the manufacturer's instructions can verify the tests. For manual systems, confirmation of the accuracy of the TCV measurement and the membrane integrity test can verify the tests.

**7.2.2.2** The test for the concentration of germicide or chemical shall be established before clinical use of the reprocessed dialyzers (11.4.1.6 and 12.3.2). For systems using heat disinfection, a means of verifying the time and temperature of disinfection shall be established before clinical use of the reprocessed dialyzers (12.3). If a chemical is

used to enhance heat disinfection, both a test for the concentration of the chemical and a means of verifying time and temperature shall be established.

### 7.2.3 Maintenance

Written maintenance procedures and a schedule of preventive maintenance activities designed to minimize equipment malfunctions should be established. In the case of purchased reprocessing equipment or safety equipment, the recommendations of the vendor should be followed unless documented experience supports alternative approaches. If the manufacturer's recommendations are unavailable, reuse equipment and safety equipment should be inspected on a semiannual basis. A record shall be kept of preventive maintenance activities (see 4.3), accompanied by the signature of the person performing the maintenance.

### 7.2.4 Repairs

If the reprocessing system fails to function as expected, qualified personnel should investigate and correct the problem. The reprocessing system function testing should be repeated after repairs of automated equipment and, if appropriate, after repairs of manual equipment before either the dialyzer is reprocessed or the reprocessed dialyzer is used for clinical dialysis.

## 8 Physical plant and environmental safety considerations

### 8.1 Reprocessing area and ventilation

The reprocessing area should be designed to suit the operation carried out and must be able to maintain acceptable ambient concentrations of harmful substances (see Table 1). The area should be kept clean and sanitary. It may be part of the dialysis treatment area, as long as equipment used is properly designed and vented to meet the requirements for environmental safety (see 8.5).

**Table 1—OSHA environmental exposure limits (29 CFR 1910, 1 July 1998), except as indicated**

| Substance or material                   | PEL <sup>a)</sup>                                                         |
|-----------------------------------------|---------------------------------------------------------------------------|
| Acetic acid                             | 10 ppm TWA <sup>b)</sup>                                                  |
| Chlorine dioxide (syn.: chlorine oxide) | 0.1 ppm TWA                                                               |
| Citric acid                             | None developed                                                            |
| Formaldehyde                            | 0.75 ppm TWA<br>2 ppm STEL <sup>c)</sup> (15 min)<br>0.5 ppm action level |
| Glutaraldehyde                          | 0.2 ppm ceiling NIOSH/OSHA                                                |
| Hydrogen peroxide                       | 1 ppm TWA                                                                 |
| Peracetic acid                          | None developed                                                            |
| Phenol                                  | 5 ppm TWA                                                                 |

ppm = parts per million; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

<sup>a)</sup> PEL (permissible exposure limit) represents the limit of what employees can be exposed to; PELs can be TWAs or STELs.

<sup>b)</sup> TWA (time-weighted average) represents the limit of what an employee can be exposed to in an 8-hour period.

<sup>c)</sup> STEL (short-term exposure limit) represents the limit of what an employee can be exposed to in any 15-minute time period.

### 8.2 Storage area

Reprocessing materials, hemodialyzers awaiting reprocessing, and reprocessed hemodialyzers should be stored so as to minimize deterioration, contamination, or breakage. Access to the storage area should be limited to protect the integrity of the reprocessed dialyzers and the confidentiality of patient information included on the labels. New, used, and reprocessed dialyzers should be segregated to make clear the status of each group of dialyzers. Environmental contamination of the storage area should be controlled and monitored if the personnel determine those actions to be necessary. Storage areas for new dialyzers and reprocessing materials should be designed to facilitate rotation of stock and cleaning. Storage arrangements should also take into account fire safety considerations, OSHA regulations, and other appropriate regulations.

### **8.3 Laboratory area**

Tests that do not require special facilities, such as certain tests for germicide levels, may be done in the reprocessing or dialysis treatment area, whichever is appropriate.

### **8.4 Personnel protection**

Personnel shall wear durable gloves and protective clothing when handling the dialyzer during initiation and termination of dialysis and during the reprocessing procedure. Standard precautions shall be observed. Personnel shall wear eye protection when performing steps that may result in spills or splashes of substances of known or suspected toxicity. These agents shall be handled only in areas with adequate ventilation, washing facilities, eyewash stations, appropriate respirators, and spill control materials. Personnel handling concentrated toxic substances shall wear aprons impervious to those substances.

### **8.5 Environmental safety**

The dialysis facility shall have written procedures for safe storage and handling of chemicals used in reprocessing (see National Institute for Occupational Safety and Health [NIOSH]/OSHA, 1980; Sax, 1979; material safety data sheets). Vapors from reprocessing materials must be maintained below potentially toxic levels (see Table 1).

## **9 Reprocessing supplies**

### **9.1 Specifications and testing**

Each reprocessing material should meet a written specification. The fulfillment of that requirement may be determined by the product supplier's certification that the product meets necessary specifications and labeling for its intended purpose or by testing procedures by trained personnel, as appropriate. The requirement may also be met by purchasing a specific grade as specified by the process, such as USP citric acid. When the user performs testing, he or she should maintain a log of the test date, the batch identifying number (lot number), the person performing any testing, and the test results. Over the past few years, bleach (sodium hypochlorite) manufacturers have begun selling many new formulas of household bleach. The concentration of sodium hypochlorite has risen from 5.25 % to 6.15 % in many cases. The Centers for Disease Control's recommendations for diluting bleach have not changed to take into account these percentage changes. Manufacturers of bleach have also begun using additives such as fragrances in products that are commercially marketed in grocery stores. When bleach is purchased from a commercial outlet, the labeled concentration should be between 5.25 % and 6.15 %, and the formula should not contain fragrances.

### **9.2 Inventory control**

Reprocessing supplies should be used on a first-in, first-out basis, and outdated supplies should be identified and discarded.

## **10 Hemodialyzer labeling**

Each reprocessed hemodialyzer shall be used for only one patient. Therefore, the labeling shall uniquely identify the patient who is using the dialyzer. The dialyzer should also be labeled with other information essential to proper reuse procedure.

### **10.1 Time of labeling**

Each hemodialyzer shall be labeled before or at the first use of the device, and the label shall be updated after each use (see 10.3).

### **10.2 Label composition**

Markings should be resistant to normal reprocessing and dialysis procedures. The dialyzer labeling should not obscure the manufacturer's model number, lot number, or indicators of the direction of blood or dialysate flow or other pertinent information unless provision is made for recording this information on the label. The label on hemodialyzers with transparent casings should permit the blood path to be readily inspected.

### **10.3 Information recorded**

The dialyzer shall be labeled with the patient's name, the number of previous uses, and the date of the last reprocessing. Dialyzers of patients with similar names should have a warning to the user to take extra care in ensuring that the name or other identifying information on the label corresponds to that of the patient. If there is sufficient room, the dialyzer may also be labeled with the results of tests, the signature or other unique means of identifying the person performing the various steps in the reprocessing procedure, and the reference values for performance parameters. Whether or not this information appears on the label, a permanent record should also be kept (see 4.2). Electronic records are acceptable. If records are electronic, the test results should be available to the

user. Home dialysis patients are exempted from the recommendation that the patient's name appear on the label, unless the dialyzers are taken to a dialysis facility for reprocessing.

## **11 Reprocessing**

The multiple use of a dialyzer begins with the labeling of the new dialyzer (see section 10) and then continues with the reprocessing procedures described in this section. Preparation of the reprocessed dialyzer for the next dialysis is described in section 12. The cycle is repeated after the next use of the dialyzer until the dialyzer no longer meets the criteria for continued use. A systems diagram of these procedures is given in annex B (normative). The results of the tests and the signature or other unique means of identifying the person performing each step should be maintained in a permanent record (see 4.2). Completion of all reprocessing steps, tests, and inspections should be documented in the reprocessing record. Documentation should be accompanied by the signature or other unique means of identification of the person completing the steps. When appropriate for the reprocessing procedure in use, all dialyzer manufacturer's instructions regarding reuse should be carefully followed.

### **11.1 Transportation and handling**

The personnel handling used dialyzers during transportation shall do so in a clean and sanitary manner maintaining standard precautions until the dialyzer is disinfected both internally and externally. As a means of inhibiting bacterial growth, dialyzers that cannot be reprocessed within 2 hours should be refrigerated but not allowed to freeze. Other transportation and handling issues (such as prolonged delays in reprocessing) not described in this recommended practice shall be validated and documented by the responsible party.

### **11.2 Rinsing and cleaning**

#### **11.2.1 Dialyzer precleaning**

Many facilities preclean dialyzers. This process is typically accomplished with an apparatus developed by users and is intended to remove gross deposits of blood and products before rinsing and cleaning with a reprocessing machine or device. When precleaning is done, it needs to be included as part of the reprocessing procedures. The facility should establish a policy and practice to limit the time between the completion of precleaning and the initiation of disinfection, particularly when no germicide remains in the dialyzer after the precleaning process. All applicable requirements for design and maintenance of equipment included in this document should be adhered to for precleaning equipment. The maximum pressures for the dialyzer, or other limits set by the manufacturer, should also be adhered to.

#### **11.2.2 Initiation of cleaning**

Dialyzer reprocessing should be initiated in sufficient time to produce a reprocessed device that meets the requirements of section 11.3. Each dialysis facility should establish its time limits. Staff members involved in handling, transporting, or storing dialyzers locally or at remote locations shall follow standard precautions to prevent exposure to the operator, cross-contamination between dialyzers, and contamination of the physical environment.

#### **11.2.3 Water quality for cleaning**

Precleaning the dialyzer (rinsing and cleaning) shall be done with a fluid or fluids made with water that meets the specification of the current version of ANSI/AAMI RD62.

#### **11.2.4 Cleaning agents**

Diluted solutions of hydrogen peroxide, sodium hypochlorite, peracetic acid, or other chemicals may be used as cleaning agents for the blood compartment, provided that the cleaning agent has been shown to be reduced to safe levels by subsequent flushing and has no significant adverse effects on the structural integrity and performance of the dialyzer.

Each chemical shall be rinsed from the dialyzer before the next chemical is added, unless mixing is known to be safe and effective for reprocessing. For example, a cleaning agent, such as sodium hypochlorite, shall be rinsed from the dialyzer before adding formaldehyde to avoid noxious fumes and degradation of disinfectant. Combining sodium hypochlorite and peracetic acid may produce hydrochloric acid vapors, which are harmful if inhaled.

### **11.3 Performance measurements**

The performance characteristics of dialyzers may change following reprocessing. The ultrafiltration coefficient may increase or decrease. Clearances of low or high molecular weight solutes may also increase or decrease depending on the chemicals, methods, and dialyzer membrane used. The dialyzer labeling and medical literature should be consulted for information related to changes in *in vitro* and *in vivo* performance.

### **11.3.1 Performance test after each use**

The purpose of the performance test is to measure the ability of the dialyzer membrane to remove low molecular weight uremic toxins. A direct or indirect measure of the *in vitro* clearance of a small molecule such as sodium or urea shall be used as the actual rejection criterion. If clearance is used, a 10 % loss is acceptable. If an indirect measure of the *in vitro* clearance is used, it shall be shown to correlate to urea or sodium clearance. TCV may be used for hollow-fiber dialyzers. The acceptable TCV is at least 80 % of the original TCV. The dialyzer prescription should take into account the 10 % loss in clearance (20 % loss in TCV) that may occur with dialyzer reuse. Dialyzers should be preprocessed to establish the original TCV.

### **11.3.2 Ultrafiltration**

*In vitro* ultrafiltration coefficients should not be used to predict *in vivo* results. If the patient's expected weight loss is not achieved with the reprocessed dialyzer, the reprocessing method and all other weight removal variables should be reevaluated.

### **11.3.3 Blood path integrity test**

A membrane integrity test such as an air pressure leak test shall be done between uses.

## **11.4 Germicide**

The rinsed and cleaned dialyzer shall be treated by a process that prevents adverse effects caused by microbial contamination. The blood and dialysate compartments of the dialyzer shall be sterilized or subjected to high-level disinfection because an inadequate germicidal process may result in infection in the patient. Low-level disinfection is sufficient for the exterior of the device. The user shall consult the dialyzer labeling for contraindications or warnings regarding methods and applicability of specific germicidal processes or chemicals.

### **11.4.1 Interior (blood/dialysate compartment)**

#### **11.4.1.1 Germicidal process**

Chemical germicides or other procedures used for disinfecting hemodialyzers shall have been shown to accomplish at least high-level disinfection when tested in dialyzers artificially contaminated with appropriate microorganisms. If formaldehyde is used as the sole germicidal agent, the Centers for Disease Control recommends that a concentration of 4 % weight/volume (W/V) be used in both the blood and dialysate compartments with a minimum contact time of 24 hours at a temperature of at least 20 °C; lower concentrations or shorter contact times are appropriate if equivalent results can be demonstrated under other conditions.

Formaldehyde used for reprocessing dialyzers should not be cloudy. Concentrated formaldehyde stored under adverse conditions can polymerize to form paraformaldehyde, a white precipitate. Formaldehyde should be of USP or better quality. When other germicides are used, the manufacturer's instructions should be followed.

If the germicide has an expiration date from the manufacturer, staff members should ensure that the chemical is not outdated. Some germicides have recommendations for maximum storage time after dilution or activation and before usage. If such recommendations exist, the expiration date of the prepared germicide solution should be marked on the outside of the germicide solution container, and that date should be checked at the beginning of each day, before reprocessing begins. If other germicides such as heat and citric acid are used, it is necessary to ensure that the correct time, temperature, and concentration are being used. If the temperature of the disinfection process is elevated, appropriate recording means shall be employed to ensure that this criterion has been met.

Germicides should be stored according to the manufacturer's recommendations, and records should be maintained to document compliance. The disinfection process shall not adversely affect the integrity of the dialyzer. Germicides shall be rinsed from the dialyzer to below known toxic levels within a rinse-out period established for the particular germicide (see 12.4). To prevent injury, staff members shall take care not to mix reactive materials such as sodium hypochlorite and formaldehyde or sodium hypochlorite and peracetic acid.

#### **11.4.1.2 Dialyzer header cleaning and disinfection**

The cleaning and disinfection of the header space should be done only when necessary and only before the dialyzer is reprocessed. The manufacturer's instructions should be followed. Header caps and O-rings shall be kept with their respective dialyzers.

If the header space is cleaned, it shall be done in a manner to prevent infection and damage to the dialyzer. If the header cap is removed to clean the header space, cleaning shall be done with water meeting the requirements of the current version of ANSI/AAMI RD62. If instruments or other materials (e.g., header caps and 4 x 4 gauze pads) are used, they should be shown not to cause damage to the end of the dialyzer and shall be new or cleaned and



disinfected between uses. Once the O-ring and the header cap have been cleaned, they should be disinfected and reassembled while wet with disinfectant. This procedure is done before reprocessing the dialyzer. Overtightening the header caps may damage the cap, and undertightening the cap may cause blood leaks. If any cracking of the header occurs, the process should be evaluated.

If the header space is cleaned with the header cap in place, it is necessary to ensure that the cleaning device does not damage the end of the fiber bundle. The water used shall meet the requirements of the current version of ANSI/AAMI RD62. If an instrument such as a tie wrap is used, it should be made of soft plastic or other material that will not damage the end of the fiber bundle and be disinfected between uses.

If automated equipment is used, the manufacturer's instruction for use shall be followed.

#### **11.4.1.3 Chemical germicide diluent**

The water used to prepare the germicide solution shall meet the requirements of the current version of ANSI/AAMI RD62.

#### **11.4.1.4 Chemical germicidal procedure**

If applicable, the hemodialyzer shall be filled with the germicide solution until the concentration in the hemodialyzer is at least 90 % of the prescribed concentration. The ports of chemically disinfected dialyzers shall be disinfected and then capped with new or disinfected caps. The caps may be disinfected with dilute bleach, with the chemical used for disinfecting the hemodialyzer, or with any other germicide approved by the FDA as a disinfectant that does not adversely affect the materials of the dialyzer.

#### **11.4.1.5 Water quality monitoring**

The water used to rinse and clean dialyzers and dilute the germicide should be tested for bacterial contamination and pyrogens according to the requirements of the current version of ANSI/AAMI RD62 before a reprocessing program is undertaken. Once dialysis with the reprocessed hemodialyzers has begun, testing for bacterial contamination should be frequent (e.g., weekly). Less frequent testing, but not less than monthly, may be appropriate if there is a documented history of at least 3 months of results consistently below the levels allowed in the current version of ANSI/AAMI RD62.

#### **11.4.1.6 Chemical germicide concentration**

For reprocessing systems in which germicide is manually prepared, each batch of germicide shall be tested before use to verify its proper concentration. (This requirement does not apply in cases in which each dialyzer is tested for concentration before setup.) When the germicide is diluted on-line, its concentration in the hemodialyzer immediately after reprocessing should be checked at least monthly for each reprocessing system. When the germicide is partially or fully diluted by the user, the solution shall be thoroughly mixed before use.

#### **11.4.2 Exterior**

The outside of the dialyzer should be soaked or wiped clean of visible blood and other foreign material. For chemically disinfected dialyzers, a low-level germicide that is compatible with the dialyzer's construction materials should be used for this purpose. Sodium hypochlorite at a concentration of 0.05 % is usually suitable. Certain commercial low-level disinfectants may cause the plastics used for some dialyzers to crack after repeated or prolonged exposure.

#### **11.5 Inspection**

The hemodialyzer shall be examined after reprocessing to ensure that the external surface is clean, the dialyzer is not damaged, and the rinsing of blood has been satisfactorily achieved. The dialyzer should also be aesthetically acceptable in appearance to patients and staff members.

**11.5.1** The dialyzer jacket should be free of visible blood or other foreign material.

**11.5.2** There shall be no leaks or cracks in the dialyzer jacket or the blood or dialysate ports.

**11.5.3** No more than a few dark, clotted fibers should be evident on inspection of the exterior of the hollow fibers.

**11.5.4** The headers of hollow-fiber dialyzers should be free of all but small peripheral clots or other deposits.

**11.5.5** Blood and dialysate ports shall be capped without evidence of leakage.

**11.5.6** The label shall be properly filled out and legible.

## **11.6 Disposition of rejected dialyzers**

Reprocessed dialyzers that have been rejected for failure to meet performance, inspection, or other release criteria should be either immediately discarded or further reprocessed and subjected to the performance requirements of 11.3, 11.4, and 11.5. If the dialyzer is to be further reprocessed, rather than discarded, it shall be labeled as rejected and stored in a quarantine area to preclude use until requirements are met.

## **11.7 Storage**

Reprocessed dialyzers that meet the performance and inspection criteria for multiple use should be stored according to the provisions of 8.2. Prolonged storage (greater than 1 month) should be documented to be safe and effective. Dialyzers that have exceeded the facility's maximum storage time shall be reprocessed or discarded. The dialyzer and disinfectant labeling should be consulted regarding proper storage conditions.

## **12 Preparation for dialysis and testing for chemical germicides and potentially toxic residues**

A written procedure that has been shown to be effective shall be followed.

### **12.1 Visual inspection**

The dialyzer should be inspected after storage, before it is prepared for use. Completion of this inspection should be recorded in the reprocessing record (see 4.2), along with the signature or other unique means of identifying the person completing the inspection. The inspection should confirm the following:

- a) The reprocessed dialyzer is legibly labeled with the information recommended in 10.3.
- b) There is no indication of structural damage or tampering with the dialyzer.
- c) The ports of the dialyzer are properly capped.
- d) There is a sufficient quantity of germicide in the dialysate and blood compartments, including headers, and no evidence of leakage from the ports or other portions of the dialyzer.
- e) The duration and conditions of storage were appropriate for the agent or method used to sterilize or disinfect the dialyzer.
- f) The cosmetic appearance of the dialyzer is aesthetically acceptable.

Should the stored reprocessed dialyzer fail to meet any of these criteria, it should be subjected to another course of reprocessing or should be discarded, as appropriate.

### **12.2 Verification of patient identification**

Except in the case of home dialysis, two people should check that the first and last names on the dialyzer and any other appropriate identifying information correspond to the identifying information on the patient's permanent record. If possible, one of the people checking identification should be the patient. Completion of this step shall be recorded, along with the signature or other unique means of identifying the person verifying patient identification.

NOTE—This step may be done later in the procedure but shall precede initiation of dialysis.

### **12.3 Verification of germicidal contact**

The contact time of the germicide or disinfection procedure shall comply with the facility's protocol and the manufacturer's recommendations. The presence of chemical germicide in each hemodialyzer shall be ensured through either direct testing or an on-line process and procedural control. If other disinfection procedures (e.g., heat) are used, there shall be methods to ensure that each hemodialyzer has been properly subjected to the disinfection process. A record shall be kept indicating that the dialyzer has undergone the appropriate storage time.

#### **12.3.1 Presence test of each hemodialyzer**

The presence of germicide may be ensured by directly testing each dialyzer for the presence of germicide. Certain germicide manufacturers require this testing before the germicide is rinsed from the hemodialyzer, and these instructions should be followed.

#### **12.3.2 Process control and sampling**

If the germicide manufacturer has no requirement for directly testing each dialyzer, the presence of germicide may be ensured through process control and sampling of dialyzers for germicide. Sections 12.3.2.1 and 12.3.2.2 provide examples of how to comply with this requirement.

#### **12.3.2.1 Process control**

- a) Use hemodialyzer germicide filling equipment with on-line automatic monitors during the germicide dilution and hemodialyzer filling process, or
- b) Use an indicator substance (e.g., FD&C Blue No. 1) that has been added to the germicide and that reliably indicates the presence of germicide. If blue dye is used, it should be added to the germicide concentrate before dilution, not to the fully diluted solution. Note that use of dye may be inappropriate with certain germicides, such as peracetic acid.

#### **12.3.2.2 Sampling for process validation**

- a) Sample at least one hemodialyzer per patient shift per reuse system with a direct presence test. Samples should be taken immediately after the dialyzers have been reprocessed.
- b) For germicide prepared in batches, sample at least one hemodialyzer from each batch with a direct presence test. Samples should be taken immediately after the dialyzers have been reprocessed.
- c) Do not use a Schiff test for formaldehyde for this purpose because a positive test result does not necessarily demonstrate the presence of an adequate concentration of formaldehyde.
- d) Sampling and testing are to be accomplished before patients use any hemodialyzers processed on that shift.

NOTE—The requirements of this section are fulfilled if every dialyzer is subjected to poststorage and prepriming direct presence testing.

### **12.4 Priming the dialyzer and rinsing the germicide**

If the manufacturer's instructions so require, a germicide presence test shall be performed before the germicide is rinsed from the dialyzer. The dialyzer shall be rinsed and primed according to a written procedure that has been documented to produce a reduction in the concentration of germicide to an acceptable level and to result in a physiological solution in the blood and dialysate compartments. The dialyzer manufacturer's instructions should be considered in developing these procedures.

#### **12.4.1 Testing for residual germicide**

Residual germicide shall be measured by a test of appropriate sensitivity according to a written procedure to ensure that the germicide level is below the maximum recommended residual concentration. In the case of formaldehyde, the recommended maximum level is 3 ppm. Completion of this step shall be documented, along with the signature or other unique means of identifying the person performing the test. A written policy should establish the maximum allowable time between rinsing the germicide from the dialyzer and beginning dialysis. Because certain germicides have been demonstrated to disperse into solid components or less rapidly exchangeable compartments of the hemodialyzer, the priming, removal, and residual testing process should be reinstituted after any delay that provides sufficient time for concentrations of germicide to rebound above the recommended level by elution from these compartments. Additional rinsing should be performed to yield a germicide level below the maximum recommended concentration before initiating dialysis. A rinse procedure should be defined and documented step by step, and all personnel should be familiar with it and follow it. If heat disinfection is used, the dialyzer should be cool to the touch before it is primed with saline.

### **12.5 Written procedure for tests for germicide or other residues**

There shall be a written procedure for all tests employed in preparing the dialyzer for use, including mention of each test's sensitivity. The germicide manufacturer's instructions for use should be consulted in determining the maximum residual level. The physician in charge of the reuse program shall approve any changes or alterations in the procedures.

## **13 Monitoring**

### **13.1 Dialysis**

The clinical course of the patient should be observed and recorded during each dialysis to identify possible complications caused by new or reprocessed dialyzers. Dialyzer failures should be recorded and systematically evaluated. Home dialysis patients and their assistants should be instructed in the appropriate observation, recording requirements, and reporting procedures.

## **13.2 Symptoms**

### **13.2.1 Fever and chills**

Patients' temperatures should be measured and recorded at least before and after dialysis with new and reprocessed dialyzers. A temperature of over 37.8 °C or 100 °F, taken orally, or chills should be reported to the physician. Any patient with an unexplained fever or chills should be evaluated for the possibility of a preexisting infection (e.g., access site). The dialysis procedure should also be evaluated to rule out the use of contaminated water, errors in treatment delivery, or incorrect dialyzer reprocessing.

### **13.2.2 Other symptoms**

Other unexplained symptoms, such as pain in the blood-access arm, at the onset of dialysis should be evaluated by the physician. Consideration should be given to the possibility that the symptom may be attributable to residual disinfectant in the new or reprocessed dialyzer or contamination of the water treatment equipment. Suspected reactions to the residual germicide should prompt reevaluation of the rinsing procedure and tests for residual germicide (see 12.4.1).

### **13.2.3 Recording**

Any significant events, such as the occurrence of symptoms listed in 13.2.1 and 13.2.2, should be recorded on an incident report form, which would include the results of the evaluations conducted by the physician and others. The event should be considered for reporting to the manufacturers in accordance with the FDA's Medical Device User Reporting procedures. The resolution of actual or suspected problems caused by reprocessed dialyzers should be indicated. This report should be kept in the complaint investigation record file (see 4.5).

## **13.3 Dialyzer failures**

Dialyzer blood leaks should be recorded in a log kept in the complaint investigation record file (see 4.5). If there is excessive deviation from the expected performance, testing methods should be evaluated (see 11.3.1) and appropriate adjustments made in the reprocessing procedure.

## **13.4 Clinical results**

Monitoring of relevant patient results is recommended to ensure that all parameters relating to hemodialyzer clearance are being met. Specifically, examination of urea reduction ratio (URR) or Kt/V over time is necessary. The failure of these results to meet the expectations of the dialysis prescription should be investigated. Deterioration of a patient's clinical condition or variability of routine dialysis requirements (heparinization, ultrafiltration, dose of erythropoiesis stimulating agent) should result in an investigation of all practices, including reuse. Reports of investigations should be filed in the complaint log.

## **14 Quality assurance**

It is the responsibility of all staff members to scrutinize all materials, practices, operations, and outcomes critically. Criteria that serve as the scale for evaluation may be drawn from local experience and practice relative to the specific activity under review, consensus documents such as AAMI guidelines or standards, aggregated regional or national data, or other accepted norms. The criteria chosen as the internal standards of a facility shall be documented in its policy or procedure manual. Process review should be part of the activity of the individual carrying out the process, and oversight of that review by another qualified staff member or a group of staff members should affirm, modify, or repeat these observations to confirm or improve the process. Clinical outcomes serve as the most important indicator of quality of all dialysis treatment practices including reuse. Final oversight is the responsibility of the medical director. See Table 2 for a summary of the audit schedule.

**Table 2—Quality assurance audit schedule**

|                                                  | Daily | Weekly | Monthly | Quarterly | Semiannually | Annually |
|--------------------------------------------------|-------|--------|---------|-----------|--------------|----------|
| Patient information policy (14.3)                |       |        |         |           |              | x        |
| Equipment manuals and procedures (14.4)          |       |        |         |           |              | x        |
| Equipment maintenance and repair policies (14.4) |       |        |         |           |              | x        |
| Environmental safety (8.1)                       |       |        |         |           |              | x        |
| Environmental safety (8.2)                       |       |        |         | x         |              |          |
| Environmental safety (8.4)                       |       |        |         | x         |              |          |
| Reprocessing supplies (9)                        |       |        |         |           | x            |          |
| Water treatment <sup>a)</sup> (11.4.1.5)         |       |        | x       |           |              |          |
| Hemodialyzer labeling (10)                       |       |        |         | x         |              |          |
| Reprocessing procedures <sup>b)</sup> (14.8)     |       |        | x       |           | x            |          |
| Procedures for preparation for dialysis (14.9)   |       |        |         | x         |              |          |

<sup>a)</sup> More frequent monitoring may be required initially as described in 11.4.1.5.

<sup>b)</sup> These functions may allow for the less frequent review period indicated according to the circumstances specified in their respective sections.

#### 14.1 Records

A record of review, comments, trend analysis, and conclusions arising from QA practices will serve as a foundation for future review and as documentation to external evaluation.

#### 14.2 Schedule of quality assurance activities

Problems in a particular aspect of operations should be reviewed and tracked until a solution is in place and demonstrated to be effective. High-volume tasks that are recognized as hazardous should have frequent (weekly or daily) oversight. Practices with little potential for harm may need critical scrutiny only quarterly or annually. The medical director is responsible for scheduling review, endorsing findings, and, when appropriate, implementing changes.

#### 14.3 Patient considerations

Personnel should audit at least annually compliance with the facility's policy to inform patients of the facility's reuse practices.

#### 14.4 Equipment

Designated staff members should audit written procedures and manuals for relevance at least annually and whenever adverse findings could be attributed to equipment failure. Designated staff should also audit maintenance and repair policies at least annually.

#### 14.5 Physical plant and environmental safety considerations

Designated staff members should audit for compliance with the provisions of 8.1 at least annually. Compliance with the provisions of 8.2 and 8.4 should be audited quarterly.

#### 14.6 Reprocessing supplies

Designated staff members should audit for compliance with the provisions of section 9 at least semiannually.

#### **14.7 Hemodialyzer labeling**

Designated staff members should audit for compliance with the provisions of section 10 at least quarterly.

#### **14.8 Reprocessing**

Initially, designated staff members should audit the written procedures for the various steps in this process and verify implementation at least monthly. Subsequently, semiannual audits may be sufficient if there is a documented history of favorable results. Trend analysis should be performed.

#### **14.9 Preparation for dialysis**

At least quarterly, designated personnel should audit the written procedures and verify their implementation. At least quarterly, designated staff members should verify the tests for the presence of germicide and the test for residual germicide, by using positive and negative control solutions, on those products that are not specifically intended for use in dialyzer reuse germicide indicator tests and that have not been cleared by the FDA.

## Annex A (informative)

### Rationale for the development and provisions of this recommended practice

#### A.1 Scope

The reuse of dialyzers has been a practice in the United States since the 1960s. Until the mid-1990s, even dialyzers labeled by manufacturers for single use were reused. Reuse was an accepted practice performed by 82 % of dialysis facilities in 1997, although the percentage of centers practicing reuse declined in subsequent years to 63 % in 2002. As an understanding grew of the effects of reuse on dialyzer performance, it became apparent that the dialysis community needed to be better informed.

In light of the widespread practice of reuse and its potential effect on patient care, the Food and Drug Administration (FDA) determined that manufacturers' labeling must reflect the actual commercial marketing and clinical use of hemodialyzers.

Labeling requirements for multiple-use dialyzers are covered in the FDA's "Guidance for Hemodialyzer Reuse Labeling," of 6 October 1995. Dialyzers labeled for multiple use must include instructions for their safe and effective reuse. Manufacturers are expected to recommend at least one method of reuse for dialyzers labeled for multiple use. *In vitro* performance data at various flow rates for  $K_{UF}$ , as well as clearance of urea, creatinine, and vitamin B<sub>12</sub>/inulin, must be provided at the 0, 1st, 5th, and 15th reuse. *In vivo* performance data at various flow rates for  $K_{UF}$ , as well as clearance of urea (spKt/V – URR), albumin, and  $\beta_2$ -microglobulin (high flux only), must also be provided.

Instructions for adequately cleaning, rinsing, and testing the dialyzer, as well as instructions for preparation before use (priming), must be included in the labeling (package insert). Warnings must be included against using any reprocessing agents or processes known to adversely affect the manufacturer's dialyzer.

Initially, blood tubing sets reprocessed as a unit with the hemodialyzer were included within the scope of this recommended practice to accommodate such reprocessing methods. The committee subsequently decided to exclude blood tubing sets because it believed that insufficient data existed on the practice of blood tubing reuse. In making this decision, the committee did not take a position either for or against the reprocessing of tubing sets. The Centers for Medicare and Medicaid Services (CMS) *Conditions for Coverage of Suppliers of End-Stage Renal Disease (ESRD) Services* limits the reuse of blood tubing to those tubing sets for which the manufacturer has developed a specific reprocessing protocol that has been accepted by the FDA.

Labeling and performance requirements for new hemodialyzers are covered by ANSI/AAMI RD16, *Cardiovascular implants and artificial organs – Hemodialyzers, hemodiafilters, hemofilters, and hemoconcentrators*.

#### A.2 Normative references

For the purposes of this recommended practice, the references cited in section 2 apply.

#### A.3 Definitions

For the purposes of this recommended practice, the definitions given in section 3 apply.

**A.3.13 hemodialyzer:** Initially, the FDA used water permeability to classify dialyzers into Class II (Conventional,  $K_{UF} < 8$  mL/h/mmHg) or Class III (High Permeability,  $K_{UF} > 8$  mL/h/mmHg). However, the dialysis community has most commonly used the terms *high flux*, *low flux*, and *high efficiency*. The Hemodialysis (HEMO) Study Group defined low-flux dialyzers as having "a mean clearance of  $\beta_2M < 10$  mL/min during first use" and high-flux dialyzers as having " (1) an ultrafiltration coefficient ( $K_{UF}$ )  $> 14$  mL/h per mmHg and (2) a mean clearance of  $\beta_2M > 20$  mL/min during first use or over the lifetime of the dialyzer model with a given reprocessing technique." (Cheung, et al., 1999). High efficiency refers to dialyzers that can remove relatively large amounts of low molecular weight solutes. Currently, the FDA still uses water permeability to differentiate between high-flux and conventional dialyzers. A high-flux dialyzer will have a  $K_{UF}$  of  $> 8$  mL/h/mmHg, whereas a conventional dialyzer will have a  $K_{UF}$  of  $< 8$  mL/h/mmHg.

In 1997, AdvaMed (formerly HIMA) filed a request with the FDA on behalf of all dialyzer manufacturers to reclassify high-flux dialyzers from Class III to Class II. This request was accepted, and all dialyzers, hemofilters, and hemoconcentrators are now Class II. This device classification has no effect on the user. It identifies the risk category and marketing clearance scheme for the manufacturers.

**A.3.16 lipopolysaccharide (LPS):** LPS is not destroyed by low-temperature chemical disinfection procedures commonly used with dialyzer reuse but may be destroyed by exposure to temperatures of 95 °C and 1.5 % citric acid for 20 hours (McAllister, Arduino, and Bland, 1994).

## **A.4 Records**

Documentation is essential to a safe, effective hemodialyzer reprocessing program. The overall dialyzer reuse procedure documentation includes reference materials, procedures, and policies, some of which may be distributed in the facility for operating purposes. The other records serve to document aspects of the reuse procedure for each dialyzer, along with QA and QC measures, so that a complete history of the reprocessing of each dialyzer and of the QA and QC procedures exists. In the committee's view, when the useful life of a dialyzer is over and no notable events have occurred, the reprocessing records for that dialyzer need not be kept. Allowance is made for keeping the reprocessing record data in the reprocessing log, the patient's chart, or a combination of the two, because both of them are traceable, permanent records, and it may be inconvenient to record all the information in one location. The committee decided not to include a specific recommendation for a checklist for initiating dialysis because, although a checklist is a convenient way to ensure that the procedure is followed, the same purpose can be served by completing the recommended documentation for preparing the reprocessed dialyzer for dialysis (see 12.1, 12.2, and 12.4.1).

### **A.4.1 Dialyzer reprocessing manual**

The committee rejected a proposal to include a statement that the dialyzer reprocessing manual should not recommend or describe any methods for which the dialyzer or disinfectant manufacturer has indicated a contraindication.

## **A.5 Personnel qualifications and training**

The committee rejected a proposal to include curricula covering the entire range of technical activities related to dialysis. The committee felt that more limited training is appropriate as a minimum for personnel who are not involved in other aspects of dialysis. Also, a proposal to recommend that training could be less extensive for personnel with relevant previous training was not rejected because certification of training (see 5.2.2) renders the recommendation superfluous.

## **A.6 Patient considerations**

### **A.6.1 Medical issues**

The committee's primary objective was not to recommend medical indications for reprocessing or evaluate the medical or economic implications of reprocessing but to provide recommendations for safe reuse practice.

At the time of this writing, the Centers for Disease Control and Prevention (CDC) does not object to reprocessing and reusing dialyzers from patients with hepatitis C or patients with known HIV infection because of the low viral burden and transmission efficiencies. The committee recommends, however, that standard precautions be used in the reprocessing of all dialyzers. These precautions include the use of gowns, masks, and gloves. Each facility should be aware of the hazards of infection and set policies accordingly.

### **A.6.2 Patient education**

The committee decided, upon legal advice, that it was inappropriate for an AAMI recommended practice to suggest elements of informed consent, although this section originally contained them. The committee considered the following arguments about this issue. Those who believe that specific informed consent for the use of reprocessed hemodialyzers should be required maintain that greater patient participation in the therapeutic process need not impair the physician's ability to deliver quality care. Rather, they say, involvement ensures that quality care will remain the primary impetus in decisions to reuse. Those who disagree with informed consent specifically for multiple use of hemodialyzers point out that specific consent is not required for the other aspects of dialysis therapy and could be counterproductive because of the confusion that could be created by personal preferences for, as examples, length of dialysis, choice of blood flow, fluid removal rate, and the like. They argue that multiple use of hemodialyzers can properly be implied in the consent for hemodialysis therapy as are other therapy parameters. Those backing this view also assert that for most patients honest, trusting interaction with their personal physicians is a sufficient guarantee of quality, and imposing a dictatorial relationship may lead patients to seek recourse through legal means.

The topic of physician-patient relationships is important in view of some patients' concerns about the adequacy and safety of reprocessing procedures and the possibility that financial savings from the multiple use of hemodialyzers might contribute to the economic benefit of others rather than to the improvement of the quality of care. The committee also considered the question of the patient's right to freely choose not to participate in a hemodialyzer reprocessing program. Consensus could not be reached on this issue because of the underlying conflict between individual self-determination and financial constraints imposed by society (Rettig, 1982).



Some patients have expressed fear of increased risk, anger over presumed profits, and frustration surrounding consent issues. Establishing QA practices such as those recommended here and sharing information with patients, educating them, responding to questions, and eliminating any impression of secrecy are encouraged as effective solutions to these problems.

The fact that most dialysis facilities reprocess hemodialyzers and the long history of this technique support the conclusion that multiple use of hemodialyzers is customary medical practice. Courts might find that consent for dialyzer reprocessing per se is not required, but this issue has not yet been adjudicated.

The National Kidney Foundation's position paper (National Kidney Foundation, 1997) and the American Association of Kidney Patients recommend that patient consent for dialyzer reuse be obtained.

## **A.7 Equipment**

Validation of dialyzer performance and of germicide concentration was initially recommended after the repair of automated equipment to guard against possible faulty functioning of this complex apparatus. The recommendation was tempered by the words "if appropriate" for manual systems because replacing hoses, valves, and the like in those simple systems will not affect performance. The recommendation was subsequently changed to include testing the function of the reprocessing system because the committee judged that demonstrating proper functioning of the system was an adequate QC measure.

An earlier recommendation that the system prevent cross-contamination of water used for reprocessing and water used for dialysis was based on an episode in which water containing formaldehyde was introduced into water used for dialysis. The committee decided to delete this recommendation because the mishap was not attributable to a reprocessing system (the formaldehyde was put into the water system for dialysis to disinfect that system) and because it may be desirable to use the same source for the water used for dialysis and the water used for reprocessing hemodialyzers to achieve the recommended water quality.

It is particularly important that all water that comes into contact with the fluid pathways for blood or dialysate be of recommended quality because the blood side of the dialyzer might take up endotoxin that could be released into the circulation during the subsequent dialysis.

## **A.8 Physical plant and environmental safety considerations**

A proposal to supply the reprocessing area with air filtered by high efficiency particulate air (HEPA) filters, a laminar flow station, and positive pressure to surrounding areas was rejected. Such measures to control bacterial contamination were deemed inappropriate for reprocessing because the exposure of the dialyzer to bacterial contamination is limited to making connections comparable to setting up the device for dialysis. Another proposal to negatively pressurize the reprocessing area to control odors was rejected because the committee agreed that other methods could achieve odor control. The committee also determined that it was unnecessary to recommend facility design, because a number of configurations have been shown to be satisfactory, including use of automated equipment in the dialysis treatment area.

The statement about personnel health monitoring was included in response to a comment referring to the Code of Federal Regulations (Chapter 29, Part 1910.20), which addresses access to employee exposure and medical records. The committee is unaware of any state department of public health that requires personnel health monitoring in this area, but the states themselves are another possible source of information on this question.

## **A.9 Reprocessing supplies**

### **A.9.1 Specifications and testing**

Testing of all incoming materials was proposed. Recognizing that most medical supplies are certified by the vendors and not tested by the user, the committee decided to recommend that supplies need not be tested by the facility doing hemodialyzer reprocessing if they are marketed for hemodialyzer reprocessing.

### **A.9.2 Inventory control**

The committee suggested that supplies should be used on a first-in, first-out basis to prevent deterioration over time in storage.

## **A.10 Hemodialyzer labeling**

### **A.10.1 Time of labeling**

The committee recognized the importance of identifying the patient who will be exclusively using the dialyzer and required the dialyzer to be labeled at the time of first use.

## **A.10.2 Label composition**

The committee initially recommended using indelible ink to label the dialyzer but changed the recommendation to any method resistant to normal reprocessing and use procedures; other satisfactory materials exist, and requiring indelible ink might preclude some techniques, such as bar coding.

## **A.10.3 Information recorded**

A proposal that the label contain all the recommended information was rejected because space is limited on the label and such extensive labeling is unnecessary. Displaying the number of previous uses on the label is recommended so that this information is readily available. Displaying the date of the last reprocessing facilitates verification that sufficient time has elapsed since the introduction of the germicide to achieve sterilization or disinfection.

Home dialysis patients are exempted from the recommendation that the patient's name appear on the label, unless the dialyzers are taken to a dialysis facility for reprocessing. It is the intent of the committee to make certain that the correct dialyzer is used on the patient. Requiring special labeling for home patients would normally be unnecessary, unless the dialyzer was being transported outside the home, because only one patient would have access to the dialyzer.

## **A.11 Reprocessing**

### **A.11.1 Transportation and handling**

It was recommended at first that only disinfected caps be used to occlude the ports of the dialyzer. This recommendation was modified to include caps from the same dialyzer maintained in a clean condition, because experience indicates that this method is acceptable. The committee later decided that this recommendation was adequately addressed by the general statement about handling the hemodialyzer in a clean and sanitary manner.

During the 2002 revision of this recommended practice, the committee recognized that the refrigeration temperature of the dialyzers stored for extended periods of time was not specified. It was decided to recommend that dialyzers not reprocessed within 2 hours should be refrigerated and not allowed to freeze. The committee believed that this was sufficient to retard bacterial growth. At the time of the 200X revision of this recommended practice, the committee was made aware of a report from the California Department of Health Services showing that clusters of bloodstream infections were associated with dialyzer reprocessing and possibly refrigeration of dialyzers (Rosenberg, 2005). Although the committee was concerned about this finding, no data were found to support changing the current recommendations concerning refrigeration of dialyzers. However, the committee strongly recommends rigorous quality control and surveillance of refrigeration practices, including minimizing the time dialyzers are held at ambient temperature before refrigeration and reprocessing and regular monitoring of the refrigeration temperature.

A suggestion was also made that unprocessed dialyzers be stored in bags until they were reprocessed to minimize the risk of cross-contamination between dialyzers. This method would accomplish the requirements in this section; other methods have also been successfully used.

### **A.11.2 Rinsing and cleaning**

**A.11.2.1** The committee considered stipulating a period of time after dialysis within which reprocessing should begin. Consensus was not reached on the period of time, and the committee decided that meeting performance guidelines was the goal of such a specification. Aqueous liquids rather than gases such as air are the preferred fluids for rinsing and cleaning (Bass, et al., 1973).

**A.11.2.2** A proposal to use only treated water or physiological saline was not at first accepted, because some safe and effective techniques use untreated water or nonphysiological concentrations of solute in the rinsing solution. The committee thought that the important goals were meeting the recommendations for satisfactory performance (see 11.3) and ensuring the presence of a physiological solution in the dialyzer before starting dialysis (see 12.4). After further comment and review, the committee endorsed as a reasonable safeguard the use of water meeting AAMI bacteriological standards (AAMI, 1982) or having a maximum level of bacterial LPS of 1 ng/mL. In 2001, the committee created a separate standard, ANSI/AAMI RD62, *Water treatment equipment for hemodialysis applications*, which is now referenced throughout this document. ANSI/AAMI RD62 includes minimum quality standards for water used in any hemodialysis application. Since dialyzer reprocessing is the one practice in which the water is deliberately introduced into the blood compartment of a dialyzer, some committee members believe that this water should be subject to a higher standard of purity, such as might be attained by including a final bacteria- and endotoxin-retentive filter at the inlet to the reprocessing equipment.

Originally, the chemical quality of the water was not specified because of a lack of consensus on this issue. Although the committee agreed that high-quality water was unnecessary to protect the patient from chemical contamination, it recognized that data exist suggesting that reprocessing with water of reverse osmosis quality yields more reuses (F. Gotch, personal communication). ANSI/AAMI RD62 now contains chemical standards for water for dialyzer reuse.

The committee had included a recommendation that any device that interfaced between the blood compartment and the permanent equipment should be cleaned and disinfected between each hemodialyzer reprocessed. The recommendation was deleted because permanent equipment sometimes makes a direct connection with the hemodialyzer and because data demonstrating the need for the recommendation are lacking.

### **A.11.3 Performance measurements**

As dialysis facilities attempted to comply rigidly with the 1986 edition of this recommended practice after its adoption by the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration), some personnel misunderstood or expressed concern about the “validation” for indirect measures such as total cell volume (TCV) as indicators of performance of reprocessed dialyzers. *In vitro* clearances require special measures and may expose the hemodialyzer to additional risks. *In vivo* clearances are subject to multiple confounding variables. In view of these misunderstandings and concerns, this requirement’s emphasis was changed. The essential function of the hemodialyzer is mass transfer adequate to provide the prescribed care to the patient. Change in TCV has been documented in the medical literature (Deane and Bemis, 1981) as an indirect measurement with a close relationship to the retained mass transfer of small molecules by the hemodialyzer, and it may be used for the routine testing of residual dialyzer performance. An integral component of the ongoing verification of the proper performance of the hemodialyzer is the monitoring requirement of section 13.

#### **A.11.3.1 Performance test after each use**

Clearance, a measure of the solute transport of the hemodialyzer, should be maintained within acceptable limits to ensure that dialysis is adequate to prevent uremic complications. Because of the established clinical importance of lower molecular weight clearance (Lowrie, et al., 1981), the committee decided that the urea clearance should be the recommended criterion for rejecting a dialyzer. The alternative of sodium clearance was included because sodium and urea clearances are similar, and measuring the former may be easier to accomplish. In developing the first edition of this recommended practice, published in 1986, the committee adopted  $\pm 10\%$  of the initial value as the maximum acceptable change in the urea or sodium clearance of a reused dialyzer. The basis for this decision was the belief that a  $\pm 10\%$  change in urea clearance would not result in a clinically significant change in a patient’s predialysis blood urea nitrogen (BUN) concentration. Subsequently, it has been recognized that predialysis BUN is a poor marker of dialysis adequacy and that a  $10\%$  decrease in urea clearance could lead to inadequate dialysis if the dialysis prescription was marginal. Therefore, in the 2002 revision of this recommended practice, the committee added a caveat that a  $\pm 10\%$  change in urea or sodium clearance was acceptable as long as the patient’s prescription took into account the possibility of a  $10\%$  decrease in urea clearance.

The committee recognized that the clearance of larger molecules is largely membrane limited (Collins and Ramirez, 1979; Dorson, et al., 1983) as opposed to the clearance of small molecules, which is largely flow-rate limited. Larger molecule clearances will therefore be disproportionately decreased by loss of membrane area or increased membrane resistance caused by protein coating of the membrane, compared with clearances of small molecules (Pizziconi, 1985). In 1986, when this recommended practice was initially developed, the committee considered, but ultimately decided against, a proposal to include vitamin B<sub>12</sub> clearance as a criterion for rejection. It made this decision because of (a) uncertainty about the significance of protein coating of the membrane in reprocessed hemodialyzers (Gotch, 1985), (b) lack of evidence supporting the clinical relevance of vitamin B<sub>12</sub> clearance when the change in clearance is within that observed with reprocessed dialyzers, and (c) extensive experience demonstrating the safety of either monitoring urea clearance or using an appropriate indirect test for the urea clearance (Deane and Bemis, 1981). By the time of the 2002 revision of ANSI/AAMI RD47, it had become widely accepted that solutes much larger than vitamin B<sub>12</sub> were involved in some of the long-term complications of end-stage renal disease. Further, the committee recognized that the type of reuse cycle used, especially the cleaning agent, may affect the clearance of larger molecules. Specifically, failure to use a cleaning agent such as bleach that effectively strips adsorbed protein from the membrane may lead to a significant decrease in the clearance of large molecules by high-flux dialyzers, even though the clearance of urea and the TCV are maintained in an acceptable range (Westhuyzen, et al., 1992; Ouseph, Smith, and Ward, 1997; Leyboldt, Cheung, and Deeter, 1998; Cheung, et al., 1999). Using bleach with some high-flux dialyzers may actually increase the clearance of large molecules, and possibly albumin, through mechanisms that are not completely understood (Diaz, et al., 1993; Kaplan, et al., 1995; Murthy, et al., 1998; Cheung, et al., 1999). These effects appear to be membrane dependent (Westhuyzen, et al., 1992; Murthy, et al., 1998; Cheung, et al., 1999). The committee is unaware of any practical test method for routine monitoring of large molecule clearance, and users are advised to consult the manufacturer’s literature for more information on the effects of different reuse practices on the performance of specific membranes.

Although direct clearance measurements could be used to demonstrate compliance with the  $\pm 10\%$  change in urea clearance, determining the urea clearance for each dialyzer reprocessed is impractical. Several dialysis machines now allow noninvasive, automated on-line measurement of the ionic clearance of a dialyzer. Because the ionic clearance has been shown to correlate closely with urea clearance (Steil, et al., 1993; Lindsay, et al., 2001), this technique can be used to follow directly the clearance of a reused dialyzer. There are also indirect tests that reflect the mass transfer characteristics of a dialyzer, which may be used in lieu of clearance measurements. A change in

the residual TCV of hollow-fiber hemodialyzers is the most widely used indirect test for changes in small molecule clearance. This method has been shown to be a good index for monitoring the solute transport capacity of the reprocessed hollow-fiber hemodialyzer (Gotch, 1985). The volume of a hollow-fiber hemodialyzer (TCV) is readily measured in the clinical setting. When methods of reprocessing are used that do not cause a significant change in the permeability or geometry of the membrane, a loss of TCV of 20 % corresponds to a loss of urea clearance of less than 10 % (Gotch, 1984a). Volume change is recommended as a QC test only for hollow-fiber hemodialyzers because other hemodialyzer geometries do not have the relatively noncompliant blood compartment necessary for the validity of this measurement in predicting solute transport.

The question of the appropriate volume to use as the reference TCV has been asked many times. The answer is not quite as clear as it might seem. Each hemodialyzer manufacturer supplies information regarding the total blood volume. However, the techniques used by hemodialyzer manufacturers are often quite different from those employed during hemodialyzer reuse and may yield somewhat different results. For example, several manufacturers measure the volume using kerosene, a liquid that does not “wet” the membrane. The TCV of dialyzers can vary from the values used to develop the original manufacturer’s literature, from lot to lot, and from hemodialyzer to hemodialyzer within a lot. In general, these variations are of little consequence in providing the proper transport properties designed into the hemodialyzer. When the hollow-fiber diameter decreases, the internal volume and surface area also decrease. Although it might appear that this decrease would cause lower urea clearance, it does not. The shorter diffusion distances of the smaller fiber diameter cause an increase in urea transport rate, offsetting the loss in surface area. Following similar scientific principles, when individual fibers become plugged as the hemodialyzer is repeatedly used, the surface area associated with those plugged fibers is lost to solute transport and overall clearance decreases. This loss in transport is not linear because the (now) higher velocity in the remaining fibers causes an increase in the diffusion rate inside each fiber. For this reason, a 20 % loss in surface area yields only about a 10 % loss in urea clearance. Therefore, what is important in the reuse setting is the loss in TCV relative to the original volume of the hemodialyzer.

The committee recommended that, whenever possible, the user measure the original volume of each hemodialyzer before the first patient use and record that value as the reference TCV (reprocessing volume) for all subsequent reprocessings. The committee also recognized that obtaining this measurement is not always practical. In the absence of a preprocessing volume measurement for an individual hemodialyzer, the user should use the calculated average preprocessing volume for that hemodialyzer model. The average preprocessing volume can be determined by averaging the preprocessing volume of approximately 10 dialyzers (or 20 % of the monthly usage of dialyzers, whichever is less) for each hemodialyzer model. This figure should be rechecked monthly. Substantial changes in average preprocessing volume should be investigated.

Initially, a change in the *in vitro* ultrafiltration coefficient of the hemodialyzer ( $K_{UF}$ ) or its inverse, the membrane hydraulic resistance ( $R_m$ ), was proposed as an alternative to a change in TCV as an indirect measure of a change in solute clearance (Pizziconi, 1985). However, this method was never validated in a clinical setting, and at the time of the 2002 revision of this recommended practice, it was considered to have no utility as a QC measure for contemporary hemodialyzers.

The committee recognized that other factors can influence the effective clearance of toxins during the dialysis session or can influence interpretation of the results. These factors include the following:

- a) fistula recirculation,
- b) accurate blood and dialysate flow rates,
- c) accurate time of dialysis,
- d) compliance with dietary limitations,
- e) selection of appropriate hemodialyzer type and blood and dialysate flow rates,
- f) membrane surface coating that may affect higher molecular weight toxins,
- g) variations in the original clearance of the hemodialyzer, and
- h) variations in the clearance of the hemodialyzer caused by reuse.

Users should be aware that the HEMO Study (Cheung, et al., 1999) identified reductions as well as increases in the clearance of  $\beta_2$ -microglobulin with the use of certain combinations of dialyzers, cleaning agents, and reuse germicides.

Of particular concern to this committee were any variations in hemodialyzer functions related to reuse procedures. Although cases have been documented (Delmez, et al., 1989), they are rare, especially when compared with the frequency of other factors listed above. For this reason, the committee strongly felt that the monitoring requirements

of section 13 were of great importance to use in conjunction with the individual hemodialyzer measurements recommended in 11.3.

#### **A.11.3.2 Ultrafiltration**

The ultrafiltration rate (UFR) is the flow rate of fluid that passes through the membrane under a given pressure gradient at a given temperature. It is the product of the ultrafiltration coefficient of the hemodialyzer ( $K_{UF}$ ) and the transmembrane pressure. The  $K_{UF}$ , and thus the UFR at a given transmembrane pressure, may be affected by changes in the intrinsic permeability of the membrane, the surface area of the membrane, and the presence of hydraulically resistive deposits on the membrane. Cleaning agents such as sodium hypochlorite may affect the intrinsic water permeability of many types of dialysis membranes (Cheung, et al., 1999).

*In vitro*  $K_{UF}$  is not recommended to predict *in vivo* ultrafiltration performance because the former overestimates the latter (Gotch, 1984a; Wineman, 1984) in hollow-fiber hemodialyzers. This difference occurs in part because of the additional hydraulic resistance of the formed elements and proteins in blood. Additionally, thrombus-occluding hollow fibers may be highly permeable to water, and ultrafiltration may occur from either water passage through the occluding thrombus or retrograde flow from the unoccluded end of the fiber. These factors give a higher ultrafiltration coefficient during aqueous perfusion *in vitro*, whereas *in vivo* ultrafiltration across clotted fibers results in hemoconcentration of blood in clotted fibers to the point where osmotic pressure and hydraulic pressure drop to equal the transmembrane pressure, thus decreasing the ultrafiltration coefficient in the occluded fiber to zero. Similar data are not available for other types of dialyzers, but because clotting also occurs in those devices, the committee decided that *in vitro*  $K_{UF}$  should not be recommended to predict *in vivo* ultrafiltration performance in those devices as well.

The committee recognized that surface deposits could significantly affect ultrafiltration (V. Pizziconi, personal communication, August 1984). This subject is not included in the recommended practice because of the controversy surrounding the clinical significance of protein deposits on the membrane (see A.11.3.1) and the lack of evidence for a significant decrease of *in vitro*  $K_{UF}$  using present-day reprocessing techniques (Gotch, 1984a; Wineman, 1984).

The committee also recognized that *in vitro*  $K_{UF}$  measurements in hollow-fiber dialyzers can be used to estimate *in vivo* ultrafiltration if they are corrected for the percentage change in priming volume to reflect the amount of clotting and the normal *in vitro*-to-*in vivo* drop caused by the ultrafiltration of blood rather than protein-free solution. The committee decided not to include this information in the recommended practice because of the lack of consensus on the utility of this approach.

Measurement of *in vitro* ultrafiltration is temperature dependent. *In vitro* aqueous  $K_{UF}$  will change approximately 2 % per °C. Thus, care should be taken to know the actual temperature at which the measurement is made. If the measurement temperature is not 37 °C, the appropriate temperature compensation algorithm should be used to correct the reading to 37 °C (see Pizziconi [1985] for an appropriate algorithm).

#### **A.11.3.3 Blood path integrity test**

The 1986 edition of this recommended practice did not include a blood path integrity test. Because of recommendations by the CDC, the committee agreed to add such a test to the second edition of the recommended practice. This test is based on the observation that only a small amount of air leaks through wetted membranes, resulting in a pressure drop of less than 10 % of the test pressure. A maximum allowable pressure drop is not given because of variations among test systems and dialyzers.

#### **A.11.4 Germicide**

Until 1996, chemical germicides used in the health care setting were regulated by two government agencies: the Environmental Protection Agency (EPA) and the FDA. Chemical germicides formulated as disinfectants or sterilants were regulated and registered by the Disinfectants Branch, Antimicrobials Division, EPA. The authority for this responsibility comes under the Federal Insecticide, Fungicide, and Rodenticide Act. The EPA required manufacturers of chemical germicides formulated as sanitizers, general disinfectants, or disinfecting or sterilizing (sporicide) products to test formulations by using specific protocols for microbicidal activity, stability, and toxicity to humans. If a germicidal chemical was advertised and marketed for use on a specific medical device (e.g., a hemodialysis machine or flexible fiberoptic endoscope), then the germicide came under the additional regulatory control of the FDA, Center for Devices and Radiological Health, which is the federal agency that regulates medical devices. Under the authority of the 1976 Medical Device Amendment to the Food, Drug, and Cosmetic Act, a germicide that was marketed for use on a specific medical device is itself considered a medical device in a regulatory sense, and the manufacturer was required, in addition to EPA registration, to contact the FDA and submit a Premarket Notification—510(k)—before legally marketing the product.

In the early 1990s, the FDA began actively regulating all liquid chemical germicides with health care indications. To avoid the potential problem of regulating the same product under multiple classes, the FDA decided to regulate liquid

chemical germicides as a separate type of medical device; therefore, it determined that they were unclassified devices. In an effort to ease the burden of this dual regulation, the FDA and the EPA signed a memorandum of understanding that gave the FDA primary responsibility for premarket efficacy data review of liquid chemical sterilants and high-level disinfectants and gave the EPA primary responsibility for premarket efficacy data review of general-purpose disinfectants.

Additionally, the FDA adapted the basic terminology and classification scheme described by Spaulding (1972) to categorize medical devices, and the four levels of processing as proposed by the CDC: sterilization, high-level disinfection, intermediate-level disinfection, and low-level disinfection (Favero and Bond, 2001). Also, the FDA regulatory authority over a particular instrument or medical device dictates that the manufacturer is obligated to provide the user with adequate instructions for the “safe and effective” use of that instrument or device. Those instructions must include methods to clean and disinfect or sterilize the item if it is marketed as a reusable medical device. The FDA regulates chemical germicides formulated as antiseptics, preservatives, or drugs that are used on or in the human body or as preparations to be used to inhibit or kill microorganisms on the skin. However, the method used to regulate and assess potency for these formulations is significantly different from the methods used for sterilants and disinfectants. The FDA has an advisory panel that reviews nonprescription antimicrobial drug products. Manufacturers of such formulations voluntarily submit data to the panel, which in turn categorizes the products for their intended use (e.g., health care personnel hand washes, patient preoperative preparations, surgical hand scrubs).

#### **A.11.4.1.1 Germicidal process**

The following discussion of germicidal agents is limited to the use of high-level germicides for reprocessing dialyzers. Sterilization is an appropriate option, if feasible, because sterilization has a greater potential for killing microorganisms.

Over the years, dialyzer reuse programs have employed many techniques and germicides, ranging from simple refrigeration to the use of quaternary ammonium compounds (which are very low-level germicides) to formaldehyde concentrations of 1 % to 6 %, glutaraldehyde solutions, solutions containing peracetic acid as the active ingredient, and, more recently, heat disinfection with and without the use of citric acid.

The reason, in part, for using formaldehyde at concentrations that are less than the sterilization cycle concentration (i.e., 8 % for 12 hours at 20 °C) is that the challenge of microorganisms is not normally composed of bacterial spores. After the hemodialyzer is removed from a patient, microbiologic risk can occur at two main points: when water is used to rinse and clean the dialyzer and when water is used to prepare the chemical germicide used for disinfection. In each case, the water is usually treated in the dialysis center itself for purposes of preparing dialysis fluids. The water that is produced is not sterile and contains water bacteria.

Gram-negative bacteria contain LPS, or bacterial endotoxins, which cause pyrogen reactions in dialyzing patients if the endotoxins are introduced into the bloodstream. Outbreaks of pyrogenic reactions during dialysis ceased when steps were taken to reduce the colony count in the dialysate, when it was counted at the end of dialysis, to fewer than 2000 per mL. The maximum allowable colony count in the water used for dialysis was estimated to be 200 per mL (ANSI/AAMI RD5:1982). The committee initially recommended this limit for the water used to dilute the germicide used for reprocessing hemodialyzers as a reasonable bioburden to be controlled by the germicidal procedure. Subsequently, it decided to add the alternative of a maximum bacterial LPS concentration of 1 ng per mL for the water used to dilute the germicide because the association of reprocessed hemodialyzers with pyrogenic reactions has been defined by the Limulus amoebocyte lysate (LAL) test rather than by culture (Petersen, Carson, and Favero, 1981) and because the LAL test detects both viable and nonviable bacterial contamination. The committee acknowledged the evidence for cross-reactions between certain LAL tests and cellulosic materials (Pearson, et al., 1984) and the concern about the reproducibility of LAL tests. There is no evidence that cross-reactions apply to reprocessed hemodialyzers, and, even so, patient safety would not be compromised because acceptable reprocessed hemodialyzers would be mistakenly discarded rather than excessively contaminated hemodialyzers used. The committee also recognized that the LAL test is the test specified by the United States Pharmacopoeia (USP) for detecting bacterial endotoxin in water. Furthermore, the committee believes that reliable, reproducible LAL tests are readily available.

Another group of water bacteria that can constitute a hazard in a dialysis center is the nontuberculous mycobacteria. They are acid-fast water bacteria and, much like the gram-negative bacteria, survive and are capable of excellent growth in all water, including reverse osmosis and deionized water. Nontuberculous mycobacteria do not contain LPS, and their presence in dialysis fluids would not tend to pose a serious pyrogenic risk to a dialyzing patient. But unlike the gram-negative bacteria, they are considerably resistant to chemical germicides (Carson, et al., 1978). For example, they are between 10 and 100 times more resistant to free chlorine than are *Pseudomonas aeruginosa* and other common gram-negative water bacteria. Some strains of nontuberculous mycobacteria studied can survive a 60-minute exposure to 2 % alkaline glutaraldehyde. By comparison, *Pseudomonas aeruginosa* at a concentration of 10<sup>6</sup> per mL would be inactivated within a matter of minutes. Using 8 % formaldehyde, some strains of nontuberculous mycobacteria have survived up to 6 hours of contact at room temperature; if the challenge had been *Pseudomonas aeruginosa*, the kill rate would have been so fast that it could not have been measured.

In an outbreak of disease among patients dialyzed at a center in Louisiana, the source of nontuberculous mycobacteria appeared to be the water used in processing dialyzers (Bolan, et al., 1985). Laboratory studies conducted by the CDC have demonstrated that the nontuberculous mycobacteria associated with the water systems in the Louisiana center can readily survive 2 % formaldehyde after 24 hours of exposure; in other instances, some strains survived for up to 96 hours. Obviously, those rates do not constitute high-level disinfection. Further laboratory studies have shown that if the concentration of formaldehyde is increased to 4 %, none of the strains of nontuberculous mycobacteria found in the water systems of the dialysis center or, for that matter, any of the strains that the CDC has stockpiled including some extraordinarily resistant strains, survive beyond 24 hours. In another more recent outbreak of mycobacterial infections in a dialysis clinic in California (Lowry, et al., 1990), the CDC also showed incomplete kill of mycobacteria in manually reprocessed high-flux dialyzers using 2.5 % Renalin.

From a conservative standpoint, one should assume that nontuberculous mycobacteria might be part of the microbiologic flora of water used for rinsing and cleaning dialyzers and for preparing aqueous chemical germicides for disinfection and sterilization. Given this assumption, a dialysis center is faced with two alternatives. It could rely entirely on aseptic techniques throughout the reprocessing procedure, use sterile rinse water and sterile germicides (membrane-filter sterilized), and employ strict QC. Most dialysis centers in this country do not have the capability to undertake such a closed-system and complex approach.

The second option would be either to use 4 % instead of 2 % formaldehyde or to use other chemical germicides at concentrations sufficient to produce sterility or high-level disinfection. Although good QA and QC practices and adherence to protocols would have to be maintained, this approach is much simpler. Moreover, a scientific basis apparently exists for considering 4 % formaldehyde at a 24-hour exposure as at least a high-level germicide process. All laboratory data acquired so far show that 24 hours of exposure with 4 % formaldehyde at room temperature (20 °C) inactivate high levels of all strains of nontuberculous mycobacteria that have been tested; many of the test strains are among the most resistant in the CDC collection.

When 4 % formaldehyde is used, both the dialysate and the blood compartments shall be filled with this concentration to prevent its reduction as a consequence of diffusion of formaldehyde from one compartment to another or of dilution by residual rinse water retained on and in the dialyzer membranes. Dilution can be prevented by passing at least three volumes of 4 % formaldehyde through each compartment before sealing the dialyzer for storage. The committee decided to specify an effluent within 10 % of the original concentration to avoid a design standard that might not be appropriate in the future.

The committee limited the recommendation for 4 % formaldehyde to processes that use formaldehyde as the sole germicide, because combinations of germicides might give a satisfactory result with less than 4 % formaldehyde. Concentrations of formaldehyde lower than 4 % and a contact time shorter than 24 hours are permitted if adequate disinfection can be demonstrated, because intermediate conditions have not been tested and might, on further evaluation, prove satisfactory.

The committee is aware of published information regarding the use of 1 % formaldehyde with dialyzers stored at 40 °C for 24 hours (Hakim, Friedrich, and Lowrie, 1985). Many dialysis facilities have adopted this procedure without resulting difficulties, and it seems to be an acceptable alternative to 4 % formaldehyde at 20 °C.

The committee is also aware of published information regarding the use of 1.5 % USP citric acid elevated to a temperature of 95 °C for 20 hours (Levin, et al., 1995). If that process is to be used, the user should consult the published data to ensure that citric acid is being applied appropriately and there is no negative effect on the dialyzer performance or integrity.

Unfortunately, no realistic procedure exists whereby a dialysis center can monitor the effectiveness of the disinfection procedure. Such sophisticated microbiologic tests cannot be performed in dialysis centers, because the tests require the use of specialized equipment and highly trained microbiologists. Instead, a center should adhere rigidly to established protocols for QA and QC. Tests for total bacteria and endotoxin in the water used to make up the germicide should be conducted at least monthly. If there are problems in maintaining water quality at the level established by ANSI/AAMI RD62, the testing may need to be performed more frequently. Some recommended approaches to maintaining water quality are given in ANSI/AAMI RD52:2004, *Dialysate for hemodialysis*. Testing the germicide's final-use concentration should be a part of the center's QC program, as should verifying that each dialyzer was filled with germicide.

The committee considered a functional reverse osmosis unit and 2 % formaldehyde disinfection but decided not to rely on this option because the CDC believes that reverse osmosis water might be inadequate to control contamination by nontuberculous mycobacteria, that there is a substantial chance that these highly resistant organisms may be in the source water, and that monitoring the water for nontuberculous mycobacteria is not clinically feasible.

The committee considered a recommendation that the chemical quality of the water used to dilute the germicide should be the same as the water used to make the dialysate. This recommendation was deleted because of the lack

of consensus on this issue, as noted earlier (see A.7). Water quality standards for dialysis and for dialyzer reprocessing were made the same in 2001 (see current version of ANSI/AAMI RD62).

Potency testing of each batch of germicide is specifically recommended for batches of manually prepared germicides regardless of whether they are used with a manual or an automated system. Germicide solutions that are diluted on-line by automated machines are to be checked for concentration at least monthly. Other requirements for verification of germicide presence are contained in section 12.

The CMS requires that dialyzers not be subjected to multiple germicide solutions because of possible combined actions of the germicides on the hemodialyzer membrane (42 CFR 405.2150). That requirement does not apply to the original sterilization process or chemical cleaning agents that the hemodialyzer might be exposed to for short periods during the cleaning process for reuse. Certain members of the committee felt that the requirement was unnecessary if each hemodialyzer is subjected to an air pressure leak test as part of the reuse process.

#### **A.11.4.1.2 Dialyzer header cleaning and disinfection**

The practice of header removal to remove clotted material has increased over the years. Many dialyzers do not have removable headers, but there are enough dialyzers with removable headers that the practice should be fully addressed. If the headers cannot be removed, other methods are used to remove this clotted material. Those methods should also be addressed. Removing the header allows the user to remove the clotted material from the end of the fiber bundle and the O-ring header assembly. The method of removal of the clotted material has been of concern. Some facilities use running water (AAMI quality) to remove the clotted material, whereas others use 4x4s or instruments to scrape away the clotted material. The main concerns of using 4x4s or instruments to scrape away the clotted material are (a) infection, (b) plugging of fibers, and (c) damage to the end of the fiber bundle.

In the past, removing the headers was associated with reported incidents of bacterial and pyrogenic reactions in patients (Flaherty, et al., 1993). The patient reactions no longer occurred when the headers were disinfected by dipping the O-ring, header and end of the dialyzer into the appropriate disinfectant. The research on this problem pointed to a double-fault failure system: (a) the bacteria seemed to be coming from a contaminated water source, and (b) the bacteria were not killed by the normal disinfection process. Dipping the dialyzer corrected that situation.

Another concern is that rags, 4x4s, or instruments that are used to clean the clotted material would reinfect the end of the dialyzer. This concern can be removed by using new rags or 4x4s for each dialyzer. When instruments are used, they can be disinfected between treatments.

Plugging of fibers has also been a concern. Because the dialyzer is cleaned and tested after the header cleaning, any plugged fibers would be detected and corrected before they became a problem.

There is also a possibility that, if instruments are used, they could damage the end of the fiber bundle. The user should ascertain that no damage occurs.

Several concerns are raised when the headers are not removed and the user attempts to clear clots from the header space. These concerns include infection and damage to the end of the fiber bundle. A multitude of items are used to clean the header space, including water sprays, paper clips, tie wraps, and the like. With water sprays, the possibility of contaminated water always exists. Other items that are inserted can damage the end of the fiber bundle. If the item inserted into the dialyzer is not disinfected between uses, it can cause bacterial transmission; however, the dialyzer is usually disinfected after the header space is cleaned.

Automated header-cleaning devices are commercially available.

#### **A.11.4.2 Exterior**

Low-level germicides satisfactorily clean the exterior of the device to a degree comparable with what a new dialyzer receives. For example, 1:100 dilution of household bleach will achieve the concentration of sodium hypochlorite specified in 11.4.2.

#### **A.11.5 Inspection**

The committee considered a recommendation not to accept hemodialyzers with visible clots because venous filters are not used for all hemodialyzer circuits, leading to the risk of embolization to the patient if a clot were to break loose. The committee decided to reject this proposal because the allowable clots are required to be small and in stagnant areas that are present during the first use of the hemodialyzer and because there is no evidence of embolization from reprocessed hemodialyzers that meet this criterion.

A proposal that the number of dark, clotted fibers evident on external inspection be limited to five was not accepted because a considerably larger number may be clotted without significant adverse effect on performance and because some authorities do not agree that this criterion is essential to an aesthetically pleasing appearance. A



recommendation that hemodialyzers with a pink or brownish tint be unacceptable was also deleted because this condition is difficult to define and because glutaraldehyde disinfection results in a slight tan color of the membranes that has not been shown to impair the safety or performance of the hemodialyzer. The committee recognized that the patient should be included in the aesthetic evaluation of the hemodialyzer.

#### **A.11.6 Disposition of rejected dialyzers**

No additional rationale was provided.

#### **A.11.7 Storage**

The committee acknowledged that the selection of 1 month as the maximum storage period permitted without validation was arbitrary. The committee was, however, unaware of any adverse effects of storage for up to 1 month and, therefore, felt that this period of time was reasonable.

#### **A.12 Preparation for dialysis and testing for chemical germicides and potentially toxic residues**

The committee considered methods other than direct testing of the germicide as a process control in each hemodialyzer. It noted that some automated systems add sodium chloride to the germicide and monitor conductivity. Brilliant Blue (FD&C Blue No. 1) added to the germicide has also been used to confirm the presence of germicide by visual inspection. There are toxicological data supporting the safety of this method (E. Lowrie, personal communication, 30 December 1984).

For the 1986 edition of this recommended practice, the committee recommended testing each hemodialyzer for the presence of germicide just before rinsing and priming. The committee noted in 1986 that certain germicide manufacturers recommended this procedure and that their recommendation should be followed. If each hemodialyzer was not tested for the presence of germicide, then a combination of process control and sampling was considered to be adequate. If the test was conducted before any dialyzer in a batch was used, all dialyzers from the batch could be quarantined or released at the same time.

The committee recognized that a residual level of less than 3 ppm for formaldehyde is the guideline for reuse in the state of California (California Code of Regulations, Title 22 §75207). This level apparently was chosen to coincide with the sensitivity of tests that detect formaldehyde. The committee decided to recommend a maximum residual level of formaldehyde of 5 ppm for the following reasons.

- a) Anti-N-like antibody formation, the only established chronic toxicity caused by formaldehyde in reused dialyzers, does not occur below a residual formaldehyde level of 10 ppm (Howell and Perkins, 1972; Crosson, et al., 1976; White, Miller, and Kaehny, 1977). Subsequently, at least two published studies (Vanholder, et al., 1988; Ng, et al., 1995) report anti-N-like antibodies in 10 % to 11 % of patients treated with reused dialyzers when the residual formaldehyde level was less than 2 ppm to 3 ppm.
- b) The maximum daily dose of formaldehyde from dialysis is less than the California OSHA daily limit, which is based on a 5-day week, whereas dialysis patients usually dialyze three or fewer times a week (Gotch, 1984b).
- c) There is no evidence of toxicity from the long-term use of methenamine by mouth for urinary tract infections at doses that release considerably more formaldehyde to the patient than comes from reused dialyzers (Keen, 1995).
- d) Although tests are commercially available to check for formaldehyde at levels of 1 ppm, residual formaldehyde levels lower than 5 ppm increase the time required to prepare the dialyzer for dialysis.

When the committee revised ANSI/AAMI RD47 in 2002, it decided that sufficient information was available to indicate that the residual level of formaldehyde should be reduced to less than 3 ppm. The testing technology for residual formaldehyde had also improved, and it was feasible to easily test to less than 3 ppm.

The committee considered establishing maximum residual levels for germicides other than formaldehyde. Because these newer germicides are all cleared by the FDA and could have different allowable levels of residuals even for the same generic type of germicide, the committee determined that it is best to recommend that the manufacturer's instructions for use be followed. The committee noted that toxicology studies are favorable for some of these agents, and the FDA reviews labeling information for them, which includes the maximum residual level.

When checking for the presence or concentration of the germicide in the hemodialyzer, nothing should be placed into the blood or dialysate ports of the device (e.g., test strip or syringe) to withdraw the sample. Doing so may damage the fibers of the dialyzer and lead to blood leaks during dialysis. If a germicide test strip or kit is being used, the instructions provided by the manufacturer should be followed.

### **A.12.1 Visual inspection**

No additional rationale was necessary.

### **A.12.2 Verification of patient identification**

No additional rationale was necessary.

### **A.12.3 Verification of germicidal contact**

No additional rationale was necessary.

### **A.12.4 Priming the dialyzer and rinsing the germicide**

No additional rationale was necessary.

#### **A.12.4.1 Testing for residual germicide**

During the 2002 review of ANSI/AAMI RD47, the committee decided that sufficient evidence was available to require the reduction of the residual level of formaldehyde from 5 ppm to 3 ppm. This evidence, along with the availability of test methods capable of making this determination, led the committee to make this reduction.

A number of procedural steps have been identified that, if not followed, may cause residual germicide to remain in the hemodialyzer following rinsing. The following list of instructions, though not all inclusive, should be carefully considered when developing a facility's rinsing procedure:

- a) Air bubbles in the fibers can cause individual fibers to become blocked. Be sure that the arterial line is fully primed before you connect it to the hemodialyzer. If you are using peracetic acid-type germicide, be sure to flush the blood side before beginning dialysate flow.
- b) Air trapped in the dialysate side of the hemodialyzer may cause germicide to also remain trapped in portions of the hemodialyzer. Rotate the hemodialyzer during the rinsing process. This action will normally release the trapped air and allow the germicide to be fully rinsed.
- c) Germicide may back up into the heparin or monitor lines. Be sure that the heparin line is clamped and that fluid is not forced into the monitor lines.
- d) Germicide may back up into the saline bag during the rinsing procedure. Be sure that your procedure accounts for all situations that may force fluid from the dialysis circuit back into the saline bag.
- e) Take care to avoid a false-negative residual disinfection test, which can happen if you sample too quickly after a quantity of saline has been infused.
- f) Discard the prime solution when beginning blood flow to the hemodialyzer. Do not connect the venous line to the venous needle until blood has reached the venous blood line.

## **A.13 Monitoring**

### **A.13.1 Dialysis**

No additional rationale was necessary.

### **A.13.2 Symptoms**

Evaluation by a physician is required to determine whether symptoms might constitute an adverse reaction to the reprocessed dialyzer, because symptoms during dialysis commonly result from other factors, such as infections not attributable to dialysis and to hypovolemia.

First-use syndrome is a symptom complex characterized by nervousness, chest pain, back pain, palpitations, pruritus, and other usually mild symptoms occurring minutes following the initiation of dialysis with a new dialyzer. Some authorities define the syndrome to include the anaphylactoid reaction that usually occurs immediately after the initiation of dialysis in some patients using dialyzers sterilized with ethylene oxide. In addition to first-use syndrome, serious reactions have been reported in patients taking ACE (angiotensin-converting enzyme) inhibitors and dialyzed on certain synthetic membranes. This reaction is now known to involve increased bradykinin release accompanied by suppression of bradykinin degradation.

### **A.13.3 Dialyzer failures**

This section establishes conditions under which some of the tests given in section 11 should be conducted. The option of adjusting the algorithm for UFR refers to a significant change of UFR without a significant change of clearance.

### **A.13.4 Clinical results**

Critical assessment of chemistries and the delivered dose of dialysis (Kt/V or urea reduction ratio), as is done monthly, provides a clear trend line to assess treatment. This scrutiny of the patient's treatment and course is the primary confirmation that hemodialyzer performance anticipated from TCV or other indirect estimation is accurate and adequate. The overall effectiveness of the entire treatment, not only the clearance of the dialyzers, is measured. No other measure of the effectiveness of new or reused dialyzers is as clear or relevant. Trend lines developed from these data characterize the quality of therapy. Other professional assessments of patient well-being should be considered. If the practitioner has concerns about "middle molecules" or other clinical parameters, these factors should also be part of the assessment of the delivered therapy.

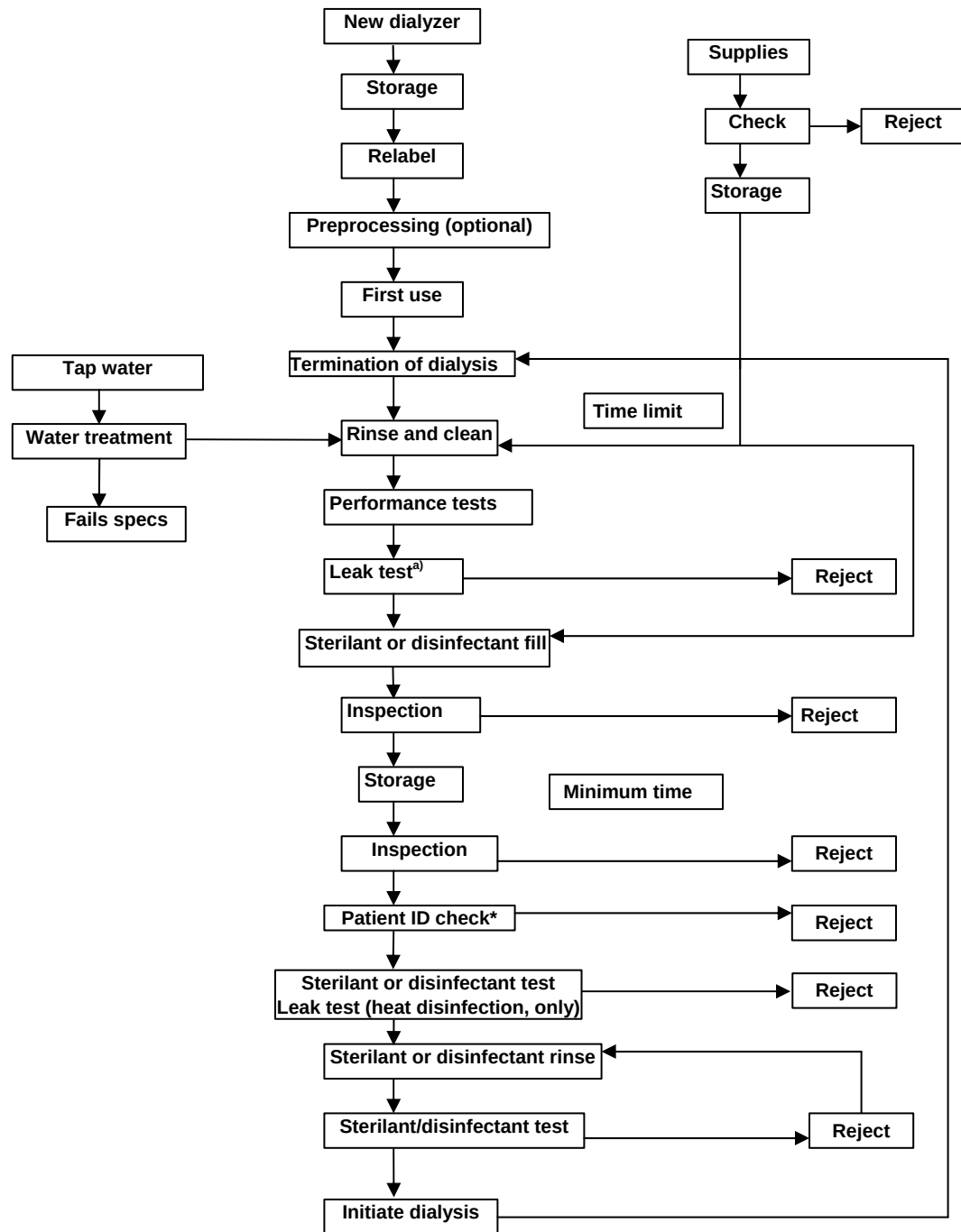
There are many reasons for an apparent reduction in the mass transfer of urea, other than decreased hemodialyzer clearance as a result of inadequate reprocessing (such as recirculation, decreased dialysis time or blood-flow rate, or an inappropriate dialysis prescription). To document adequate mass transfer, one may find parallel measurements of pre- and postcreatinines helpful. When problems develop with any patient or group of patients, monitoring intensity should be increased, and other methods should be used to analyze the problem and define corrective action.

Techniques to compare survival among facilities and for individual facilities against national and regional standard mortality rates are an important instrument for a facility to use in self-assessment (Wolfe, et al., 1992). The committee recommends periodic review of this outcome measure.

## **A.14 Quality assurance**

The FDA's 1987 compliance policy guide (7124.16) advises reuse practitioners to establish the following: (a) adequate device cleaning and sterilization; (b) lack of adverse effects on device quality or physical characteristics; and (c) certainty that the device remains safe, reliable, and effective for its intended use. The committee believes that compliance with those recommendations necessitates use of regularly examined reprocessing procedures that are based on methods of demonstrated effectiveness and are carried out under conditions safe to the patient and the personnel.

## Systems diagram for reprocessing dialyzers



a) This step may be done later but shall precede initiation of dialysis.

## **Annex C**

(informative)

### **Self-assessment of compliance with recommendations for hemodialyzer reprocessing**

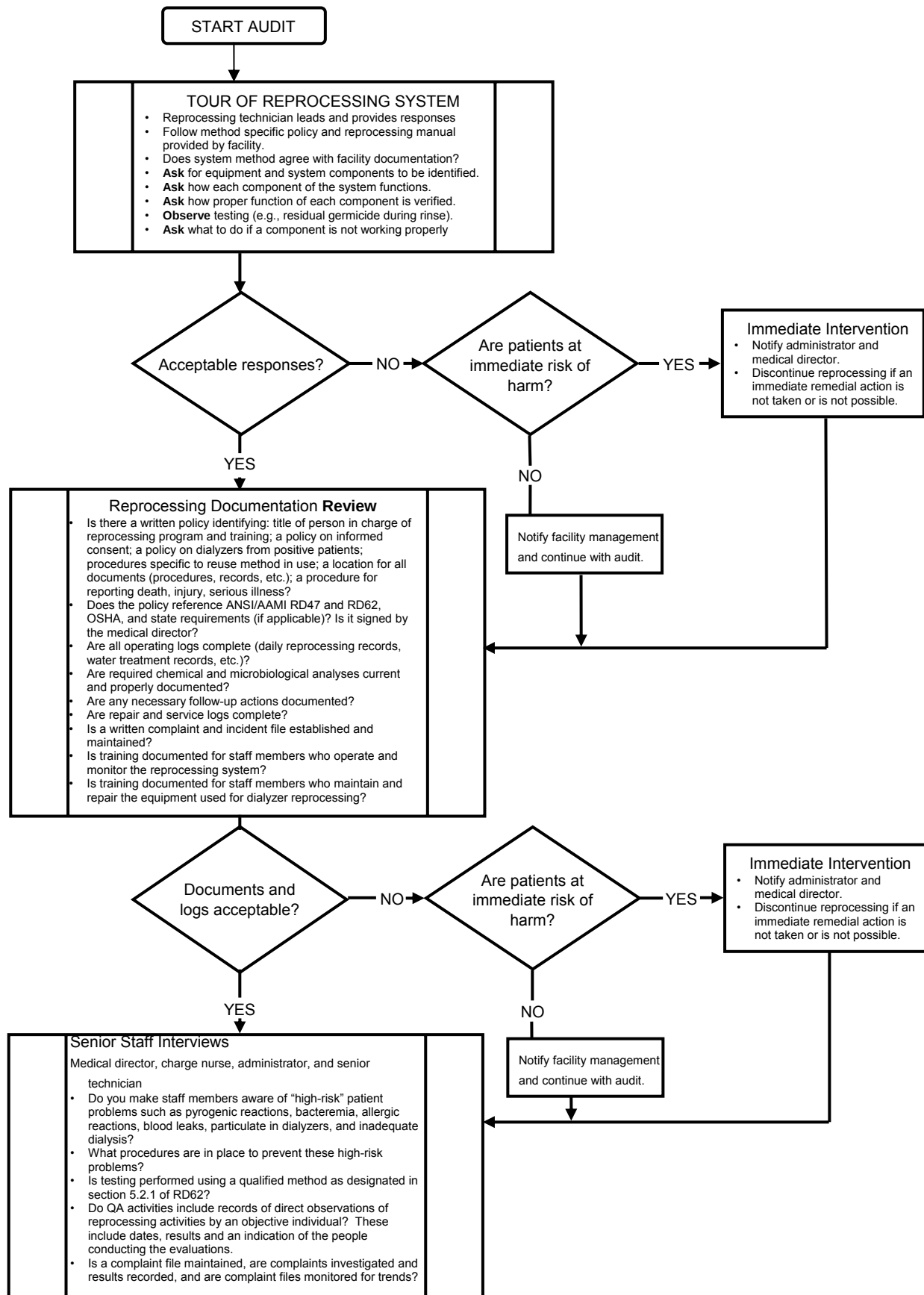
#### **C.1 General**

This recommended practice reflects the conscientious efforts of health care professionals, patients, and medical device manufacturers to develop recommendations for optimal hemodialyzer reprocessing procedures. These recommendations are not meant to be construed as universally applicable in all circumstances. This document is intended to guide physicians in charge of hemodialyzer reprocessing, particularly the directors of dialysis facilities, in initiating a new hemodialyzer reprocessing program or evaluating an existing program against present-day technology and accepted practice.

Reprocessed dialyzers that routinely meet the recommended level of quality require ongoing attention to all aspects of a dialyzer reprocessing program. This surveillance may be provided by a number of means, including continuous quality improvement programs. To help users understand the intent of the recommendations contained in this recommended practice and to aid in establishing a surveillance program, the AAMI Renal Disease and Detoxification Committee developed the self-assessment tools contained in this annex. These self-assessment tools are designed for auditing systems used in dialysis facilities treating multiple patients. Parts of these self-assessment tools may not apply in situations where a single patient is treated, such as in home dialysis or acute dialysis. Further, these tools are not intended to be exhaustive or to be the only way of providing ongoing surveillance of a dialyzer reprocessing program.

#### **C.2 Audit flow chart**

This section presents an example of a structured approach to auditing a dialyzer reprocessing program.



### C.3 Systematic audit for compliance with the main recommendations of ANSI/AAMI RD47

This section provides a table of the main recommendations of this ANSI/AAMI RD47, together with a series of audit questions that may be used to assess whether the recommendation is being met.

|                                    | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Tour of Reprocessing System</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 1                                  | <p><u>Equipment</u></p> <p>Each piece of <b>equipment</b> used for reprocessing shall be appropriately designed, constructed, and tested to perform its intended task. Satisfactory operation of manual and automated systems shall be ensured by appropriate functional tests. Strict QA and QC shall be maintained for any type of dialyzer reprocessing equipment.</p> <p>The system providing <b>water for reprocessing</b> shall meet all of the requirements for pressure and flow rate for operating the reprocessing equipment under minimal and peak load conditions. Product water used for rinsing, cleaning, filling, and diluting the germicide shall be shown to comply with the chemical and microbiological quality requirements specified in the current version of ANSI/AAMI RD62, <i>Water treatment equipment for hemodialysis applications</i>. Water bacteriology monitoring shall be carried out where the dialyzer is connected to the reuse system or as close as possible to that point.</p> <p><b>Dialyzer test methods</b> shall be established before clinical use of the reprocessed dialyzers. Verification of tests should be repeated after each significant change in the reprocessing system.</p> | <p>Types of reprocessing systems vary from sophisticated microprocessor-controlled systems to hand-operated valving systems.</p> <p>Complete documentation of system function, operating procedures, potential system failures, and dialyzer-reuse criteria shall be included in the dialyzer reprocessing manual, known to the operator, and be available for <b>review</b>.</p> <p>The quality, pressure, flow rate, and temperature of the water used for reprocessing should be specified in the dialyzer reprocessing manual, established before the initiation of a reprocessing program, and maintained thereafter. The manufacturer's or designer's recommendations for the water supply should be followed.</p> <p>It is particularly important that all water coming into contact with the fluid pathways for blood or dialysate be of recommended quality (ANSI/AAMI RD62), because the blood side of the dialyzer might take up endotoxin that could be released into the circulation during the subsequent dialysis.</p> <p>Provision should also be made for adequate drains, ventilation, and electrical power for reprocessing systems.</p> <p>For automated systems, adherence to the manufacturer's instructions can verify the tests. For manual systems, confirmation of the accuracy of total cell volume (TCV) measurement and the membrane integrity test can verify the tests.</p> | <p><b>Observe:</b></p> <p>Is the reprocessing system, and other equipment, designed for dialyzer reprocessing? (section 7)</p> <p>Do you have an operator's manual if using an automated system or a procedure manual if using a manual system? (section 7)</p> <p><b>Ask and Review:</b></p> <p>Is the water system, designed, installed, and monitored appropriately? (section 7.1)</p> <p><b>Ask:</b></p> <p>How do you know your water for reprocessing meets the requirements of ANSI/AAMI RD62? (section 7.1)</p> <p><b>Observe and Ask:</b></p> <p>Have you ever had a problem with your drains, ventilation, or electrical power? If so, what steps have been taken to correct the problem and are they documented? Are there any current problems with drains, ventilation, or electrical power? (section 7.1)</p> <p><b>Ask:</b></p> <p>What procedures do you use for testing dialyzers?</p> <p>What tests are performed to ensure the integrity and adequacy of your dialyzers?</p> |

|   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|   | <p>The test for the concentration of germicide or chemical shall be established before clinical use of the reprocessed dialyzers.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>Verification of the presence of an adequate concentration of germicide before clinical use is a surrogate test for high-level disinfection or sterilization of the reprocessed dialyzer.</p> <p>For systems using heat disinfection, verifiable evidence shall be available before the next use that dialyzers have been exposed to the appropriate temperature for the time required.</p> <p>If chemicals are used to enhance heat disinfection, both a presence test and a verification of time and temperature shall be performed.</p> | <p><b>Observe:</b></p> <p>Does the facility follow the automated system's manufacturer's instructions? (section 7.2.2.1)</p> <p>If the facility uses a manual system, how are membrane integrity and TCV confirmed? (section 7.2.2.1)</p> <p><b>Ask:</b></p> <p>What test is used to verify the concentration of germicide before clinical use of the reprocessed dialyzers? (section 7.2.2.2)</p>                                                                                                                                                                                  |
| 2 | <p><u>Physical plant and environmental safety</u></p> <p>The <b>reprocessing area</b> should be designed to suit the operation carried out and maintain acceptable ambient concentrations of harmful substances. The area should be kept clean and sanitary. It may be part of the dialysis treatment area, as long as equipment used is properly designed and vented to meet the requirements for environmental safety.</p> <p>Reprocessing materials, hemodialyzers awaiting reprocessing, and reprocessed hemodialyzers should be <b>stored</b> so as to minimize deterioration, contamination, or breakage. New, used, and reprocessed dialyzers should be segregated to make clear the status of each group of dialyzers.</p> <p>Environmental contamination of the storage area should be controlled and monitored if personnel determine those</p> | <p>Storage areas for new dialyzers and reprocessing materials should be designed to facilitate rotation of stock and cleaning. Storage arrangements should also take into account fire safety considerations, OSHA regulations, and other appropriate regulations.</p> <p>Tests that do not require special facilities, such as certain tests for germicide levels, may be done in the reprocessing or dialysis treatment area, whichever is appropriate.</p>                                                                                | <p><b>Observe</b></p> <p>Is the area clean and sanitary? (section 8.1)</p> <p><b>Ask:</b></p> <p>What would cause you to test air levels for the germicide you use?</p> <p><b>Observe</b></p> <p>Are you bothered by germicide smells or fumes? <b>Ask</b> that air-level testing be performed.</p> <p><b>Observe:</b></p> <p>How are the storage areas designed?</p> <p>Are new, used, and reprocessed dialyzers clearly segregated?</p> <p>Are reprocessed dialyzers protected from casual access (in accordance with the Health Insurance Portability and Accountability Act</p> |



|   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|   | <p>actions to be necessary.</p> <p>Personnel shall wear durable gloves and protective clothing when handling the dialyzer during initiation and termination of dialysis and during the reprocessing procedure.</p>                                                                                                                                                                                                                                                                                  | <p><b>Standard precautions shall be observed.</b> Personnel shall wear eye protection when performing steps that may result in spills or splashes of substances of known or suspected toxicity. These agents shall be handled only in areas with adequate ventilation, washing facilities, eyewash stations, appropriate respirators, and spill control materials. When personnel are handling concentrated toxic substances, they shall wear aprons impervious to these substances</p> <p>Also:</p> <p>See National Institute for Occupational Safety and Health [NIOSH]/OSHA, 1980; Sax, 1979; material safety data sheets [MSDS]). Vapors from reprocessing materials must be maintained below potentially toxic levels (see Table 1).</p>                                                                                                                                                                                                                                                                                                                                               | <p>{HIPAA}}?</p> <p>Does the storage area meet the storage specifications for the germicide in use? (section 8.2)</p> <p>Is the storage area clean?</p> <p>Does the storage area facilitate rotation of stock and cleaning? (section 8.2)</p> <p><b>Observe:</b></p> <p>Do reprocessing personnel wear appropriate personal protective equipment when performing reprocessing steps/ (section 8.4)</p> <p>Are appropriate washing facilities, eyewash stations, respirators and other personnel safety devices in place? (section 8.4)</p> |
| 3 | <p><u>Reprocessing supplies</u></p> <p>Each <b>reprocessing material</b> should meet a written specification. The fulfillment of that requirement may be determined by the product's supplier certification that the product meets necessary specifications and labeling for its intended purpose or by testing procedures by trained personnel, as appropriate. The requirement may also be complied with by purchasing a specific grade as specified by the process, such as USP citric acid.</p> | <p>In recognition of the fact that most medical supplies are certified by the vendor and not tested by the user, supplies need not be tested by the facility doing hemodialyzer reprocessing if they are marketed for hemodialyzer reprocessing. When the user performs testing, he or she should maintain a log of the date of test, the identifying number (lot number) of the batch, the person performing any testing, and the test results.</p> <p>Over the past few years, bleach (sodium hypochlorite) manufacturers have begun selling household bleach in many new formulas. The concentration of sodium hypochlorite has risen from 5.25 % to 6.15 % in many cases. The Centers for Disease Control and Prevention (CDC) has not changed its recommendations for diluting the bleach to take into account these percentage changes. However, bleach manufacturers have also begun using additives such as fragrances in their products commercially marketed in grocery stores.</p> <p>When bleach is purchased from a commercial outlet, the labeled concentration should be</p> | <p><b>Ask and Observe:</b></p> <p>Are supplies used for reprocessing certified or labeled by the supplier for dialyzer reprocessing? (section 9.1)</p> <p>Are there written specifications or are the supplies labeled by the supplier for dialyzer reprocessing? (section 9.1)</p> <p>If not labeled for dialyzer reprocessing, how are supplies validated against the specification upon receipt? (section 9.1)</p> <p>Is in-house testing is done in lieu of manufacturer's certification or labeling? (section 9.1)</p>                |

|   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|   | <p>Reprocessing supplies should be used on a first-in, first-out basis, and outdated supplies should be identified and discarded.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>between 5.25 % and 6.15 %, and the formula should not contain fragrances.</p> <p>First-in, first-out basis is used, for inventory control, to avoid deterioration over time in storage.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p><b>Ask:</b></p> <p>Does the policy call for first-in, first-out inventory control? (section 9.2)</p> <p>Are expiration dates checked before use? (section 9.2)</p> <p>Are all supplies within the dates specified for use?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 4 | <p><u>Hemodialyzer labeling</u></p> <p>Each reprocessed hemodialyzer shall be used for only one patient. Therefore, the <b>labeling</b> shall uniquely identify the patient who is using the dialyzer. The dialyzer should also be labeled with other information essential to proper reuse procedure.</p> <p>Each hemodialyzer shall be labeled before or at the first use of the device, and the label shall be updated after each use.</p> <p>Markings should be resistant to normal reprocessing and dialysis procedures. The dialyzer labeling should not obscure the manufacturer's model number, lot number, or indicators of the direction of blood or dialysate flow or other pertinent information unless provision is made for recording this information on the label. The label on hemodialyzers with transparent casings should permit the blood path to be readily inspected.</p> <p>The dialyzer shall be labeled with the patient's name, the number of previous uses, and the date of the last reprocessing. Dialyzers of patients with similar last names should have a warning to the user to take extra care in ensuring that the name or other identifying information on the label</p> | <p>Use of indelible ink to label the dialyzer is unnecessary as any method resistant to normal reprocessing and use procedures is acceptable. Electronic bar-code labels are acceptable. For protection against degradation, a clear plastic protector typically covers bar-code labels.</p> <p>If there is sufficient room, the dialyzer may also be labeled with the results of tests, the signature or other unique means of identifying the person performing the various steps in the reprocessing procedure, and the reference values for performance parameters. If this information appears on the label, a permanent record should also be kept (electronic records are acceptable). Displaying the number of</p> | <p><b>Observe:</b></p> <p>Are all reprocessed dialyzers in use during treatment labeled for the patient?</p> <p>Does the labeling uniquely identify the patient who is using the dialyzer? (section 10)</p> <p>Are dialyzers being labeled before their first use in a treatment? (section 10.1)</p> <p>Are the labels updated after each use? (section 10.1)</p> <p><b>Observe:</b></p> <p>Is the labeling protected from chemicals used in reuse and dialysis treatments? (section 10.2)</p> <p>Does the reuse label obscure pertinent information on the manufacturer's label or is this pertinent information recorded elsewhere on the reuse label? (section 10.2)</p> <p>Is the blood path visible? (section 10.2)</p> <p><b>Observe:</b></p> <p>Do dialyzer labels contain the patient's name, number of reuses and date of last reprocessing? (section 10.3)</p> <p><b>Ask:</b></p> |

|   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|   | <p>corresponds to that of the patient.</p> <p>Electronic records are acceptable.</p> <p>Home dialysis patients are exempted from the recommendation that the patient's name appear on the label, unless the dialyzers are taken to a dialysis facility for reprocessing.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>previous uses on the label is recommended so that this information is readily available. Displaying the date of the last reprocessing facilitates verification that sufficient time has elapsed since the introduction of the germicide to achieve sterilization or disinfection.</p> <p>If records are electronic, the test results should be available to the user.</p> <p>It is important to ascertain that the correct dialyzer is used on the patient. Requiring special labeling for home patients would normally be unnecessary, unless the dialyzer was being transported outside the home, because only one patient would have access to the dialyzer.</p>                                                                                                                                                                                                                                                                                                                                     | <p>What method is used to alert the staff of patients with the same or similar last names? (section 10.3)</p> <p>Are the dialyzers checked before use to ensure that an appropriate amount of time has passed since reprocessing the dialyzer? (section 10.3)</p> <p><b>Ask:</b></p> <p>Are electronic records available to the user? (section 10.3)</p> <p><b>Ask:</b></p> <p>If the dialyzers from home hemodialysis patients are taken to a dialysis facility for reprocessing, do they comply with the labeling requirements in section 10? (section 10.3)</p> |
| 5 | <p><b>Reprocessing</b></p> <p>Completion of all <b>reprocessing steps, tests, and inspections</b> should be documented in the reprocessing record, accompanied by the signature or other unique means of identification of the person completing them. When appropriate for the reprocessing procedure in use, all dialyzer manufacturer's instructions regarding reuse should be carefully followed.</p> <p>Persons handling used dialyzers during <b>transportation</b> shall do so in a clean and sanitary manner maintaining standard precautions until the dialyzer is disinfected both internally and externally. To inhibit bacterial growth, dialyzers that cannot be reprocessed within 2 hours should be refrigerated and not allowed to freeze. Other transportation and handling issues (such as prolonged delays in reprocessing) not described in this recommended practice shall be validated and documented by the responsible party.</p> | <p>The multiple use of a dialyzer begins with the labeling of the new dialyzer and continues with the reprocessing procedures and preparation of the reprocessed dialyzer for the next dialysis. The cycle is repeated after the next use of the dialyzer until the dialyzer does not meet the criteria for continued use. A systems diagram of these procedures is given in annex B (normative). The results of the tests and the signature or other unique means of identifying the person performing each step should be maintained in a permanent record (this record can be electronic).</p> <p>During the 2002 revision of this recommended practice, the committee recognized that the refrigeration temperature of the dialyzers stored for extended periods of time was not specified. It decided to recommend that dialyzers not reprocessed within 2 hours be refrigerated and not allowed to freeze. The committee believed that this procedure was sufficient to retard bacterial growth.</p> | <p><b>Ask:</b></p> <p>How is the person doing reprocessing identified in the records?</p> <p><b>Observe:</b></p> <p>Note the entire reprocessing sequence. (section 11)</p> <p><b>Observe:</b></p> <p>Note set up and take down of reprocessed dialyzers on the treatment floor. Are dialyzers handled and transported in a clean and sanitary manner? (section 11.1)</p> <p><b>Ask:</b></p> <p>What is the policy and procedure when a dialyzer is not reprocessed within the recommended 2 hours?</p> <p>If dialyzers are refrigerated,</p>                      |

|  | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|  | <p>When <b>precleaning</b> is done, it is necessary to include it as part of the reprocessing procedures. All applicable requirements for design and maintenance of equipment included in this document should be adhered to. The maximum pressures for the dialyzer, or other limits set by the manufacturer, should also be adhered to.</p> <p><b>Dialyzer reprocessing</b> should be initiated in sufficient time to produce a reprocessed device that meets all performance requirements established in the current version of ANSI/AAMI RD47. Each dialysis facility should establish its time limits. Staff members involved in handling, transporting, or storing dialyzers locally or at remote locations shall follow standard precautions to prevent exposure to the operator and contamination of the physical environment.</p> <p>Diluted solutions of hydrogen peroxide, sodium hypochlorite, peracetic acid, or other chemicals may be used as <b>cleaning agents</b> for the blood compartment, provided that the cleaning agent has been shown to be reduced to safe levels by subsequent flushing and has no significant adverse effects on the structural integrity and performance of the dialyzer.</p> <p>A direct or indirect measure of the <i>in vitro</i> clearance of a small molecule such as sodium or urea shall be used as the actual <b>rejection criterion</b>. If clearance is used, a 10 % loss is</p> | <p>Many facilities preclean dialyzers. This process is typically accomplished with an apparatus developed by users, by a precleaning cycle in an automated reprocessing machine, or by a dedicated automated precleaning machine. Precleaning is intended to remove gross deposits of blood and products before rinsing and cleaning with a reprocessing machine or device.</p> <p>To prevent a possible adverse reaction, each chemical shall be rinsed from the dialyzer before the next chemical is added, unless mixing is known to be safe and effective for reprocessing. For example, a cleaning agent, such as sodium hypochlorite, shall be rinsed from the dialyzer before adding formaldehyde to avoid noxious fumes and degradation of disinfectant. Combining sodium hypochlorite and peracetic acid may produce hydrochloric acid vapors, which are harmful if inhaled.</p> <p>The <b>performance characteristics</b> of dialyzers may change following reprocessing. The ultrafiltration coefficient may increase or decrease. Clearances of small or large molecular weight solutes may also increase or decrease depending on the chemicals,</p> | <p><b>review:</b></p> <p>Check the temperature and time logs to verify that they match the policy.</p> <p><b>Ask:</b></p> <p>Is precleaning performed?</p> <p>Do you have a policy and a procedure for the precleaning of dialyzers? (section 11.2.1)</p> <p><b>Observe:</b></p> <p>Watch the precleaning process to confirm that maximum pressures or other limits for the dialyzer set by the dialyzer manufacturer are adhered to. (section 11.2.1)</p> <p><b>Ask:</b></p> <p>How soon after the end of treatment is a dialyzer to be reprocessed? (section 11.2.2)</p> <p><b>Observe:</b></p> <p>What standard precautions are followed? (section 11.2.2)</p> <p><b>Ask and Observe:</b></p> <p>What chemicals are used in the reprocessing of dialyzers? (section 11.2.4)</p> <p>If more than one chemical is used to clean and disinfect a dialyzer is there information that validates that each chemical is reduced to safe levels before introduction of the next chemical and has no adverse effect on the dialyzer performance and integrity? (section 11.2.4)</p> <p><b>Ask:</b></p> <p>What is the minimum acceptable TCV? (section 11.3.1)</p> |

|  | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|  | <p>acceptable. TCV may be used for hollow-fiber dialyzers. The acceptable TCV is at least 80 % of the original TCV.</p> <p><b>In vitro ultrafiltration coefficients</b> should not be used to predict <i>in vivo</i> results. If the expected weight loss is not achieved with the reprocessed dialyzer, the reprocessing method and all other weight removal variables should be reevaluated.</p> <p>A <b>membrane integrity test</b> such as an air pressure leak test shall be done between uses.</p> <p><b>Chemical germicides</b> or other procedures used for disinfecting of hemodialyzers shall have been shown to accomplish at least high-level disinfection. If maximum storage temperature limitations exist, records should be maintained to document this criterion. The disinfection process shall not adversely affect the integrity of the dialyzer. Germicides shall be rinsed from the dialyzer to below known toxic levels within a rinse-out period established for the particular germicide.</p> | <p>methods, and dialyzer membrane used. The dialyzer labeling and medical literature should be consulted for information related to changes in <i>in vitro</i> and <i>in vivo</i> performance.</p> <p>The dialyzer prescription should take into account the 10 % loss in clearance (20 % loss in TCV) that may occur with dialyzer reuse. Whenever possible, dialyzers should be preprocessed to establish the original TCV. If it is not possible to preprocess the dialyzer to obtain a baseline TCV, other methods, such as volume averaging of the lot, should be used.</p> <p>Some germicides have recommendations for maximum storage time after dilution or activation and before usage. If this is the case, the expiration date of the prepared germicide solution should be marked on the outside of the germicide solution container, and that date should be checked at the beginning of each day, before reprocessing begins. If other germicides such as heat and citric acid are used, it is necessary to ensure that the correct time, temperature, and concentration are being used. If the temperature of the disinfection process is elevated, appropriate recording means shall be employed to ensure that this criterion has been met.</p> <p>The rinsed and cleaned dialyzer shall be treated by a process that prevents adverse effects caused by microbial contamination. The blood and dialysate compartments of the dialyzer shall be sterilized or subjected to high-level disinfection because an inadequate germicidal process may result in infection in the patient. Low-level disinfection is sufficient for the exterior of the device. The user shall consult the dialyzer labeling for contraindications or warnings regarding methods and applicability of specific germicidal processes or chemicals.</p> <p>When other germicides are used, the manufacturer's instructions should be followed. If the germicide has an expiration date from the manufacturer, staff members should ensure that the chemical is not outdated.</p> | <p>How is the TCV determined? (section 11.3.1)</p> <p>When preprocessing is not possible, how is the baseline TCV determined? (section 11.3.1)</p> <p><b>Ask:</b></p> <p>When is the air pressure test performed? (section 11.3.3)</p> <p>How is the air pressure test performed? (section 11.3.3)</p> <p><b>Ask:</b></p> <p>Is there a maximum storage temperature for the germicide in use, and if so, how is compliance documented? (section 11.4.1.1)</p> <p>How is the expiration of diluted chemicals documented? (section 11.4.1.1)</p> <p>What steps are taken to assure that expired germicide is not used? (section 4.1.1.1)</p> |

|  | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|  | <p>The cleaning and <b>disinfection of the header space</b> should be done only when necessary and only before the dialyzer is reprocessed. The manufacturer's instructions should be followed. Header caps and O-rings shall be kept with their respective dialyzers. Once the O-ring and the header cap are cleaned and before they are reassembled at the end of the dialyzer, they should be disinfected. The disinfectant shall not be rinsed and shall be allowed to remain on the dialyzer components as they are reassembled. This procedure is done before reprocessing the dialyzer.</p> <p>If the header space is cleaned with the header cap in place, it is necessary to ensure that the end of the fiber bundle is not damaged. If water is used, it shall meet the requirements of the current version of ANSI/AAMI RD62. If an instrument such as a tie wrap is used, it should be made of soft plastic or other material that will not damage the end of the fiber bundle and will be disinfected between uses.</p> <p>If automated equipment is used, the manufacturer's instruction for use shall be followed.</p> <p>The water used to prepare the <b>germicide solution</b> shall meet the requirements of the current version of ANSI/AAMI RD62.</p> <p>If applicable, the hemodialyzer shall be filled with the germicide solution until the concentration in the hemodialyzer is at least 90 %</p> | <p>If the header space is cleaned, it shall be done in a manner to prevent infection and damage to the dialyzer. If the header cap is removed to clean the header space, cleaning shall be done with water meeting the requirements of the current version of ANSI/AAMI RD62. If instruments or other materials (e.g., header caps and 4x4 gauze pads) are used, they should be shown not to cause damage to the end of the dialyzer and shall be new or cleaned and disinfected between uses.</p> <p>Over-tightening the header caps may cause damage to the cap, and under-tightening the cap may cause blood leaks. If any cracking of the header occurs, the process should be evaluated.</p> <p>The CDC recommends that only a stream of reverse osmosis water be used to rinse clots from the headers of the dialyzer.</p> <p>The water used to rinse and clean dialyzers and dilute the germicide should be tested for bacterial contamination and pyrogens according to the requirements of the current version of ANSI/AAMI RD62 before a reprocessing program is undertaken. Once dialysis with the reprocessed hemodialyzers has begun, testing for bacterial contamination should be frequent (e.g., weekly). Less frequent testing, but not less than monthly, may be appropriate if there is a documented history of at least 3 months of results consistently below the levels allowed in the current version of ANSI/AAMI RD62.</p> <p>Automated reprocessing systems have been validated by the manufacturer to deliver the prescribed concentration of germicide. Manual reprocessing systems may take as</p> | <p><b>Observe and Ask:</b></p> <p>Do you remove header caps? (section 11.4.1.2)</p> <p>What safeguard is in place to ensure the original o-ring and header caps are kept with their respective dialyzer? (section 11.4.1.2)</p> <p><b>Ask:</b></p> <p>Are instruments or other material used in header cleaning, and if so, are they new or cleaned and disinfected between uses and has the user determined that the instrument or material does not damage the end of the dialyzer? (section 11.4.1.2)</p> <p><b>Ask:</b></p> <p>Does the facility use water that complies with ANSI/AAMI RD62 for header cleaning? (section 11.4.1.2)</p> <p><b>Ask:</b></p> <p>If you use automated equipment for header cleaning do you have the manufacturer's instructions and do you follow them? (section 11.4.1.2)</p> <p><b>Ask:</b></p> <p>Does the water used to dilute germicide meet ANSI/AAMI RD62? (sections 11.4.1.3 and 11.4.1.5)</p> <p><b>Ask:</b></p> <p>If a manual reprocessing system is used, how is final germicide</p> |

|  | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|  | <p>of the prescribed concentration.</p> <p>The ports of chemically disinfected dialyzers shall be disinfected and then capped with new or disinfected caps.</p> <p>For reprocessing systems in which each batch of <b>germicide is manually prepared</b>, each batch shall be tested before use to verify the proper concentration of the germicide.</p> <p>The <b>outside of the dialyzer</b> should be soaked or wiped clean of visible blood and other foreign material.</p> <p>The hemodialyzer shall be examined after reprocessing to ensure that the external surface is clean, the dialyzer is not damaged, and the rinsing of blood has been satisfactorily completed.</p> <p>The dialyzer should also be aesthetically acceptable in appearance to patients and staff members.</p> <p>Reprocessed dialyzers that have been <b>rejected for failure</b> to meet performance, inspection, or other release criteria should either be immediately discarded or further reprocessed and subjected to the performance requirements of the current version of ANSI/AAMI</p> | <p>much as three compartment volumes (both blood and dialysate, approximately 700 to 1000 cc) to reach these concentrations.</p> <p>The caps may be disinfected with dilute bleach, with the chemical used for disinfecting the hemodialyzer, or with any other germicide approved by the FDA as a disinfectant that does not adversely affect the materials of the dialyzer.</p> <p>This requirement does not apply to cases in which each dialyzer is tested for concentration before setup.</p> <p>When the germicide is diluted on-line, its concentration in the hemodialyzer immediately after reprocessing should be checked at least monthly for each reprocessing system. When the germicide is partially or fully diluted by the user, <b>it is of great importance that the solution be thoroughly mixed.</b></p> <p>For chemically disinfected dialyzers, a low-level germicide that is compatible with the dialyzer's materials of construction should be used for this purpose. Sodium hypochlorite at a concentration of 0.05 % is usually suitable. Certain commercial low-level disinfectants may cause some plastics used for dialyzers to crack after repeated or prolonged exposure.</p> <p>The dialyzer jacket should be free of visible blood or other foreign material.</p> <p>There shall be no leaks or cracks in the dialyzer jacket or the blood or dialysate ports.</p> <p>The label shall be properly filled out and legible.</p> <p>No more than a few dark, clotted fibers should be evident on inspection of the exterior of the hollow fibers.</p> <p>The headers of hollow-fiber dialyzers should be free of all but small peripheral clots or other deposits.</p> <p>Blood and dialysate ports shall be capped without evidence of leakage.</p> <p>If the dialyzer is to be further reprocessed, rather than discarded, it shall be labeled as rejected and stored in a quarantine area to preclude use until requirements are met.</p> | <p>concentration measured? (section 11.4.1.4)</p> <p><b>Ask and observe:</b></p> <p>Are properly disinfected port caps used? (section 11.4.1.4)</p> <p><b>Ask and observe:</b></p> <p>If batches of germicide are manually prepared, how is the proper concentration verified? (section 11.4.1.6)</p> <p>If automated equipment is used to dilute germicide on line, is the concentration in the hemodialyzer tested immediately after reprocessing for each reprocessing system? (section 11.4.1.6)</p> <p><b>Ask and observe:</b></p> <p>Is the outside of reprocessed dialyzers cleaned with a low-level germicide? (section 11.4.2)</p> <p><b>Observe:</b></p> <p>Examine a number of randomly selected reprocessed dialyzers to ensure that external surfaces are clean, the dialyzer has not been damaged, the dialyzer has been satisfactorily rinsed of blood, and the appearance is aesthetically acceptable and properly labeled. (11.5)</p> <p><b>Ask and observe:</b></p> <p>What do you do with failed dialyzers? (section 11.6)</p> |

|   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|   | <p>RD47.</p> <p>Reprocessed dialyzers that meet the performance and inspection criteria for multiple use should be <b>stored</b> according to the provisions of the current version of ANSI/AAMI RD47. Prolonged storage (greater than 1 month) should be documented to be safe and effective.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                           | <p>Dialyzers that have exceeded the facility's maximum storage time shall be reprocessed or discarded. The dialyzer and germicide labeling should be consulted regarding proper storage conditions.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p><b>Ask:</b></p> <p>What is the maximum storage time for reprocessed dialyzers? (section 11.7)</p> <p><b>Ask:</b></p> <p>What happens to a dialyzer that exceeds maximum storage time? (section 11.7)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 6 | <p><u>Preparation and Testing</u></p> <p>The <b>dialyzer should be inspected</b> before it is prepared for use. Completion of this inspection should be recorded in the reprocessing record, along with the signature or other unique means of identifying the person completing the inspection.</p> <p>Except in the case of home dialysis, two people should check that the first and last names on the dialyzer and any other appropriate <b>identifying information</b> correspond to the identifying information on the patient's permanent record.</p> <p>The <b>contact time of the germicide</b> or disinfection procedure shall comply with the facility's protocol and the manufacturer's recommendations. The <b>presence</b></p> | <p>A written procedure that has been shown to be effective shall be followed.</p> <p>The inspection should include the following:</p> <ul style="list-style-type: none"> <li>a) The reprocessed dialyzer shall be legibly labeled with the information recommended in section 10.</li> <li>b) There should be no indication of structural damage or tampering with the dialyzer.</li> <li>c) The ports of the dialyzer should be properly capped.</li> <li>d) The presence of germicide in the dialysate and blood compartments, including headers, should be confirmed, and there should be no evidence of leakage from the ports or other portions of the dialyzer.</li> <li>e) The duration and conditions of storage should be appropriate for the agent or method used to sterilize or disinfect the dialyzer.</li> <li>f) The cosmetic appearance of the dialyzer should be aesthetically acceptable to the staff and the patient.</li> </ul> <p>If possible, one of the people checking identification should be the patient. Completion of this step shall be recorded, along with the signature or other unique means of identifying the person verifying patient identification.</p> <p>NOTE—This step may be done later in the procedure but shall precede initiation of dialysis.</p> <p>Certain germicide manufacturers require testing for the presence of germicide in each hemodialyzer before the rinsing step. These instructions should be followed. In the absence of a germicide manufacturer's requirement, the presence of germicide may</p> | <p><b>Observe:</b></p> <p>Monitor the inspection of reprocessed dialyzers before preparation for use. (section 12.1)</p> <p><b>Ask:</b></p> <p>What do you inspect before use of a reprocessed dialyzer?</p> <p>What is done with a dialyzer that has lost a cap during storage or handling? (section 12.1)</p> <p>What is the allowable time after rinsing and testing before a dialysis treatment?</p> <p>What do you do if this time is exceeded?</p> <p><b>Observe:</b></p> <p>Monitor the identification check of dialyzers to verify that two people check and record that the identifying information on the dialyzer corresponds to the patient to be dialyzed. (section 12.2)</p> <p><b>Ask:</b></p> <p>What is the contact time for the chemical germicide used? (section 12.3)</p> <p>How is the presence of</p> |



|  | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Audit Questions                                                                                                                                                                                                                                                                                                       |
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|  | <p><b>of chemical germicide</b> in each hemodialyzer shall be ensured through either direct testing or an on-line process and procedural control. If other disinfection procedures (e.g., heat) are used, there shall be methods to ensure that each hemodialyzer has been properly subjected to the disinfection process. A record shall be kept indicating that the dialyzer has undergone the appropriate storage time, and the record shall be appropriately verified.</p> <p>If the manufacturer's instructions so require, a germicide presence test shall be performed before the germicide is rinsed from the dialyzer.</p> <p><b>Residual germicide</b> shall be measured by a test of appropriate sensitivity according to a written procedure to ensure that the germicide level is below the maximum recommended residual</p> | <p>be ensured by a direct presence test of each hemodialyzer or the use of process control and sampling of the dialyzer for germicide. For example:</p> <p>Direct testing of each dialyzer</p> <p>a) Use hemodialyzer germicide filling equipment with on-line automatic monitors during the germicide dilution and hemodialyzer filling process, or</p> <p>b) Use an indicator substance (e.g., FD&amp;C Blue No. 1) that has been added to the germicide and that reliably indicates the presence of germicide. If blue dye is used, it should be added to the germicide concentrate before dilution, not to the fully diluted solution. Note that use of dye may be inappropriate with certain germicides, such as peracetic acid.</p> <p>Process control sampling</p> <p>a) Sample at least one hemodialyzer per patient shift per reuse system with a direct presence test (do not use a Schiff test for formaldehyde for this purpose because it will detect the presence of inadequate concentrations of formaldehyde). Samples should be taken immediately after the dialyzers have been reprocessed.</p> <p>b) For germicide prepared in batches, sample at least one hemodialyzer from each batch with a direct presence test. Samples should be taken immediately after the dialyzers have been reprocessed.</p> <p>c) Sampling and testing are to be accomplished before patients use any hemodialyzers processed on this shift.</p> <p>NOTE—The requirements of this section are fulfilled if every dialyzer is subjected to post-storage and pre-priming direct presence testing.</p> <p>The dialyzer shall be rinsed and primed according to a written procedure that has been documented to produce a reduction in the concentration of germicide to an acceptable level and to result in a physiological solution in the blood and dialysate compartments. The dialyzer manufacturer's instructions should be considered in developing these procedures</p> <p>In the case of formaldehyde, the recommended maximum level is 3 ppm. Completion of this step shall be documented, along with the signature or other unique means of identifying the person performing the test.</p> | <p>chemical germicide verified and documented? (section 12.3.1)</p> <p><b>Ask and review:</b></p> <p>May I see the written procedure for the priming, rinsing and testing of a processed dialyzer?</p> <p><b>Observe:</b></p> <p>Rinse procedure to verify that the written procedure is followed. (section 12.4)</p> |

|                                   | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                    |
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|                                   | concentration.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>A rinse procedure should be defined and documented step by step, and all personnel should be familiar with it and follow it. If heat disinfection is used, the dialyzer should be cool to the touch before it is primed with saline.</p> <p>The priming, removal, and residual testing process should be reinstituted after a delay sufficient to bring concentrations of germicide above the recommended level (rebound). Additional rinsing should be performed to yield a germicide level below the maximum recommended concentration before initiating dialysis.</p>                                                         | <p><b>Ask:</b></p> <p>How is residual germicide tested and documented? (section 12.4.1)</p> <p>What is the maximum allowable time between rinsing and testing the dialyzer and beginning dialysis? (section 12.4.1)</p>                                                                                                                                                                                            |
| 7                                 | <p><b>Monitoring</b></p> <p>Patients' temperatures should be measured and recorded at least before and after dialysis with new and reprocessed dialyzers. A temperature of over 37.8 °C or 100 °F, taken orally, or chills should be reported to the physician.</p> <p>Other <b>unexplained symptoms</b> such as pain in the blood-access arm at the onset of dialysis should be evaluated by the physician. Consideration should be given to the possibility that the symptom may be attributable to residual disinfectant in the new or reprocessed dialyzer or contamination of the water treatment equipment.</p> | <p>Any patient with an unexplained fever or chills should be evaluated for the possibility of a pre-existing infection (e.g., access site). The dialysis procedure should also be evaluated to rule out the use of contaminated water, errors in treatment delivery, or incorrect dialyzer reprocessing.</p> <p>Suspected reactions to the residual germicide should prompt reevaluation of the rinsing procedure and a test for residual germicide.</p>                                                                                                                                                                            | <p><b>Ask:</b></p> <p>What do you do if a patient has an oral temperature greater than 100 °F or chills? (section 13.2.1)</p> <p><b>Ask:</b></p> <p>What are the symptoms of a germicide reaction? (section 13.2.2)</p>                                                                                                                                                                                            |
| <b>Reprocessing Documentation</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 8                                 | <p><u>Records</u></p> <p><b>Records</b> should be kept that meet the requirements for medical records, including completeness, legibility, and security. A place should be provided for the signature or other unique mark of identification of the person completing each step of the reprocessing procedure (i.e. the person performing preventive maintenance procedures, investigating complaints, conducting QA and QC activities, etc).</p>                                                                                                                                                                     | <p>Documentation is essential to a safe, effective hemodialyzer reprocessing program. The overall dialyzer reuse procedure documentation includes reference materials, procedures, and policies, some of which may be distributed in the facility for operating purposes. The other records serve to document aspects of the reuse procedure for each dialyzer, along with QA and QC measures, so that a complete history of the reprocessing of each dialyzer and QA and QC procedures exists. Additionally, if formaldehyde is used as a reprocessing germicide health records for reprocessing personnel must be maintained.</p> | <p><b>Review:</b></p> <p>Are reprocessing records complete, legible and secure (not available to casual access)? (section 4)</p> <p>Are records signed or initialed by the appropriate reprocessing personnel? (section 4)</p> <p>Are there records for the maintenance of the reprocessing equipment, of results of complaint investigations and of quality monitoring? (section 4)</p> <p>Look over selected</p> |

|                       | Recommended Practice                                                                                                                                                                            | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
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|                       |                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>portions of the reprocessing manual (section 4.1) Check the reprocessing histories of a randomly selection of reprocessed dialyzers with multiple uses (electronic or hard copy) (sections 4.2 and 11)</p> <p>Check selected preventive maintenance calibration verification records for the reprocessing equipment (section 4.3)</p> <p><b>Ask:</b></p> <p>Does the germicide used for reprocessing require health screenings? (section 4.4)</p> <p>If so, review selected records of screenings.</p> <p><b>Review</b> complaint file:</p> <p>Are the results of investigations monitored for trends? (section 4.5)</p> <p>Are direct observations of reprocessing by an objective individual recorded and evaluated? (section 4.6)</p> |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| 9                     | <p><u>Physical plant and environmental safety</u></p> <p>The <b>reprocessing area</b> should be designed to maintain acceptable ambient concentrations of harmful substances (see Table 1).</p> | <p><b>Table 1—OSHA environmental exposure limits (29 CFR 1910, 1 July 1998), except as indicated</b></p> <table><tr><th>Substance or material</th><th>PEL<sup>a)</sup></th></tr><tr><td>Acetic acid</td><td>10 ppm TWA<sup>b)</sup></td></tr><tr><td>Chlorine dioxide</td><td>0.1 ppm TWA</td></tr><tr><td>Citric acid</td><td>None developed</td></tr><tr><td>Formaldehyde</td><td>0.75 ppm TWA</td></tr><tr><td></td><td>2 ppm STEL<sup>c)</sup> (15 min)</td></tr><tr><td></td><td>0.5 ppm action level</td></tr><tr><td>Glutaraldehyde</td><td>0.2 ppm ceiling</td></tr><tr><td>NIOSH/OSHA</td><td></td></tr><tr><td>Hydrogen peroxide</td><td>1 ppm TWA</td></tr><tr><td>Peracetic acid</td><td>None developed</td></tr><tr><td>Phenol</td><td>5 ppm TWA</td></tr></table> <p>ppm = parts per million; NIOSH = National</p> | Substance or material                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | PEL <sup>a)</sup> | Acetic acid | 10 ppm TWA <sup>b)</sup> | Chlorine dioxide | 0.1 ppm TWA | Citric acid | None developed | Formaldehyde | 0.75 ppm TWA |  | 2 ppm STEL <sup>c)</sup> (15 min) |  | 0.5 ppm action level | Glutaraldehyde | 0.2 ppm ceiling | NIOSH/OSHA |  | Hydrogen peroxide | 1 ppm TWA | Peracetic acid | None developed | Phenol | 5 ppm TWA | <p><b>Review</b> documentation of testing of air levels:</p> <p>Does the frequency of testing match facility policy? (see Table 1, section 8.1)</p> |
| Substance or material | PEL <sup>a)</sup>                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Acetic acid           | 10 ppm TWA <sup>b)</sup>                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Chlorine dioxide      | 0.1 ppm TWA                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Citric acid           | None developed                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Formaldehyde          | 0.75 ppm TWA                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
|                       | 2 ppm STEL <sup>c)</sup> (15 min)                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
|                       | 0.5 ppm action level                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Glutaraldehyde        | 0.2 ppm ceiling                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| NIOSH/OSHA            |                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Hydrogen peroxide     | 1 ppm TWA                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Peracetic acid        | None developed                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |
| Phenol                | 5 ppm TWA                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |             |                          |                  |             |             |                |              |              |  |                                   |  |                      |                |                 |            |  |                   |           |                |                |        |           |                                                                                                                                                     |

|    | Recommended Practice                                                                                                                                                                                                                                                     | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                           |
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|    |                                                                                                                                                                                                                                                                          | <p>Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.</p> <p>a) PEL (permissible exposure limit) represents the limit of what employees can be exposed to; PELs can be TWAs or STELs.</p> <p>b) TWA (time-weighted average) represents the limit of what an employee can be exposed to in an 8-hour period.</p> <p>c) STEL (short-term exposure limit) represents the limit of what an employee can be exposed to in any 15-minute time period.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                           |
| 10 | <p><u>Personnel qualifications and training</u></p> <p>Personnel shall possess adequate <b>education, training</b>, or experience to understand and perform procedures outlined by the individual dialysis facility relevant to the facility's multiple-use program.</p> | <p>New personnel range in knowledge from those with no medical background who are fully trained by the facility, to licensed practitioners with extensive medical background. Education should be geared to meet the needs of this wide range of personnel.</p> <p>The dialysis facility's physician or director shall establish a training course for persons performing hemodialyzer reprocessing. A written document should give details about the curriculum and, in particular, address the potential risks to patients and staff members of not following correct procedures.</p> <p>The curriculum should include at least the following information:</p> <p>a) the facility's specific reprocessing procedure, including a rationale for each step;</p> <p>b) basic documentation requirements of the program;</p> <p>c) the operation and maintenance of the facility's specific equipment for reprocessing hemodialyzers and, if appropriate, the dialysis systems and components;</p> <p>d) microbiology with respect to aseptic technique, the collection and handling of samples, and personnel safety precautions for infectious hazards;</p> <p>e) the risks and hazards of multiple use of hemodialyzers;</p> <p>f) the consequences of not performing tasks properly;</p> <p>g) the risks and hazards associated with toxic substances used in reprocessing hemodialyzers, proper handling of these substances, and procedures for handling spills and proper disposal of toxic substances;</p> <p>h) the use and location of protective eyewear, respirators, masks, and special clothing;</p> | <p><b>Review:</b></p> <p>Do personnel records show that staff members performing reuse of dialyzers or repairing equipment have been trained and certified by the medical director? (section 5.2.2)</p> <p>Does the training curriculum include the required elements? (section 5.2.1)</p> <p><b>Ask and Review:</b></p> <p>Is retraining conducted if new procedures are undertaken? (section 5.2.2)</p> |

|    | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p>i) emergency procedures as required by the facility; and</p> <p>j) the principles of dialysis, emphasizing the characteristics of the hemodialyzer and the effect of reuse on these characteristics.</p> <p>Retraining is necessary when new procedures are undertaken.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 11 | <p><b>Dialyzer reprocessing</b></p> <p>Precleaning the dialyzer (rinsing and cleaning) shall be done with a fluid or fluids made with water that meets the specification of the current version of ANSI/AAMI RD62.</p> <p>The water used to prepare the <b>germicide solution</b> shall meet the requirements of the current version of ANSI/AAMI RD62.</p> <p>Reprocessed dialyzers that meet the performance and inspection criteria for multiple use should be <b>stored</b> according to the provisions of the current version of ANSI/AAMI RD47. Prolonged storage (greater than 1 month) should be documented to be safe and effective.</p> | <p>An important goal is to meet the recommendations for satisfactory performance and to ensure the presence of a physiological solution in the dialyzer before starting dialysis. To this end, a reasonable safeguard is the use of water meeting ANSI/AAMI RD62 requirements.</p> <p>The water used to rinse and clean dialyzers and dilute the germicide should be tested for bacterial contamination and pyrogens according to the requirements of the current version of ANSI/AAMI RD62 before a reprocessing program is undertaken. Once dialysis with the reprocessed hemodialyzers has begun, testing for bacterial contamination should be frequent (e.g., weekly). Less frequent testing, but not less than monthly, may be appropriate if there is a documented history of at least 3 months of results consistently below the levels allowed in the current version of ANSI/AAMI RD62.</p> <p>Dialyzers that have exceeded the facility's maximum storage time shall be reprocessed or discarded. The dialyzer and germicide labeling should be consulted regarding proper storage conditions.</p> | <p><b>Review:</b></p> <p>Confirm results from cultures, endotoxin testing, and chemical analysis of water used for precleaning. (section 11.2.3)</p> <p><b>Review:</b></p> <p>Examine the documentation of bacterial and endotoxin testing of water used for dialyzer reprocessing. (section 11.4.1.5)</p> <p><b>Review:</b></p> <p>Examine the policy for maximum storage time for reprocessed dialyzers and compare against randomly selected dialyzers from the reprocessed dialyzer storage area. (section 11.7)</p> |
| 12 | <p><b>Written maintenance procedures</b> and a schedule of preventive maintenance activities designed to minimize equipment malfunctions should be established. A record shall be kept of preventive maintenance activities, accompanied by the signature of the person performing the maintenance.</p> <p>If the reprocessing system fails to function as expected, qualified personnel should investigate and <b>repair</b> the problem. The reprocessing system function testing should be repeated after</p>                                                                                                                                  | <p>In the case of purchased reprocessing equipment or safety equipment, the recommendations of the vendor should be followed unless documented experience supports alternative approaches. If the manufacturer's recommendations are unavailable, reuse equipment and safety equipment should be inspected on a semiannual basis.</p> <p>Demonstrating proper functioning of the system is an adequate QC measure.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p><b>Ask:</b></p> <p>How often are preventive maintenance procedures performed? (section 7.2.3)</p> <p><b>Review:</b></p> <p>Are preventative maintenance procedures performed in accordance with manufacturer's guidelines or semiannually if the manufacturer's recommendations are not available? (section 7.2.3)</p> <p>Is there appropriate</p>                                                                                                                                                                    |

|    | Recommended Practice                                                                                                                                                                                                                                                                                                                                    | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Audit Questions                                                                                                                                                                                                                                                                                                                           |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | repairs of automated equipment and, if appropriate, after repairs of manual equipment before either the dialyzer is reprocessed or the reprocessed dialyzer is used for clinical dialysis.                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | documentation of preventative maintenance activities? (section 7.2.3)<br><br>Is the person performing repairs on reprocessing equipment qualified? (section 7.2.4)<br><br>Review preventive maintenance logs<br><br>Are preventive maintenance procedures being followed and documented?                                                  |
| 13 | <u>Reprocessing supplies</u><br><br>The dialysis facility shall have written procedures for <b>safe storage and handling of chemicals</b> used in reprocessing.                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <b>Review:</b><br><br>Check written procedures for safe storage and handling of chemicals. (section 8.5)<br><br>Check testing logs.<br><br>Verify name, date, lot number, and test results.<br><br>Have the personnel responsible for testing been properly trained?<br><br><b>Ask</b> to see training records.                           |
| 14 | <u>Preparation and Testing</u><br><br><b>Residual germicide</b> shall be measured by a test of appropriate sensitivity according to a written procedure to ensure that the germicide level is below the maximum recommended residual concentration.<br><br>There shall be a written procedure for all tests employed in preparing the dialyzer for use. | A written policy should establish the maximum allowable time between rinsing the germicide from the dialyzer and beginning dialysis. Certain germicides have been demonstrated to disperse into solid components or less rapidly exchangeable compartments of the hemodialyzer.<br><br>These procedures will include mention of each test's sensitivity. The germicide manufacturer's instructions for use should be consulted in determining the maximum residual level. The physician in charge of the reuse program shall approve any alterations in the procedures. | <b>Review:</b><br><br>Study the policy establishing maximum allowable time between rinsing and testing the dialyzer and beginning of dialysis. (section 12.4.1)<br><br><b>Review:</b><br><br>Monitor the procedure for all tests used in preparing dialyzers for use. The procedure is to include each test's sensitivity. (section 12.5) |
| 15 | <u>Monitoring</u><br><br>The <b>clinical course of the patient should be observed</b> and recorded during each dialysis to identify possible complications caused by new or reprocessed dialyzers.                                                                                                                                                      | Dialyzer failures should be recorded and systematically evaluated. Home dialysis patients and their assistants should be instructed in the appropriate observation, recording requirements, and reporting procedures.                                                                                                                                                                                                                                                                                                                                                   | <b>Review:</b><br><br>Examine the procedure for patient monitoring during dialysis.<br><br>Are dialyzer failures recorded and systematically evaluated? (section 13.1)                                                                                                                                                                    |

|                                | Recommended Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                | <p>Any <b>significant events</b>, such as the occurrence of symptoms listed in this section, should be recorded on an incident report form.</p> <p><b>Dialyzer blood leaks</b> should be recorded in a log kept in the complaint investigation record file.</p> <p>If there is excessive deviation from the expected performance, testing should be repeated and appropriate adjustments made in the reprocessing procedure.</p> <p>Monitoring of relevant patient results is recommended to ensure that all parameters relating to hemodialyzer clearance are being met.</p> | <p>The incident report should include the results of any evaluations conducted by the physician and others, and the event should be considered for reporting to the manufacturers in accordance with the FDA's Medical Device User Reporting procedures. The resolution of actual or suspected problems caused by reprocessed dialyzers should be indicated. This form should be kept in the complaint investigation record file.</p> <p>Specifically, examination of urea reduction ratio (URR) or Kt/V over time is necessary. The failure of these results to meet the expectations of the dialysis prescription should be investigated. Deterioration of a patient's clinical condition or variability of routine dialysis procedures (heparinization, ultrafiltration, erythropoietin requirement) requires investigation of all practices, including reuse. Reports of investigations should be filed in the complaint log.</p> | <p><b>Review:</b></p> <p>Examine the patient treatment records.</p> <p>Do the records reflect that patients' temperatures are measured and recorded at least before and after dialysis? (section 13.2.3)</p> <p><b>Ask and review:</b></p> <p>Are blood leaks recorded in a log and are the results trended? (section 13.3)</p> <p><b>Review:</b></p> <p>Examine selected patient records. Do the records reflect that URR or Kt/V is being met for each patient over time? If not, is an explanation provided? Was reprocessing being considered as a cause?</p>                                                       |
| <b>Senior Staff Interviews</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 16                             | <p><u>Patient considerations</u></p> <p>An order to reprocess hemodialyzers shall be made by a physician knowledgeable about reprocessing and its <b>medical and economic implications</b>. Because the current human immunodeficiency virus, hepatitis B, or hepatitis C status of a patient cannot be known with certainty, all staff potentially exposed to the patient's blood shall observe standard precautions. Dialyzers should from patients who have tested positive for hepatitis B surface antigens should not be reprocessed.</p>                                | <p>Precautions for all infectious hazards should be emphasized and included in the reprocessing procedures. Written procedures should stipulate whether and how reprocessing will be done for patients who have shown sensitivity to materials used in the reprocessing of hemodialyzers.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p><b>Observe:</b></p> <p>Does the facility staff observe standard precautions? ( section 6.1)</p> <p>Are patients who are positive for hepatitis B virus (HBV) excluded from the reuse program?</p> <p><b>Review:</b></p> <p>Are standard precautions included in the written reprocessing procedures? (section 6.1)</p> <p>Do the written reprocessing procedures specify whether and how reprocessing will be done for patients who have shown sensitivity to materials used in reprocessing? (section 6.1)</p> <p><b>Ask:</b></p> <p>Does the facility reprocess dialyzers from HBV-positive patients? (section</p> |





|  | Recommended Practice      | Guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Audit Questions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|  |                           | <p>Quarterly audit of the following is necessary:<br/> environmental safety (storage area),<br/> environmental safety (personnel protection),<br/> hemodialyzer labeling, and<br/> procedures for preparation for dialysis.</p> <p>The following should be audited semi-annually:<br/> reprocessing supplies and<br/> reprocessing procedures.</p> <p>These functions may allow for a less frequent <b>review</b> period according to the circumstances specified in ANSI/AAMI RD47.</p> <p>An annual audit should be made of the following:<br/> patient information policy,<br/> equipment manuals and procedures,<br/> equipment maintenance and repair policies, and<br/> environmental safety (reprocessing area and ventilation).</p> <p>A record of <b>review</b>, comments, trend analysis, and conclusions arising from QA practices will serve as a foundation for future <b>review</b> and as documentation to external evaluation.</p> <p>Problems in a particular aspect of operations should be <b>reviewed and tracked</b> until a solution is in place and demonstrated to be effective. High-volume tasks that are recognized as hazardous should have frequent (weekly or daily) oversight. Practices with little potential for harm may need critical scrutiny on only a quarterly or annual basis.</p> <p>The medical director is responsible for scheduling review, endorsing findings, and, when appropriate, implementing changes.</p> <p>Personnel should audit at least annually compliance with the facility's policy to inform patients of the facility's reuse practices.</p> | <p>various steps in this process and verify implementation semi-annually?</p> <p>Is trend analysis performed?</p> <p>Are personnel designated to audit the written procedures and verify their implementation at least quarterly?</p> <p>Are staff members designated to verify at least quarterly the tests for the presence of germicide and the test for residual germicide by using positive and negative control solutions, on those products that are not specifically intended for use in dialyzer reuse germicide indicator tests and that have not been cleared by the FDA?</p> <p><b>Ask and review:</b></p> <p>May I see the complaint investigation record file?</p> <p>Does the file contain a significant event incident report form?</p> <p><b>Ask and review:</b></p> <p>May I see the complaint investigation log?</p> <p>Are any significant events and important information documented?</p> <p>Are there results of evaluations conducted by the physician and others?</p> <p>Are events considered for reporting to the manufacturers in accordance with the FDA's Medical Device User Reporting procedures?</p> <p>Is resolution of actual or suspected problems caused by reprocessed dialyzers indicated?</p> |
|  | QA records                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|  | Schedule of QA Activities |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|  | Patient considerations    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|  | <b>Recommended Practice</b>                      | <b>Guidance</b>                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Audit Questions</b>                                                                                                                                   |
|--|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | Equipment                                        | Designated staff members should audit written procedures and manuals for relevance at least annually and whenever adverse findings could be attributed to equipment failure. Designated staff should also audit maintenance and repair policies at least annually.                                                                                                                                                                                         | Are dialyzer blood leaks recorded?                                                                                                                       |
|  | Physical plant and environmental safety concerns | Designated staff members should audit provisions for the reprocessing area and ventilation at least annually. The provisions for the storage area and personnel protection should be audited quarterly.                                                                                                                                                                                                                                                    | If there is excessive deviation from the expected performance, was testing repeated and were appropriate adjustments made in the reprocessing procedure? |
|  | Reprocessing supplies                            | Designated staff members should audit the provisions for reprocessing supplies at least semiannually.                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                          |
|  | Hemodialyzer labeling                            | Designated staff members should audit the provisions for dialyzer labeling.                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                          |
|  | Reprocessing                                     | Initially, designated staff members should audit the written procedures for the various steps in this process and verify implementation at least monthly. Subsequently, semiannual audits may be sufficient if there is a documented history of favorable results. Trend analysis should be performed.                                                                                                                                                     |                                                                                                                                                          |
|  | Preparation for dialysis                         | At least quarterly, designated personnel should audit the written procedures and verify their implementation. At least quarterly, designated staff members should verify the tests for the presence of germicide and the test for residual germicide by using positive and negative control solutions, on those products that are not specifically intended for use in dialyzer reuse germicide indicator tests and that have not been cleared by the FDA. |                                                                                                                                                          |

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# Medical electrical equipment — Part 2-16: Particular requirements for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment

Approved 20 August 2012 by  
**Association for the Advancement of Medical Instrumentation**

Approved 5 September 2012 by  
**American National Standards Institute, Inc.**

**Abstract:** Specifies the minimum safety requirements for single-patient hemodialysis, hemodiafiltration and hemofiltration equipment. These devices are intended for use either by medical staff or under the supervision of medical expertise, including hemodialysis, hemodiafiltration and hemofiltration equipment operated by the patient.

**Keywords:** medical equipment, blood, dialysis, packaging, marking, labeling

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### *Published by*

Association for the Advancement of Medical Instrumentation  
4301 N. Fairfax Drive, Suite 301  
Arlington, VA 22203-1633  
[www.aami.org](http://www.aami.org)

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Printed in the United States of America

ISBN 1-57020-458-6



## CONTENTS

|                                                                                                                                       |      |
|---------------------------------------------------------------------------------------------------------------------------------------|------|
| Glossary of equivalent standards.....                                                                                                 | v    |
| Committee representation.....                                                                                                         | viii |
| Background of AAMI adoption of IEC 60601-2-16:2012.....                                                                               | x    |
| FOREWORD .....                                                                                                                        | xi   |
| INTRODUCTION .....                                                                                                                    | xiv  |
| 201.1 Scope, object and related standards .....                                                                                       | 1    |
| 201.2 Normative references.....                                                                                                       | 3    |
| 201.3 Terms and definitions .....                                                                                                     | 4    |
| 201.4 General requirements .....                                                                                                      | 6    |
| 201.5 General requirements for testing of ME EQUIPMENT .....                                                                          | 10   |
| 201.6 Classification of ME EQUIPMENT and ME SYSTEMS.....                                                                              | 11   |
| 201.7 ME EQUIPMENT identification, marking and documents .....                                                                        | 11   |
| 201.8 Protection against electrical HAZARDS from ME EQUIPMENT .....                                                                   | 15   |
| 201.9 Protection against MECHANICAL HAZARDS of ME EQUIPMENT and ME SYSTEMS .....                                                      | 16   |
| 201.10 Protection against unwanted and excessive radiation HAZARDS .....                                                              | 16   |
| 201.11 Protection against excessive temperatures and other HAZARDS .....                                                              | 16   |
| 201.12 * Accuracy of controls and instruments and protection against hazardous outputs .....                                          | 17   |
| 201.13 HAZARDOUS SITUATIONS and fault conditions .....                                                                                | 27   |
| 201.14 PROGRAMMABLE ELECTRICAL MEDICAL SYSTEMS (PEMS) .....                                                                           | 28   |
| 201.15 Construction of ME EQUIPMENT .....                                                                                             | 28   |
| 201.16 * ME SYSTEMS.....                                                                                                              | 29   |
| 201.17 Electromagnetic compatibility of ME EQUIPMENT and ME SYSTEMS .....                                                             | 30   |
| 202 Electromagnetic compatibility – Requirements and tests .....                                                                      | 30   |
| 208 General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems .....   | 30   |
| 210 Process requirements for the development of PHYSIOLOGIC CLOSED-LOOP CONTROLLERS .....                                             | 32   |
| 211 * Requirements for MEDICAL ELECTRICAL EQUIPMENT and MEDICAL ELECTRICAL SYSTEMS used in the HOME HEALTHCARE ENVIRONMENT .....      | 32   |
| Annexes .....                                                                                                                         | 32   |
| Annex G (normative) Protection against HAZARDS of ignition of flammable anesthetic mixtures .....                                     | 33   |
| Annex AA (informative) Particular guidance and rationale.....                                                                         | 34   |
| Annex BB (informative) Examples of HAZARDS, foreseeable sequences of events, and HAZARDOUS SITUATIONS in HEMODIALYSIS EQUIPMENT ..... | 54   |
| Bibliography .....                                                                                                                    | 62   |
| Index of defined terms used in this particular standard .....                                                                         | 63   |

|                                                                                                    |    |
|----------------------------------------------------------------------------------------------------|----|
| Figure 201.101 – Continuous air infusion test set-up with example dimensions .....                 | 24 |
| Figure AA.1 – Example of the HEMODIALYSIS ME SYSTEM .....                                          | 49 |
| Table 201.101 – ESSENTIAL PERFORMANCE requirements.....                                            | 7  |
| Table AA.1: Possible ALARM CONDITION priorities according to 6.1.2 of<br>IEC 60601-1-8:2006, ..... | 52 |
| Table BB.1 – Hazardous situation list following ISO 14971:2007, Annex E .....                      | 54 |

## Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation. The code in the US column, “(R)20xx” indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

| International designation                                                         | U.S. designation                                                                                                                                                    | Equivalency                                                                                                 |
|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| IEC 60601-1:2005<br>IEC 60601-1:2005/A1:2012<br>IEC Technical Corrigendum 1 and 2 | ANSI/AAMI ES60601-1:2005/(R)2012<br>ANSI/AAMI ES60601-1:2005/A1:2012<br>ANSI/AAMI ES60601-1:2005/C1:2009/(R)2012 (amdt)<br>ANSI/AAMI ES60601-1:2005/A2:2010/(R)2012 | Major technical variations<br>A1 identical<br>C1 identical to Corrigendum 1 & 2<br>A2 applies to AAMI, only |
| IEC 60601-1-11:2010                                                               | ANSI/AAMI HA60601-1-11:2011                                                                                                                                         | Major technical variations                                                                                  |
| IEC 60601-1-2:2007                                                                | ANSI/AAMI/IEC 60601-1-2:2007/(R)2012                                                                                                                                | Identical                                                                                                   |
| IEC 60601-2-2:2009                                                                | ANSI/AAMI/IEC 60601-2-2:2009                                                                                                                                        | Identical                                                                                                   |
| IEC 60601-2-4:2010                                                                | ANSI/AAMI/IEC 60601-2-4:2010                                                                                                                                        | Identical                                                                                                   |
| IEC 60601-2-16:2012                                                               | ANSI/AAMI/IEC 60601-2-16:2012                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-19:2009                                                               | ANSI/AAMI/IEC 60601-2-19:2009                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-20:2009                                                               | ANSI/AAMI/IEC 60601-2-20:2009                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-21:2009                                                               | ANSI/AAMI/IEC 60601-2-21:2009                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-24:1998                                                               | ANSI/AAMI ID26:2004/(R)2009                                                                                                                                         | Major technical variations                                                                                  |
| IEC 60601-2-25:2011                                                               | ANSI/AAMI/IEC 60601-2-25:2011                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-27:2011                                                               | ANSI/AAMI/IEC 60601-2-27:2011                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-47:2012                                                               | ANSI/AAMI/IEC 60601-2-47:2012                                                                                                                                       | Identical                                                                                                   |
| IEC 60601-2-50:2009                                                               | ANSI/AAMI/IEC 60601-2-50:2009                                                                                                                                       | Identical                                                                                                   |
| IEC/TR 60878:2009                                                                 | ANSI/AAMI/IEC TIR60878:2003                                                                                                                                         | Identical                                                                                                   |
| IEC/TR 61289:2011                                                                 | ANSI/AAMI/IEC TIR61289:2011                                                                                                                                         | Identical                                                                                                   |
| IEC/TR 62296:2009                                                                 | ANSI/AAMI/IEC TIR62296:2009                                                                                                                                         | Identical                                                                                                   |
| IEC 62304:2006                                                                    | ANSI/AAMI/IEC 62304:2006                                                                                                                                            | Identical                                                                                                   |
| IEC/TR 62348:2006                                                                 | ANSI/AAMI/IEC TIR62348:2006                                                                                                                                         | Identical                                                                                                   |
| IEC/TR 62354:2009                                                                 | ANSI/AAMI/IEC TIR62354:2009                                                                                                                                         | Identical                                                                                                   |
| IEC 62366:2007                                                                    | ANSI/AAMI/IEC 62366:2007                                                                                                                                            | Identical                                                                                                   |
| IEC 80001-1:2010                                                                  | ANSI/AAMI/IEC 80001-1:2010                                                                                                                                          | Identical                                                                                                   |
| IEC/TR 80001-2-1:2012                                                             | ANSI/AAMI/IEC 80001-2-1:2012                                                                                                                                        | Identical                                                                                                   |
| IEC/TR 80001-2-2:2012                                                             | ANSI/AAMI/IEC 80001-2-2:2012                                                                                                                                        | Identical                                                                                                   |
| IEC/TR 80001-2-3:2012                                                             | ANSI/AAMI/IEC 80001-2-3:2012                                                                                                                                        | Identical                                                                                                   |
| IEC/TR 80002-1:2009                                                               | ANSI/IEC/TR 80002-1:2009                                                                                                                                            | Identical                                                                                                   |
| IEC 80601-2-30:2009 and Technical Corrigendum 1                                   | ANSI/AAMI/IEC 80601-2-30:2009 and ANSI/AAMI/IEC 80601-2-30:2009/C1:2009 (amdt) – consolidated text                                                                  | Identical (with inclusion)<br>C1 Identical to Corrigendum 1                                                 |
| IEC 80601-2-58:2008                                                               | ANSI/AAMI/IEC 80601-2-58:2008                                                                                                                                       | Identical                                                                                                   |
| ISO 5840:2005                                                                     | ANSI/AAMI/ISO 5840:2005/(R)2010                                                                                                                                     | Identical                                                                                                   |
| ISO 7198:1998                                                                     | ANSI/AAMI/ISO 7198:1998/2001/(R)2010                                                                                                                                | Identical                                                                                                   |
| ISO 7199:2009 and Amendment 1:2012                                                | ANSI/AAMI/ISO 7199:2009 and Amendment 1:2012                                                                                                                        | Identical                                                                                                   |
| ISO 8637:2010                                                                     | ANSI/AAMI/ISO 8637:2010                                                                                                                                             | Identical                                                                                                   |
| ISO 8638:2010                                                                     | ANSI/AAMI/ISO 8638:2010                                                                                                                                             | Identical                                                                                                   |

| <b>International designation</b>      | <b>U.S. designation</b>                                         | <b>Equivalency</b>         |
|---------------------------------------|-----------------------------------------------------------------|----------------------------|
| ISO 10993-1:2009                      | ANSI/AAMI/ISO 10993-1:2009                                      | Identical                  |
| ISO 10993-2:2006                      | ANSI/AAMI/ISO 10993-2:2006/(R)2010                              | Identical                  |
| ISO 10993-3:2003                      | ANSI/AAMI/ISO 10993-3:2003/(R)2009                              | Identical                  |
| ISO 10993-4:2002 and Amendment 1:2006 | ANSI/AAMI/ISO 10993-4:2002/(R)2009 and Amendment 1:2006/(R)2009 | Identical                  |
| ISO 10993-5:2009                      | ANSI/AAMI/ISO 10993-5:2009                                      | Identical                  |
| ISO 10993-6:2007                      | ANSI/AAMI/ISO 10993-6:2007/(R)2010                              | Identical                  |
| ISO 10993-7:2008                      | ANSI/AAMI/ISO 10993-7:2008/(R)2012                              | Identical                  |
| ISO 10993-9:2009                      | ANSI/AAMI/ISO 10993-9:2009                                      | Identical                  |
| ISO 10993-10:2010                     | ANSI/AAMI/ISO 10993-10:2010                                     | Identical                  |
| ISO 10993-11:2006                     | ANSI/AAMI/ISO 10993-11:2006/(R)2010                             | Identical                  |
| ISO 10993-12:2012                     | ANSI/AAMI/ISO 10993-12:2012                                     | Identical                  |
| ISO 10993-13:2010                     | ANSI/AAMI/ISO 10993-13:2010                                     | Identical                  |
| ISO 10993-14:2001                     | ANSI/AAMI/ISO 10993-14:2001/(R)2006                             | Identical                  |
| ISO 10993-15:2000                     | ANSI/AAMI/ISO 10993-15:2000/(R)2006                             | Identical                  |
| ISO 10993-16:2010                     | ANSI/AAMI/ISO 10993-16:2010                                     | Identical                  |
| ISO 10993-17:2002                     | ANSI/AAMI/ISO 10993-17:2002/(R)2008                             | Identical                  |
| ISO 10993-18:2005                     | ANSI/AAMI BE83:2006/(R)2011                                     | Major technical variations |
| ISO/TS 10993-19:2006                  | ANSI/AAMI/ISO TIR10993-19:2006                                  | Identical                  |
| ISO/TS 10993-20:2006                  | ANSI/AAMI/ISO TIR10993-20:2006                                  | Identical                  |
| ISO 11135-1:2007                      | ANSI/AAMI/ISO 11135-1:2007                                      | Identical                  |
| ISO/TS 11135-2:2008                   | ANSI/AAMI/ISO TIR11135-2:2008                                   | Identical                  |
| ISO 11137-1:2006                      | ANSI/AAMI/ISO 11137-1:2006/(R)2010                              | Identical                  |
| ISO 11137-2:2012                      | ANSI/AAMI/ISO 11137-2:2012                                      | Identical                  |
| ISO 11137-3:2006                      | ANSI/AAMI/ISO 11137-3:2006/(R)2010                              | Identical                  |
| ISO 11138-1:2006                      | ANSI/AAMI/ISO 11138-1:2006/(R)2010                              | Identical                  |
| ISO 11138-2:2006                      | ANSI/AAMI/ISO 11138-2:2006/(R)2010                              | Identical                  |
| ISO 11138-3:2006                      | ANSI/AAMI/ISO 11138-3:2006/(R)2010                              | Identical                  |
| ISO 11138-4:2006                      | ANSI/AAMI/ISO 11138-4:2006/(R)2010                              | Identical                  |
| ISO 11138-5:2006                      | ANSI/AAMI/ISO 11138-5:2006/(R)2010                              | Identical                  |
| ISO/TS 11139:2006                     | ANSI/AAMI/ISO 11139:2006                                        | Identical                  |
| ISO 11140-1:2005                      | ANSI/AAMI/ISO 11140-1:2005/(R)2010                              | Identical                  |
| ISO 11140-3:2007                      | ANSI/AAMI/ISO 11140-3:2007/(R)2012                              | Identical                  |
| ISO 11140-4:2007                      | ANSI/AAMI/ISO 11140-4:2007/(R)2012                              | Identical                  |
| ISO 11140-5:2007                      | ANSI/AAMI/ISO 11140-5:2007/(R)2012                              | Identical                  |
| ISO 11607-1:2006                      | ANSI/AAMI/ISO 11607-1:2006/(R)2010                              | Identical                  |
| ISO 11607-2:2006                      | ANSI/AAMI/ISO 11607-2:2006/(R)2010                              | Identical                  |
| ISO 11658:2012                        | ANSI/AAMI/ISO 11658:2012                                        | Identical                  |
| ISO 11663:2009                        | ANSI/AAMI/ISO 11663:2009                                        | Identical                  |
| ISO 11737-1:2006                      | ANSI/AAMI/ISO 11737-1:2006                                      | Identical                  |
| ISO 11737-2:2009                      | ANSI/AAMI/ISO 11737-2:2009                                      | Identical                  |
| ISO/TS 12417:2011                     | ANSI/AAMI/ISO TIR12417:2011                                     | Identical                  |
| ISO 13022:2012                        | ANSI/AAMI/ISO 13022:2012                                        | Identical                  |
| ISO 13408-1:2008                      | ANSI/AAMI/ISO 13408-1:2008/(R)2011                              | Identical                  |
| ISO 13408-2:2003                      | ANSI/AAMI/ISO 13408-2:2003                                      | Identical                  |
| ISO 13408-3:2006                      | ANSI/AAMI/ISO 13408-3:2006                                      | Identical                  |
| ISO 13408-4:2005                      | ANSI/AAMI/ISO 13408-4:2005                                      | Identical                  |
| ISO 13408-5:2006                      | ANSI/AAMI/ISO 13408-5:2006                                      | Identical                  |
| ISO 13408-6:2006                      | ANSI/AAMI/ISO 13408-6:2006                                      | Identical                  |

| <b>International designation</b> | <b>U.S. designation</b>                                | <b>Equivalency</b>          |
|----------------------------------|--------------------------------------------------------|-----------------------------|
| ISO 13408-7:2012                 | ANSI/AAMI/ISO 13408-7:2012                             | Identical                   |
| ISO 13485:2003                   | ANSI/AAMI/ISO 13485:2003/(R)2009                       | Identical                   |
| ISO 13958:2009                   | ANSI/AAMI/ISO 13958:2009                               | Identical                   |
| ISO 13959:2009                   | ANSI/AAMI/ISO 13959:2009                               | Identical                   |
| ISO 14155:2011                   | ANSI/AAMI/ISO 14155:2011                               | Identical                   |
| ISO 14160:2011                   | ANSI/AAMI/ISO 14160:2011                               | Identical                   |
| ISO 14161:2009                   | ANSI/AAMI/ISO 14161:2009                               | Identical                   |
| ISO 14708-3:2008                 | ANSI/AAMI/ISO 14708-3:2008                             | Identical                   |
| ISO 14708-4:2008                 | ANSI/AAMI/ISO 14708-4:2008                             | Identical                   |
| ISO 14708-5:2010                 | ANSI/AAMI /ISO 14708-5:2010                            | Identical                   |
| ISO 14937:2009                   | ANSI/AAMI/ISO 14937:2009                               | Identical                   |
| ISO/TR 14969:2004                | ANSI/AAMI/ISO TIR14969:2004                            | Identical                   |
| ISO 14971:2007                   | ANSI/AAMI/ISO 14971:2007/(R)2010                       | Identical                   |
| ISO 15223-1:2012                 | ANSI/AAMI/ISO 15223-1:2012                             | Identical                   |
| ISO 15223-2:2010                 | ANSI/AAMI/ISO 15223-2:2010                             | Identical                   |
| ISO 15225:2010                   | ANSI/AAMI/ISO 15225:2010                               | Identical                   |
| ISO 15674:2009                   | ANSI/AAMI/ISO 15674:2009                               | Identical                   |
| ISO 15675:2009                   | ANSI/AAMI/ISO 15675:2009                               | Identical                   |
| ISO 15882:2008                   | ANSI/AAMI/ISO 15882:2008                               | Identical                   |
| ISO 15883-1:2006                 | ANSI/AAMI ST15883-1:2009 and A2:2012                   | Major technical variations  |
| ISO/TR 16142:2006                | ANSI/AAMI/ISO TIR16142:2005                            | Identical                   |
| ISO 17664:2004                   | ANSI/AAMI ST81:2004                                    | Major technical variations  |
| ISO 17665-1:2006                 | ANSI/AAMI/ISO 17665-1:2006                             | Identical (with inclusions) |
| ISO/TS 17665-2:2009              | ANSI/AAMI/ISO TIR17665-2:2009                          | Identical                   |
| ISO 18472:2006                   | ANSI/AAMI/ISO 18472:2006/(R)2010                       | Identical                   |
| ISO/TS 19218-1:2011              | ANSI/AAMI/ISO TIR19218:2011                            | Identical                   |
| ISO 20857:2010                   | ANSI/AAMI/ISO 20857:2010                               | Identical                   |
| ISO 22442-1:2007                 | ANSI/AAMI/ISO 22442-1:2007                             | Identical                   |
| ISO 22442-2:2007                 | ANSI/AAMI/ISO 22442-2:2007                             | Identical                   |
| ISO 22442-3:2007                 | ANSI/AAMI/ISO 22442-3:2007                             | Identical                   |
| ISO/TR 22442-4:2010              | ANSI/AAMI/ISO TIR22442-4:2010                          | Identical                   |
| ISO 23500:2011                   | ANSI/AAMI/ISO 23500:2011                               | Identical                   |
| ISO/TS 23810:2012                | ANSI/AAMI/ISO TIR23810:2012                            | Identical                   |
| ISO 25539-1:2003 and A1:2005     | ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009 | Identical                   |
| ISO 25539-2:2008                 | ANSI/AAMI/ISO 25539-2:2008                             | Identical                   |
| ISO 25539-3:2011                 | ANSI/AAMI/ISO 25539-3:2011                             | Identical                   |
| ISO 26722:2009                   | ANSI/AAMI/ISO 26722:2009                               | Identical                   |
| ISO 27185:2012                   | ANSI/AAMI/ISO 27185:2012                               | Identical                   |
| ISO 27186:2010                   | ANSI/AAMI/ISO 27186:2010                               | Identical                   |
| ISO 80369-1:2010                 | ANSI/AAMI/ISO 80369-1:2010                             | Identical                   |
| ISO 81060-1:2007                 | ANSI/AAMI/ISO 81060-1:2007                             | Identical                   |
| ISO 81060-2:2009                 | ANSI/AAMI/ISO 81060-2:2009                             | Identical                   |

## Committee representation

**Association for the Advancement of Medical Instrumentation**

## Renal Disease and Detoxification Committee

The adoption of IEC 60601-2-16 Ed. 4 as an American National Standard was initiated by the AAMI Renal Disease and Detoxification Committee.

Committee approval of the standard does not necessarily imply that all committee members voted for its approval. At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

**Cochairs:** Conor Curtin  
Richard A. Ward, PhD

**Members:**  
 G Steven Acres, MD, Carolina Regional Nephrology Associates  
 Larry Alexander, Florian Services  
 James Weldon Baker, AmeriWater  
 Robert Berube, Church & Dwight Co Inc.  
 Judy Brown, Ascend Clinical LLC  
 Karla S. Byrne, Rockwell Medical Inc.  
 Wayne Carlson, Minntech Corporation  
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 R. Barry Deeter, RN MSN, University of Utah Dialysis Program  
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NOTE--Participation by federal agency representatives in the development of this document does not constitute endorsement by the federal government or any of its agencies.

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# INTERNATIONAL ELECTROTECHNICAL COMMISSION

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## MEDICAL ELECTRICAL EQUIPMENT –

### **Part 2-16: Particular requirements for the basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment**

#### FOREWORD

- 1) The International Electrotechnical Commission (IEC) is a worldwide organization for standardization comprising all national electrotechnical committees (IEC National Committees). The object of IEC is to promote international co-operation on all questions concerning standardization in the electrical and electronic fields. To this end and in addition to other activities, IEC publishes International Standards, Technical Specifications, Technical Reports, Publicly Available Specifications (PAS) and Guides (hereafter referred to as “IEC Publication(s)”). Their preparation is entrusted to technical committees; any IEC National Committee interested in the subject dealt with may participate in this preparatory work. International, governmental and non-governmental organizations liaising with the IEC also participate in this preparation. IEC collaborates closely with the International Organization for Standardization (ISO) in accordance with conditions determined by agreement between the two organizations.
- 2) The formal decisions or agreements of IEC on technical matters express, as nearly as possible, an international consensus of opinion on the relevant subjects since each technical committee has representation from all interested IEC National Committees.
- 3) IEC Publications have the form of recommendations for international use and are accepted by IEC National Committees in that sense. While all reasonable efforts are made to ensure that the technical content of IEC Publications is accurate, IEC cannot be held responsible for the way in which they are used or for any misinterpretation by any end user.
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- 6) All users should ensure that they have the latest edition of this publication.
- 7) No liability shall attach to IEC or its directors, employees, servants or agents including individual experts and members of its technical committees and IEC National Committees for any personal injury, property damage or other damage of any nature whatsoever, whether direct or indirect, or for costs (including legal fees) and expenses arising out of the publication, use of, or reliance upon, this IEC Publication or any other IEC Publications.
- 8) Attention is drawn to the Normative references cited in this publication. Use of the referenced publications is indispensable for the correct application of this publication.
- 9) Attention is drawn to the possibility that some of the elements of this IEC Publication may be the subject of patent rights. IEC shall not be held responsible for identifying any or all such patent rights.

International standard IEC 60601-2-16 has been prepared by IEC subcommittee 62D: Electromedical equipment, of IEC technical committee 62: Electrical equipment in medical practice.

This fourth edition cancels and replaces the third edition of IEC 60601-2-16, published in 2008. This edition constitutes a technical revision. Changes since the previous edition include, among others, better adaptation of IEC 60601-1-8 and improvement of subclause 201.8.3.

The text of this particular standard is based on the following documents:

|              |                  |
|--------------|------------------|
| FDIS         | Report on voting |
| 62D/972/FDIS | 62D/987/RVD      |

Full information on the voting for the approval of this particular standard can be found in the report on voting indicated in the above table.

This publication has been drafted in accordance with the ISO/IEC Directives, Part 2.

In this standard, the following print types are used:

- Requirements and definitions: roman type.
- *Test specifications: italic type.*
- Informative material appearing outside of tables, such as notes, examples and references: in smaller type. Normative text of tables is also in a smaller type.
- TERMS DEFINED IN CLAUSE 3 OF THE GENERAL STANDARD, IN THIS PARTICULAR STANDARD OR AS NOTED: SMALL CAPITALS.

In referring to the structure of this standard, the term

- “clause” means one of the seventeen numbered divisions within the table of contents, inclusive of all subdivisions (e.g. Clause 7 includes subclauses 7.1, 7.2, etc.);
- “subclause” means a numbered subdivision of a clause (e.g. 7.1, 7.2 and 7.2.1 are all subclauses of Clause 7).

References to clauses within this standard are preceded by the term “Clause” followed by the clause number. References to subclauses within this particular standard are by number only.

In this standard, the conjunctive “or” is used as an “inclusive or” so a statement is true if any combination of the conditions is true.

The verbal forms used in this standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this standard, the auxiliary verb:

- “shall” means that compliance with a requirement or a test is mandatory for compliance with this standard;
- “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this standard;
- “may” is used to describe a permissible way to achieve compliance with a requirement or test.

An asterisk (\*) as the first character of a title or at the beginning of a paragraph or table title indicates that there is guidance or rationale related to that item in Annex AA.

A list of all parts of the IEC 60601 series, published under the general title: *Medical electrical equipment*, can be found on the IEC website.

The committee has decided that the contents of this publication will remain unchanged until the stability date indicated on the IEC web site under "<http://webstore.iec.ch>" in the data related to the specific publication. At this date, the publication will be

- reconfirmed,
- withdrawn,
- replaced by a revised edition, or
- amended.

**IMPORTANT – The 'color inside' logo on the cover page of this publication indicates that it contains colors which are considered to be useful for the correct understanding of its contents. Users should therefore print this document using a color printer.**

## INTRODUCTION

The minimum safety requirements specified in this particular standard are considered to provide for a practical degree of safety in the operation of HEMODIALYSIS, HEMODIAFILTRATION and HEMOFILTRATION EQUIPMENT.

**MEDICAL ELECTRICAL EQUIPMENT –****Part 2-16: Particular requirements for the basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment****201.1 Scope, object and related standards**

Clause 1 of the general standard<sup>1</sup> applies, except as follows:

**201.1.1 Scope***Addition:*

This International Standard applies to the BASIC SAFETY and ESSENTIAL PERFORMANCE of HEMODIALYSIS, HEMODIAFILTRATION and HEMOFILTRATION EQUIPMENT, hereafter referred to as HEMODIALYSIS EQUIPMENT.

This International Standard does not take into consideration the DIALYSIS FLUID control system of HEMODIALYSIS EQUIPMENT using regeneration of DIALYSIS FLUID and CENTRAL DELIVERY SYSTEMS. It does however take into consideration the specific safety requirements of such HEMODIALYSIS EQUIPMENT concerning electrical safety and PATIENT safety.

This International Standard specifies the minimum safety requirements for HEMODIALYSIS EQUIPMENT. These devices are intended for use either by medical staff or for use by the PATIENT or other trained personnel under the supervision of medical expertise.

This International Standard includes all ME EQUIPMENT that is intended to deliver a HEMODIALYSIS, HEMODIAFILTRATION and HEMOFILTRATION treatment to a PATIENT suffering from kidney failure.

The particular requirements in this International standard do not apply to:

- EXTRACORPOREAL CIRCUITS;
- DIALYZERS;
- DIALYSIS FLUID CONCENTRATES;
- water treatment equipment;
- equipment used to perform PERITONEAL DIALYSIS (see IEC 60601-2-39).

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<sup>1</sup> The general standard is IEC 60601-1:2005, *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance*.

If a clause or subclause is specifically intended to be applicable to ME EQUIPMENT only, or to ME SYSTEMS only, the title and content of that clause or subclause will say so. If that is not the case, the clause or subclause applies both to ME EQUIPMENT and to ME SYSTEMS, as relevant.

HAZARDS inherent in the intended physiological function of ME EQUIPMENT or ME SYSTEMS within the scope of this standard are not covered by specific requirements in this standard except in 7.2.13 and 8.4.1 of IEC 60601-1.

NOTE See also 4.2 of IEC 60601-1:2005.

### **201.1.2 Object**

#### *Replacement:*

The object of this particular standard is to establish BASIC SAFETY and ESSENTIAL PERFORMANCE requirements for HEMODIALYSIS EQUIPMENT

### **201.1.3 Collateral standards**

#### *Addition:*

This particular standard refers to those applicable collateral standards that are listed in Clause 2 of IEC 60601-1, and Clause 201.2 of this International Standard.

IEC 60601-1-2, IEC 60601-1-8, IEC 60601-1-10 and IEC 60601-11 apply as modified in Clauses 202, 208, 210 and 211 respectively. IEC 60601-1-3 does not apply. All other published collateral standards in the IEC 60601-1 series apply as published..

### **201.1.4 Particular standards**

#### *Replacement:*

In the IEC 60601 series, particular standards may modify, replace or delete requirements contained in the general standard and collateral standards as appropriate for the particular ME EQUIPMENT under consideration, and may add other BASIC SAFETY and ESSENTIAL PERFORMANCE requirements.

A requirement of a particular standard takes priority over IEC 60601-1.

For brevity, IEC 60601-1 is referred to in this particular standard as the general standard. Collateral standards are referred to by their document number.

The numbering of clauses and subclauses of this particular standard corresponds to that of the general standard with the prefix "201" (e.g. 201.1 in this standard addresses the content of Clause 1 of the general standard) or applicable collateral standard with the prefix "20x" where x is the final digit(s) of the collateral standard document number (e.g. 202.4 in this particular standard addresses the content of Clause 4 of the IEC 60601-1-2 collateral standard, 203.4 in this particular standard addresses the content of Clause 4 of the IEC 60601-1-3 collateral standard, etc.). The changes to the text of the general standard are specified by the use of the following words:

"Replacement" means that the clause or subclause of the general standard or applicable collateral standard is replaced completely by the text of this particular standard.

"Addition" means that the text of this particular standard is additional to the requirements of the general standard or applicable collateral standard.

"Amendment" means that the clause or subclause of the general standard or applicable collateral standard is amended as indicated by the text of this particular standard.

Subclauses, figures or tables which are additional to those of the general standard are numbered starting from 201.101. However due to the fact that definitions in the general standard are numbered 3.1 through 3.139, additional definitions in this standard are numbered beginning from 201.3.201. Additional annexes are lettered AA, BB, etc., and additional items aa), bb), etc.

Subclauses, figures or tables which are additional to those of a collateral standard are numbered starting from 20x, where "x" is the number of the collateral standard, e.g. 202 for IEC 60601-1-2, 203 for IEC 60601-1-3, etc.

The term "this standard" is used to make reference to the general standard, any applicable collateral standards and this particular standard taken together.

Where there is no corresponding, clause or subclause in this particular standard, the clause or subclause of the general standard or applicable collateral standard, although possibly not relevant, applies without modification; where it is intended that any part of the general standard or applicable collateral standard, although possibly relevant, is not to be applied, a statement to that effect is given in this particular standard.

## **201.2 Normative references**

NOTE Informative references are listed in the bibliography beginning on page 63.

Clause 2 of the general standard applies, except as follows:

### *Amendment:*

IEC 60601-1-2:2007, *Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests*

IEC 60601-1-6:2010, *Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability*

IEC 60601-1-8:2006, *Medical electrical equipment – Part 1-8: General requirements for basic safety and essential performance – Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.*

### *Addition:*

IEC 60601-1-10:2007, *Medical electrical equipment – Part 1-10: General requirements for basic safety and essential performance – Collateral Standard: Requirements for the development of physiologic closed-loop controllers*

IEC 60601-1-11:2010, *Medical electrical equipment – Part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment*

IEC 62366:2007, *Medical devices – Application of usability engineering to medical devices*

ISO 594-2, *Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment – Part 2: Lock fittings*

ISO 3744, *Acoustics – Determination of sound power levels of noise sources using sound pressure – Engineering method in an essentially free field over a reflecting plane*

ISO 8638, *Cardiovascular implants and artificial organs – Extracorporeal blood circuit for haemodialysers, haemodiafilters and haemofilters*

### **201.3 Terms and definitions**

For the purposes of this document, the terms and definitions given in IEC 60601-1:2005, and IEC 60601-1-10:2007 apply, except as follows:

NOTE An index of defined terms is found beginning on page 64.

#### **201.3.8**

##### **\*APPLIED PART**

*Replacement:*

EXTRACORPOREAL CIRCUIT and all parts permanently and conductively connected to it (e.g. DIALYSIS FLUID circuit)

Note 1 to entry: See Figure AA.1 in Annex AA.

#### **201.3.78**

##### **PATIENT CONNECTION**

*Addition:*

Note 1 to entry: The PATIENT blood lines connectors are the individual points on the APPLIED PART through which current can flow between the PATIENT and the HEMODIALYSIS EQUIPMENT in NORMAL CONDITION or SINGLE FAULT CONDITION.

*Additions:*

#### **201.3.201**

##### **ARTERIAL PRESSURE**

pressure measured in the blood withdrawal line of the EXTRACORPOREAL CIRCUIT

Note 1 to entry: A difference can be made between the pre-pump pressure, which is upstream of the blood pump, and post pump pressure, which is downstream of the blood pump .

#### **201.3.202**

##### **\*BLOOD LEAK**

leakage of blood from the blood compartment to the DIALYSIS FLUID compartment of the DIALYZER

Note 1 to entry: When performing an HF process, this involves the filtration fluid section.



### **201.3.203**

#### **CENTRAL DELIVERY SYSTEM**

part of a ME SYSTEM which proportions DIALYSIS FLUID CONCENTRATE and water for distribution as DIALYSIS FLUID to the HEMODIALYSIS EQUIPMENT or distributes DIALYSIS FLUID CONCENTRATE

### **201.3.204**

#### **DIALYZER**

a device containing a semi-permeable membrane that is used to perform HD, HDF or HF

### **201.3.205**

#### **DIALYSIS FLUID**

solution intended to exchange solutes and/or water with blood during HD or HDF

Note 1 to entry: The words "dialysate", "dialysis solution" and "dialyzing fluid" are commonly used as synonyms of DIALYSIS FLUID.

### **201.3.206**

#### **DIALYSIS FLUID CONCENTRATE**

substances which, when appropriately diluted or dissolved with purified water, produce the DIALYSIS FLUID

### **201.3.207**

#### **EXTRACORPOREAL CIRCUIT**

blood lines and any integral ACCESSORY thereof

### **201.3.208**

#### **HEMODIAFILTRATION**

##### **HDF**

process whereby concentrations of water-soluble substances in a PATIENT's blood and an excess of fluid of a PATIENT with renal insufficiency are corrected by a simultaneous combination of HD and HF

### **201.3.209**

#### **HEMODIALYSIS**

##### **HD**

process whereby concentrations of water-soluble substances in a PATIENT's blood and an excess of fluid of a PATIENT with renal insufficiency are corrected by bidirectional diffusive transport and ULTRAFILTRATION across a semi-permeable membrane separating the blood from the DIALYSIS FLUID

Note 1 to entry: This process normally includes fluid removal by filtration. This process is usually also accompanied by diffusion of substances from the DIALYSIS FLUID into the blood.

### **201.3.210**

#### **\* HEMODIALYSIS EQUIPMENT**

ME EQUIPMENT or ME SYSTEM used to perform HEMODIALYSIS, HEMODIAFILTRATION and/or HEMOFILTRATION

Note 1 to entry: When the term ME EQUIPMENT is used in headings it is equivalent to HEMODIALYSIS EQUIPMENT. When the term ME EQUIPMENT is used in the text it is referring to a general ME EQUIPMENT.

### **201.3.211**

#### **HEMOFILTRATION**

##### **HF**

process whereby concentrations of water-soluble substances in a PATIENT's blood and an excess of fluid of a PATIENT with renal insufficiency are corrected by unidirectional convective transport

via ULTRAFILTRATION across a semi-permeable membrane separating the blood from the DIALYSIS FLUID AND ultrafiltrate is simultaneously replaced by an approximately isoosmolar SUBSTITUTION FLUID at a rate such that the difference between the ULTRAFILTRATION rate and the rate of SUBSTITUTION FLUID addition will lead to removal of the excess fluid over the course of the treatment

#### **201.3.212**

##### **NET FLUID REMOVAL**

fluid loss from the PATIENT

Note 1 to entry: Historically this term was “weight loss”.

#### **201.3.213**

##### **\*ONLINE HDF**

HEMODIAFILTRATION procedure where the HEMODIALYSIS EQUIPMENT, based on the DIALYSIS FLUID, produces the SUBSTITUTION FLUID for the HDF treatment, suitable for injection

#### **201.3.214**

##### **\*ONLINE HF**

HEMOFILTRATION procedure where the HEMODIALYSIS EQUIPMENT, based on the DIALYSIS FLUID, produces the SUBSTITUTION FLUID for the HF treatment, suitable for injection

#### **201.3.215**

##### **\*PROTECTIVE SYSTEM**

automatic system, or a constructional feature, specifically designed to protect the PATIENT against HAZARDS which can arise

#### **201.3.216**

##### **SUBSTITUTION FLUID**

a fluid administered to the PATIENT via the EXTRACORPOREAL CIRCUIT during HF or HDF

#### **201.3.217**

##### **TRANSMEMBRANE PRESSURE**

##### **TMP**

fluid pressure difference exerted across a semi-permeable membrane

Note 1 to entry: Generally the mean TMP is used. In practice, the displayed TRANSMEMBRANE PRESSURE is usually estimated from the measured EXTRACORPOREAL CIRCUIT pressure and the measured DIALYSIS FLUID pressure, each obtained at a single point.

#### **201.3.218**

##### **\*ULTRAFILTRATION**

process of fluid removal from the PATIENT'S blood across the DIALYZER

#### **201.3.219**

##### **VENOUS PRESSURE**

pressure measured in the blood return line of the EXTRACORPOREAL CIRCUIT

### **201.4 General requirements**

Clause 4 of the general standard applies, except as follows:

### 201.4.3 \* ESSENTIAL PERFORMANCE

*Additional subclauses:*

#### 201.4.3.101 \* Additional ESSENTIAL PERFORMANCE requirements

ESSENTIAL PERFORMANCE of HEMODIALYSIS EQUIPMENT includes, but is not limited to the functions found in the subclauses listed in Table 201.101, which shall be met within the tolerances specified by the MANUFACTURER under NORMAL CONDITIONS, if applicable:

**Table 201.101 – ESSENTIAL PERFORMANCE requirements**

| Requirement                    | Subclause   |
|--------------------------------|-------------|
| Blood flow                     | 201.4.3.102 |
| DIALYSIS FLUID flow            | 201.4.3.103 |
| NET FLUID REMOVAL              | 201.4.3.104 |
| SUBSTITUTION FLUID flow        | 201.4.3.105 |
| Dialysis time                  | 201.4.3.106 |
| DIALYSIS FLUID composition     | 201.4.3.107 |
| DIALYSIS FLUID temperature     | 201.4.3.108 |
| SUBSTITUTION FLUID temperature | 201.4.3.109 |

NOTE Some ESSENTIAL PERFORMANCES listed in Table 201.101 are dependent on the characteristics of the disposable used (e.g. blood flow is dependent upon the pump segment inner diameter in rotary peristaltic pumps).

#### 201.4.3.102 Blood flow

The blood flow for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

NOTE 1 Only a blood flow lower than the set value is considered as negative for the treatment. Therefore the goal of testing is to find the highest negative blood flow error.

*Compliance is checked under the following test conditions for typical peristaltic pumps.*

- Apply a pump segment to the HEMODIALYSIS EQUIPMENT and let it run for at least 30 min.
- Apply a fluid (e.g. water) with a temperature of 37 °C in the EXTRACORPOREAL CIRCUIT.
- Set the blood flow of the HEMODIALYSIS EQUIPMENT to 400 ml/min or – if not possible - to the highest possible blood flow.
- Set the ARTERIAL PRESSURE to -200 mmHg.
- Measure the blood flow.

*The values of the measured blood flow shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

NOTE 2 Pump segment fatigue can reduce the blood flow rate.

NOTE 3 The blood flow rate in peristaltic pumps can be affected by negative input pressures

#### 201.4.3.103 DIALYSIS FLUID flow

*The DIALYSIS FLUID flow for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.*

NOTE Only a DIALYSIS FLUID flow lower than the set value is considered as negative for the treatment.

*Compliance is checked under the following test conditions.:*

- Set the HEMODIALYSIS EQUIPMENT to the HEMODIALYSIS mode as specified by the MANUFACTURER.
- Set the HEMODIALYSIS EQUIPMENT to maximum DIALYSIS FLUID flow.  
*Measure the DIALYSIS FLUID flow during 30 min.*
- Set the HEMODIALYSIS EQUIPMENT to minimum DIALYSIS FLUID flow.
- Measure the DIALYSIS FLUID flow during 30 min.

*The values of the DIALYSIS FLUID flow shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

#### **201.4.3.104 NET FLUID REMOVAL**

The NET FLUID REMOVAL for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

*Compliance is checked under the following test conditions.*

*Test 1 for the balancing part of the HEMODIALYSIS EQUIPMENT only:*

- Set the HEMODIALYSIS EQUIPMENT in the HEMODIALYSIS mode, if applicable, with a DIALYZER according to the MANUFACTURER's recommendation.
- Apply fluid (e.g. water) in THE EXTRACORPOREAL CIRCUIT.
- Set the highest DIALYSIS FLUID flow, if applicable.
- Set the DIALYSIS FLUID temperature to 37 °C, if applicable.
- Set the NET FLUID REMOVAL rate to 0 ml/h or the lowest adjustable value.
- Create a blood outlet pressure of 50 mmHg below the highest pressure specified by the MANUFACTURER.
- Measure the NET FLUID REMOVAL during an appropriate time interval.

*Continue with test 2:*

- Set the NET FLUID REMOVAL rate to the maximum value.
- Measure the NET FLUID REMOVAL during an appropriate time interval.

*Continue with test 3:*

- Create a blood outlet pressure 20 mmHg above the lowest specified pressure.
- Measure the NET FLUID REMOVAL during an appropriate time interval.

*The values of the NET FLUID REMOVAL shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

#### **201.4.3.105 SUBSTITUTION FLUID flow**

For HEMOFILTRATION and HEMODIAFILTRATION equipment only:

The SUBSTITUTION FLUID flow for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

NOTE Only a SUBSTITUTION FLUID flow lower than the set value is considered as negative for the treatment.

*Compliance is checked under the following test conditions:*

*Test 1 for the balancing part of the HEMODIALYSIS EQUIPMENT and of the therapeutic relevant SUBSTITUTION FLUID flow:*

- *Set the HEMODIALYSIS EQUIPMENT to the HDF or HF mode with a DIALYZER according to the MANUFACTURER's recommendation.*
- *Apply fluid (e.g. water) in the EXTRACORPOREAL CIRCUIT.*
- *Set the NET FLUID REMOVAL flow to 0 ml/h, or – if not possible – to the minimum.*
- *Set the maximum SUBSTITUTION FLUID flow.*
- *Set the temperature of the SUBSTITUTION FLUID to 37 °C, if applicable.*
- *Measure the SUBSTITUTION FLUID flow and the NET FLUID REMOVAL.*

*Continue with test 2:*

- *Set the minimum SUBSTITUTION FLUID flow.*
- *Measure the SUBSTITUTION FLUID flow and the NET FLUID REMOVAL.*

*The values of SUBSTITUTION FLUID flow and NET FLUID REMOVAL shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

#### **201.4.3.106 Dialysis time**

The accuracy of the dialysis time for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

*Compliance is checked by functional measurements relevant for the definition of dialysis time specified by the MANUFACTURER.*

#### **201.4.3.107 \* DIALYSIS FLUID composition**

*Test method specified by the MANUFACTURER.*

#### **201.4.3.108 DIALYSIS FLUID temperature**

The DIALYSIS FLUID temperature for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

NOTE This test applies only to HEMODIALYSIS EQUIPMENT having a heater for the DIALYSIS FLUID.

*Compliance is checked under the following test conditions:*

- *Let the HEMODIALYSIS EQUIPMENT run until it is in a thermally stable condition.*
- *The environmental temperature is within 20 °C to 25 °C.*
- *Set the DIALYSIS FLUID temperature to 37 °C, if applicable.*
- *Set the highest DIALYSIS FLUID flow.*

- *Measure the temperature at the DIALYZER inlet.*
- *Record the temperature during a period of 30 min.*
- *Set the lowest DIALYSIS FLUID flow.*
- *Measure the temperature at the DIALYZER inlet.*
- *Record the temperature during a period of 30 min.*

*The values of the DIALYSIS FLUID temperature shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

#### **201.4.3.109 SUBSTITUTION FLUID temperature**

The tolerances of the SUBSTITUTION FLUID temperature for the HEMODIALYSIS EQUIPMENT shall be as specified by the MANUFACTURER.

NOTE This test applies only to HEMODIALYSIS EQUIPMENT having a heater for the SUBSTITUTION FLUID.

*Compliance is checked under the following test conditions.*

- *Let the HEMODIALYSIS EQUIPMENT run until it is in a thermally stable condition.*
- *The environmental temperature is within 20 °C to 25 °C.*
- *Set the SUBSTITUTION FLUID temperature to 37 °C, if applicable.*
- *Set the highest SUBSTITUTION FLUID flow.*
- *Measure the temperature of the SUBSTITUTION FLUID at the connection point of the SUBSTITUTION FLUID line to the blood line.*
- *Record the temperature over a period of 30 min.*
- *Set the lowest SUBSTITUTION FLUID flow.*
- *Measure the temperature of the SUBSTITUTION FLUID at the connection point of the SUBSTITUTION FLUID line to the blood line.*
- *Record the temperature over a period of 30 min.*

*The values of the SUBSTITUTION FLUID temperature shall be within the tolerances specified by the MANUFACTURER in the instructions for use.*

#### **201.4.7 SINGLE FAULT CONDITION for ME EQUIPMENT**

*Addition:*

An example of SINGLE FAULT CONDITION is a failure of a PROTECTIVE SYSTEM (see 201.12.4.4.101, 201.12.4.4.102, 201.12.4.4.103, 201.12.4.4.104, 201.12.4.4.105);

NOTE If air is permanently present in the EXTRACORPOREAL CIRCUIT when the HEMODIALYSIS EQUIPMENT is used as intended by the MANUFACTURER, the air is not regarded as a SINGLE FAULT CONDITION, but as NORMAL CONDITION.

### **201.5 General requirements for testing of ME EQUIPMENT**

Clause 5 of the general standard applies.

## **201.6 Classification of ME EQUIPMENT and ME SYSTEMS**

Clause 6 of the general standard applies.

## **201.7 ME EQUIPMENT identification, marking and documents**

Clause 7 of the general standard applies, except as follows:

### **201.7.4.3 Units of measure**

*Addition:*

mmHg may be used for measurement of pressures in any part of the HEMODIALYSIS EQUIPMENT.

### **201.7.9.2 Instructions for use**

#### **201.7.9.2.2 Warning and safety notices**

*Addition:*

The instructions for use shall additionally include the following, if applicable:

- a statement which draws the OPERATOR's attention to the precautions necessary to prevent any cross-infection between PATIENTS;
- a statement which draws the OPERATOR's attention to the HAZARDS associated with connection and disconnection of the PATIENT;
- a statement which draws the OPERATOR's attention to the potential HAZARDS including any HAZARDOUS SITUATIONS arising from improper connections of the EXTRACORPOREAL CIRCUIT;
- a statement on the HAZARDS related to incorrect choice of DIALYSIS FLUID CONCENTRATE(S);
- a quantitative description of the possible deviation of each component of the DIALYSIS FLUID in SINGLE FAULT CONDITION depending on the ALARM LIMITS of the PROTECTIVE SYSTEM;
- \* a statement on the potential HAZARDS related to a possible transport of undesired substances from the DIALYSIS FLUID compartment to the blood compartment of the DIALYZER;
- for the PROTECTIVE SYSTEM employed according to 201.12.4.4.104 1a) Note 2:
  - a warning stating that this PROTECTIVE SYSTEM reduces the HAZARD in part only and an explanation of the remaining HAZARDS;
  - a description of further measures to reduce the RISK;
- an explanation of the adequate OPERATOR action upon an alarm and potential HAZARDS, if the alarm is repeatedly cleared without solving the underlying problem;
- \* a warning specifying that any narrow passages in the EXTRACORPOREAL CIRCUIT (such as kinks in the blood line or cannula that are too thin) may cause hemolysis and that this HAZARDOUS SITUATION may not be detected by the PROTECTIVE SYSTEMS;
- if a PROTECTIVE SYSTEM, according to 201.12.4.4.105 a) Note 1, is applied: a warning stating that improper functioning of an ultrasonic air detector may be caused by a coagulum or the application of ultrasound gel;
- a warning stating that air may enter into the EXTRACORPOREAL CIRCUIT at connection points downstream of the air detector, if pressures are negative; this can occur in cases such as single needle applications or central venous catheter applications;

- for ONLINE HDF and ONLINE HF:
  - a warning stating that only the disinfection procedures defined and validated by the MANUFACTURER may be used for ONLINE HDF and ONLINE HF;
  - information on the required quality of the incoming water and of the DIALYSIS FLUID CONCENTRATES used;
  - intervals at which wearing parts (e.g. filter) should be exchanged;
- a warning that the blood flow and thus the treatment efficacy may be reduced when the pre-pump ARTERIAL PRESSURE is extremely negative; and the range and accuracy of the flow of such pump(s) and the inlet and outlet pressure range over which this accuracy is maintained.
- for HEMODIALYSIS EQUIPMENT with APPLIED PARTS other than TYPE CF APPLIED PARTS a warning, addressed to both the OPERATOR and the RESPONSIBLE ORGANIZATION, to ensure that no electrical equipment (non-ME EQUIPMENT and ME EQUIPMENT) with TOUCH CURRENTS and PATIENT LEAKAGE CURRENTS above the respective limits for type CF APPLIED PARTS is used in the PATIENT ENVIRONMENT in combination with central venous catheters with atrial location.

NOTE For information see subclause 201.8.3 in Annex AA

#### **201.7.9.2.5 ME EQUIPMENT description**

*Addition:*

The instructions for use shall additionally include the following, if applicable:

- a definition of TRANSMEMBRANE PRESSURE if the MANUFACTURER makes use of one different from that stated in 201.3.217;
- an explanation of the colored markings on the DIALYSIS FLUID CONCENTRATE connectors;
- information on the effective delivered blood flow in single-needle treatments;
- information on the recirculation of blood in the EXTRACORPOREAL CIRCUIT in single-needle treatments;
- the delay time after which an audible alarm is activated after interruption of the power supply;
- for PHYSIOLOGIC CLOSED-LOOP CONTROLLER functions:
  - a) the technical working principle;
  - b) the PATIENT parameters which are measured and the physiological parameters which are controlled;
  - c) the methods by which these feedback control modes have been evaluated including beneficial and adverse effects recorded during clinical testing;
 see also the collateral standard IEC 60601-1-10.
- \* for any data that is displayed or indicated by the HEMODIALYSIS EQUIPMENT and that may be used for adjusting the treatment or measuring or confirming the treatment efficacy:
  - a) a description of the technical working principle;
  - b) if the measurement is indirect: a statement to the accuracy and possible influencing factors;
  - c) the method by which the technical working principle has been evaluated relative to standard medical care;
- for HEMODIALYSIS EQUIPMENT with APPLIED PARTS other than TYPE CF APPLIED PARTS a statement if this HEMODIALYSIS EQUIPMENT can be used together with central venous catheters with atrial location. If the HEMODIALYSIS EQUIPMENT is not suitable for central venous catheters with atrial location possible HAZARDS shall be listed.



#### **201.7.9.2.6 Installation**

*Addition:*

The instructions for use shall additionally include the following, if applicable:

- a statement that it is essential for the HEMODIALYSIS EQUIPMENT to be installed and used in compliance with appropriate regulations/recommendations on quality of water and other relevant fluids;
- for CLASS I HEMODIALYSIS EQUIPMENT, a statement of the importance of the quality of the protective earth in the electrical installation;
- a statement of the applications in which a POTENTIAL EQUALIZATION CONDUCTOR should be used;
- the acceptable range of temperature, flow and pressure for inlet water and any CENTRAL DELIVERY SYSTEM;
- a note emphasizing the importance of compliance with all local regulations regarding the separation of the HEMODIALYSIS EQUIPMENT from the water supply, the prevention of back flow to the potable water source, and prevention of contamination via the drain connection of the HEMODIALYSIS EQUIPMENT from any sewer connection;
- if different schemes for color coding of visual alarms can be configured, a statement that the RESPONSIBLE ORGANIZATION should select the color coding scheme which minimizes the RISK of confusion in their environment;
- if settings of operating parameters or PROTECTIVE SYSTEMS can be configured, a statement that the RESPONSIBLE ORGANIZATION should select the configuration(s) or explicitly confirm the default configuration.

#### **201.7.9.2.12 Cleaning, disinfection and sterilization**

*Addition:*

The instructions for use shall additionally include the following, if applicable:

- a description of the method(s) by which sanitization or disinfection is achieved;
- \* a statement that the test procedure by which the effectiveness of sanitization or disinfection has been verified is available on request;
- a warning stating to follow the MANUFACTURER'S instructions to disinfect the HEMODIALYSIS EQUIPMENT. If other procedures are used it is the responsibility of the RESPONSIBLE ORGANIZATION to validate the disinfection procedure for efficacy and safety. This warning shall specifically list HAZARDS including the failure mode that may result from other procedures;
- a warning that the RESPONSIBLE ORGANIZATION is responsible for the hygienic quality of any delivery system(s), e.g. central water supply system, CENTRAL DELIVERY SYSTEMS, HEMODIALYSIS EQUIPMENT connecting devices, including the fluid lines from connection points to the HEMODIALYSIS EQUIPMENT.

#### **201.7.9.2.14 ACCESSORIES, supplementary equipment, used material**

*Addition:*

The instructions for use shall additionally include the following, if applicable:

- information on DIALYSIS FLUID CONCENTRATES, DIALYZERS and blood lines intended to be used together with the HEMODIALYSIS EQUIPMENT.

*Compliance is checked by inspection of the instructions for use.*

### **201.7.9.3 Technical description**

#### **201.7.9.3.1 General**

*Addition:*

The technical description shall additionally include the following, if applicable:

- *Installation:*
  - a description of the particular measures or conditions to be observed when installing the HEMODIALYSIS EQUIPMENT or bringing it into use. These shall include guidance on the type and number of tests to be carried out;
  - the maximum temperature which can occur at the drain of the HEMODIALYSIS EQUIPMENT;
  - \* information about energy consumption, energy delivery to the environment and energy delivery to the drain under typical operating conditions and as a function of inlet water temperature;
  - \* information about consumption of water and DIALYSIS FLUID CONCENTRATE(S) under typical operating conditions;
- *Device specification:*
  - \* for HEMODIALYSIS EQUIPMENT that includes integral anticoagulant pump(s): the type of the pump(s), the range and the accuracy of the flow for such pump(s) and the pressures against which this accuracy is maintained;
  - any additional measures foreseen by the MANUFACTURER in case of the interruption of the power supply;
  - the type, the measurement accuracy and the value(s) or range(s) of the ALARM LIMIT(s) of the PROTECTIVE SYSTEM required by 201.12.4.4.101 (DIALYSIS FLUID composition);
  - the type, the measurement accuracy and the value(s) or range of the ALARM LIMIT(s) of the PROTECTIVE SYSTEM required by 201.12.4.4.102 (DIALYSIS FLUID and SUBSTITUTION FLUID temperature);
  - the type, the measurement accuracy and the value(s) or range(s) of the ALARM LIMIT(s) of the PROTECTIVE SYSTEM required by 201.12.4.4.103 (NET FLUID REMOVAL);
  - the type, the measurement accuracy and the value(s) or range(s) of the ALARM LIMIT(s) of the PROTECTIVE SYSTEM required by 201.12.4.4.104.1 (extracorporeal blood loss to the environment);
  - \* the type and the measurement accuracy of the PROTECTIVE SYSTEM required by 201.12.4.4.104.2 (BLOOD LEAK to the DIALYSIS FLUID) and the ALARM LIMIT of the PROTECTIVE SYSTEM at the minimum and maximum flow through the BLOOD LEAK detector;
  - the type and the ALARM LIMIT(s) of the PROTECTIVE SYSTEM required by 201.12.4.4.104.3 (extracorporeal blood loss due to coagulation);
  - the method employed and the sensitivity under test conditions specified by the MANUFACTURER for the PROTECTIVE SYSTEM required by 201.12.4.4.105 (air infusion);
  - the override time(s) for any PROTECTIVE SYSTEM;

- the audible alarm AUDIO PAUSED period;
- the range of sound pressure levels of any adjustable audible alarm source;
- a disclosure of all materials intended to come into contact with the water, DIALYSIS FLUID and DIALYSIS FLUID CONCENTRATE;
- for ONLINE HDF and ONLINE HF: the method of preparation of the SUBSTITUTION FLUID, the method of the automatic integrity test of the SUBSTITUTION FLUID filters (if applicable) and the accuracy of these tests.

*Compliance is checked by inspection of the technical description.*

## **201.8 Protection against electrical HAZARDS from ME EQUIPMENT**

Clause 8 of the general standard applies, except as follows:

### **201.8.3 \* Classification of APPLIED PARTS**

*Addition:*

HEMODIALYSIS EQUIPMENT with LEAKAGE CURRENTS complying with TYPE CF APPLIED PARTS requirements are considered to be suitable for being used with central venous catheters with atrial location.

If HEMODIALYSIS EQUIPMENT having an APPLIED PART other than a TYPE CF APPLIED PART is intended to be used for treatment of PATIENTS with central venous catheter(s) with atrial location, the following shall apply:

- aa) under NORMAL CONDITIONS, the PATIENT LEAKAGE CURRENTS and the TOUCH CURRENTS shall be within the limits for TYPE CF APPLIED PARTS.
- bb) under SINGLE FAULT CONDITIONS, the PATIENT LEAKAGE CURRENTS, TOUCH CURRENTS and EARTH LEAKAGE CURRENTS shall be within the limits for TYPE CF APPLIED PARTS.

If the HEMODIALYSIS EQUIPMENT does not comply with point 2, external means have to be provided justified by the MANUFACTURER'S RISK MANAGEMENT PROCESS to keep the PATIENT LEAKAGE CURRENT within the limits for TYPE CF APPLIED PARTS under SINGLE FAULT CONDITIONS.

*Compliance is checked by inspection*

#### **201.8.7.4.7 Measurement of the PATIENT LEAKAGE CURRENT**

*Addition:*

- \* aa) *The measuring device shall be connected where both extracorporeal blood lines are connected to the PATIENT. For the duration of the test, a test solution with the highest selectable conductivity, referenced to a temperature of 25 °C, and to the highest selectable DIALYSIS FLUID temperature in the application, shall be flowing in the DIALYSIS FLUID circuit and in the EXTRACORPOREAL CIRCUIT. The HEMODIALYSIS EQUIPMENT shall be operated in typical treatment mode with highest possible blood flow and no alarms activated. For practical reasons the measuring device may be connected to the DIALYSIS FLUID connectors.*

NOTE 101 The measurement of PATIENT LEAKAGE CURRENTS described above does not include the measurement according to 8.7.4.7b) (voltage applied to the APPLIED PART) of the general standard for HEMODIALYSIS EQUIPMENT with TYPE B APPLIED PARTS.

NOTE 102 The highest possible blood flow leads to the lowest resistance of the air gap in the venous drip chamber

#### **201.8.11.2 \* MULTIPLE SOCKET-OUTLETS**

*Addition:*

If a MULTIPLE SOCKET-OUTLET is provided and a mutual interchange or interchange with other MULTIPLE SOCKET-OUTLETS of the HEMODIALYSIS EQUIPMENT could create a HAZARDOUS SITUATION, the MULTIPLE SOCKET-OUTLET shall be of a type, which prevents such an interchange.

*Compliance is checked by inspection and functional test*

### **201.9 Protection against MECHANICAL HAZARDS of ME EQUIPMENT and ME SYSTEMS**

Clause 9 of the general standard applies.

### **201.10 Protection against unwanted and excessive radiation HAZARDS**

Clause 10 of the general standard applies.

### **201.11 Protection against excessive temperatures and other HAZARDS**

Clause 11 of the general standard applies, except as follows:

#### **201.11.6.3 Spillage on ME EQUIPMENT and ME SYSTEMS**

*Addition:*

*Compliance is checked by test according to code IPX1 of IEC 60529.*

#### **201.11.6.6 \*Cleaning and disinfection of ME EQUIPMENT and ME SYSTEMS**

*Addition:*

For HEMODIALYSIS EQUIPMENT employing non-disposable fluid lines, means shall be provided for disinfection of such fluid lines.

The disinfection procedures shall not deteriorate internal components or external accessories (e.g. DIALYSIS FLUID filters) that could become a HAZARD.

*Compliance is checked by inspection of the ACCOMPANYING DOCUMENTS and of the HEMODIALYSIS EQUIPMENT.*

#### **201.11.8 \*Interruption of the power supply / SUPPLY MAINS to ME EQUIPMENT**

*Addition:*

a) HEMODIALYSIS EQUIPMENT without INTERNAL ELECTRICAL POWER SOURCE:

In the event of an interruption of the power supply / SUPPLY MAINS to the HEMODIALYSIS EQUIPMENT, the following safe conditions shall be achieved:

- activation of an audible ALARM SIGNAL, lasting for at least 1 min;
- additional measures may be needed as determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS;
- the HEMODIALYSIS EQUIPMENT may restart automatically on restoration of the power supply, only if this does not cause any HAZARD to the PATIENT as determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS.

*Compliance is checked by inspection of the RISK MANAGEMENT FILE and by functional tests.*

b) HEMODIALYSIS EQUIPMENT with INTERNAL ELECTRICAL POWER SOURCE:

In the event of an interruption of the power supply / SUPPLY MAINS to the HEMODIALYSIS EQUIPMENT, the following safe conditions shall be achieved:

- activation of a visual ALARM SIGNAL;
- activation of an audible ALARM SIGNAL after a time interval specified by the MANUFACTURER;
- additional measures may be needed as determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS;
- if functions of the HEMODIALYSIS EQUIPMENT were stopped in the event of an interruption of the power supply they may restart automatically on restoration of the power supply only if this does not cause any HAZARD to the PATIENT as determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS;
- if the INTERNAL ELECTRICAL POWER SOURCE is interrupted or discharged, the HEMODIALYSIS EQUIPMENT shall meet the requirements described in 201.11.8 a).

*Compliance is checked by inspection of the RISK MANAGEMENT FILE and by functional tests.*

## **201.12 \* Accuracy of controls and instruments and protection against hazardous outputs**

Clause 12 of the general standard applies, except as follows:

### **201.12.4.4 Incorrect output**

*Addition:*

The test procedures in the following subclauses give an overview of the minimum requirements for the validation of HEMODIALYSIS EQUIPMENT. All details are not included for each test procedure and it is incumbent upon the test laboratory to address these details based on the specific HEMODIALYSIS EQUIPMENT and the MANUFACTURER'S RISK MANAGEMENT PROCESS.

#### **201.12.4.4.101 \*DIALYSIS FLUID composition**

- a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of any fluid preparation control system, which prevents DIALYSIS FLUID reaching the DIALYZER that, due to its composition, may cause a HAZARD.

The design of the PROTECTIVE SYSTEM to prevent a hazardous composition of the DIALYSIS FLUID shall consider a potential failure in any phase of preparation of the DIALYSIS FLUID.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101). The audible alarm may be delayed as specified in 208.6.3.3.101 b);

- stopping of the DIALYSIS FLUID flow to the DIALYZER;
- in ONLINE HDF or ONLINE HF mode, stopping of the SUBSTITUTION FLUID flow to the EXTRACORPOREAL CIRCUIT.

b) Conductivity profiles and PHYSIOLOGIC CLOSED-LOOP CONTROLLERS:

In case of pre-programmed time-dependent variation of the DIALYSIS FLUID composition or in case of feedback control of the DIALYSIS FLUID composition by measuring a physiologic relevant parameter of the PATIENT, the HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of the control system, which prevents any unintentional changes in the control system that could cause a HAZARD.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- other measures, if defined by MANUFACTURER'S RISK MANAGEMENT PROCESS.

c) If the HEMODIALYSIS EQUIPMENT is equipped with a concentration bolus administration feature, the HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of the control system, which prevents the concentration bolus administration function to cause a HAZARD to the PATIENT.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- interruption of the concentration bolus administration.

*Compliance is checked by functional tests and by the following tests.*

- *Test 1 for determining the ALARM LIMITS*
  - *Set the unit under test to the lowest and the highest ALARM SIGNAL free compositions of the DIALYSIS FLUID respectively.*
  - *Slowly change the DIALYSIS FLUID composition until the PROTECTIVE SYSTEM activates an ALARM SIGNAL.*
  - *Take samples at the DIALYZER inlet under NORMAL CONDITIONS and immediately after the alarm.*
  - *Determine the difference of the DIALYSIS FLUID composition of the samples taken in NORMAL CONDITIONS and after alarm (e.g. by flame photometry).*
- *Test 2 for in-time alarm reaction*
  - *Set the unit under test to the highest possible DIALYSIS FLUID flow*
  - *Simulate complete interruption of each DIALYSIS FLUID CONCENTRATE supply, one at a time.*
  - *Take samples at the DIALYZER inlet under NORMAL CONDITIONS and immediately after the alarm.*
  - *Determine the difference of the DIALYSIS FLUID composition of the samples taken under NORMAL CONDITIONS and after alarm (e.g. by flame photometry).*
- *Test 3 for foreseeable misuse*
  - *Exchange DIALYSIS FLUID CONCENTRATES, if possible.*
  - *Determine the alarm activation.*

#### **201.12.4.4.102 \*DIALYSIS FLUID and SUBSTITUTION FLUID temperature**

- a) The range for setting the temperature of the DIALYSIS FLUID and SUBSTITUTION FLUIDS shall not be outside the range of 33 °C to 42 °C unless justified by the MANUFACTURER'S RISK MANAGEMENT PROCESS.
- b) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of any temperature control system, which prevents DIALYSIS FLUID reaching the DIALYZER and SUBSTITUTION FLUID reaching the EXTRACORPOREAL CIRCUIT at a temperature below 33 °C or above 42 °C, measured at the HEMODIALYSIS EQUIPMENT DIALYSIS FLUID outlet and/or at the SUBSTITUTION FLUID outlet.
- c) For a short time temperatures up to 46 °C and below 33 °C are acceptable, but time and value have to be justified in the MANUFACTURER'S RISK MANAGEMENT PROCESS.
- d) Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:
  - activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101). The audible alarm may be delayed as specified in 208.6.3.3.101 b);
  - stopping of the DIALYSIS FLUID flow to the DIALYZER and/or SUBSTITUTION FLUID flow to the EXTRACORPOREAL CIRCUIT.

*Compliance is checked by functional tests and by the following tests.*

- *Test 1 for DIALYSIS FLUID*
  - *Set the unit under test to the highest DIALYSIS FLUID flow, if this setting is possible.*
  - *Set the highest / lowest DIALYSIS FLUID temperature.*
  - *Wait for stable temperatures at the DIALYZER inlet.*
  - *Slowly increase / decrease the temperature of DIALYSIS FLUID until the PROTECTIVE SYSTEM activates an ALARM SIGNAL.*
  - *Measure the temperature continuously at the DIALYZER inlet and determine the maximum / minimum value.*
- *Test 2 for SUBSTITUTION FLUID*
  - *Set the unit under test to the highest SUBSTITUTION FLUID flow, if this setting is possible.*
  - *Set the highest / lowest DIALYSIS FLUID / SUBSTITUTION FLUID temperature.*
  - *Wait for stable temperatures at the inlet to the EXTRACORPOREAL CIRCUIT.*
  - *Slowly increase / decrease the temperature of the DIALYSIS FLUID / SUBSTITUTION FLUID until the PROTECTIVE SYSTEM activates an ALARM SIGNAL.*
  - *Measure the temperature of the SUBSTITUTION FLUID continuously at the inlet to the EXTRACORPOREAL CIRCUIT and determine the maximum / minimum value.*

#### **201.12.4.4.103 \*NET FLUID REMOVAL**

- a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of any ULTRAFILTRATION control system, which prevents a variation in the NET FLUID REMOVAL of the HEMODIALYSIS EQUIPMENT from the set value of the controlling parameter that may cause a HAZARD.

In case of HDF and HF the HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of any SUBSTITUTION FLUID control system, which prevents an incorrect administration of the SUBSTITUTION FLUID that can cause a HAZARD.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- prevention of the continuation of the fluid balancing error.

b) ULTRAFILTRATION profiles and PHYSIOLOGIC CLOSED-LOOP CONTROLLERS:

In case of pre-programmed time dependent variation of ULTRAFILTRATION or in case of feedback control of ULTRAFILTRATION by a monitor measuring a physiologic relevant parameter of the PATIENT, the HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of the control system, which prevents any unintentional changes in the control system that could cause a HAZARD.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- other measures, if defined by MANUFACTURER'S RISK MANAGEMENT PROCESS.

c) If the HEMODIALYSIS EQUIPMENT is equipped with a fluid bolus administration feature, the HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM, independent of the control system, which prevents the fluid bolus administration function to cause a HAZARD to the PATIENT.

Operation of the PROTECTIVE SYSTEM shall achieve the following safe conditions:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- interruption of the fluid bolus administration.

*Compliance is checked by functional tests and failure simulations, including the following tests.*

- *Test for deviations of the NET FLUID REMOVAL rate*
  - *Set the unit under test to the highest DIALYSIS FLUID flow.*
  - *Set the highest SUBSTITUTION FLUID flow, if this is adjustable.*
  - *Set the DIALYSIS FLUID temperature to 37 °C, if applicable.*
  - *Set the highest and the lowest ULTRAFILTRATION flow rates (one at a time).*
  - *Simulate a low and a high failure in each of the pump control systems (one at a time) which influence the NET FLUID REMOVAL rate until the PROTECTIVE SYSTEM activates an ALARM SIGNAL.*
  - *Determine the volume difference in relation to the theoretical volume.*

#### **201.12.4.4.104 Extracorporeal blood loss**

##### **201.12.4.4.104.1 Extracorporeal blood loss to the environment**

- \*a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM to protect the PATIENT from extracorporeal blood loss to the environment that may cause a HAZARD.

NOTE 1 Today no system has been developed that can totally be relied upon to detect blood loss to the environment. The following recommendation is the best known system to detect blood loss to the environment.

If a PROTECTIVE SYSTEM is utilizing measurement of the VENOUS PRESSURE, the OPERATOR should have at least the possibility to adjust the lower ALARM LIMIT manually as closely as possible to the current measurement value. The single needle treatment mode needs additional measures.



- b) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM to protect the PATIENT from extracorporeal blood loss to the environment caused by a rupture or separation in the EXTRACORPOREAL CIRCUIT due to excessive pressure, unless this is prevented by inherent safe design.

NOTE 2 This is not related to separation of the PATIENT CONNECTION or access needle but related to the potential pressure that can be generated by the pump which could cause tubing rupture or joint separation in the EXTRACORPOREAL CIRCUIT.

- \*c) Operation of the PROTECTIVE SYSTEM shall achieve the following safe condition:

- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
- stoppage of the blood flow to the environment caused by the HEMODIALYSIS EQUIPMENT, even under SINGLE FAULT CONDITIONS.
- In the case of HEMOFILTRATION or HEMODIAFILTRATION, stoppage of the SUBSTITUTION FLUID flow.

*Compliance is checked by functional tests and by the following test:*

- *Test for PROTECTIVE SYSTEMS utilizing the VENOUS PRESSURE measurement*
  - *Set the unit under test to the medium blood flow.*
  - *Adjust the VENOUS PRESSURE to a medium value.*
  - *Lower the VENOUS PRESSURE until an ALARM SIGNAL is activated.*
  - *Determine the difference between the alarm point and the reference value.*

#### **201.12.4.4.104.2 \*BLOOD LEAK to the DIALYSIS FLUID**

- a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM to protect the PATIENT from a BLOOD LEAK that may cause a HAZARD.
- b) Operation of the PROTECTIVE SYSTEM shall achieve the following safe condition:
- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
  - prevention of further blood loss to the DIALYSIS FLUID.

*Compliance is checked by functional tests and by the following test.*

- *Test for determining the ALARM LIMITS:*
  - *Create maximum flow through the BLOOD LEAK detector (highest DIALYSIS FLUID flow, highest ULTRAFILTRATION flow, if relevant also highest SUBSTITUTION FLUID flow).*
  - *Add bovine blood (Hct 32%) to the DIALYSIS FLUID so that the flow through the BLOOD LEAK detector represents the BLOOD LEAK ALARM LIMIT as specified by the MANUFACTURER.*

#### **201.12.4.4.104.3 \* Extracorporeal blood loss due to coagulation**

- a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM to protect the PATIENT from blood loss due to coagulation as a consequence of the interruption of the blood flow that may cause a HAZARD.

NOTE An acceptable method of complying with this requirement is, for example, a PROTECTIVE SYSTEM operating if the blood pump(s) advertently or inadvertently stop(s) for a longer period of time.

- b) Operation of the PROTECTIVE SYSTEM shall activate an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101).

- c) Other effects which may result in a blood loss due to coagulation, e.g. stopping or missing start of any anticoagulation pump, or excessive substitution flow in case of HDF with post-dilution, shall be addressed in the MANUFACTURER'S RISK MANAGEMENT PROCESS.

*Compliance is checked by functional tests and failure simulation*

#### **201.12.4.4.105 \* Air infusion**

- a) The HEMODIALYSIS EQUIPMENT shall include a PROTECTIVE SYSTEM to protect the PATIENT from air infusion which may cause a HAZARD, even under SINGLE FAULT CONDITIONS.

NOTE 1 An acceptable method of complying with this requirement is, for example, a PROTECTIVE SYSTEM utilizing an air detector (e. g. ultrasonic) capable of detecting non-dissolved air.

- b) Operation of the PROTECTIVE SYSTEM shall achieve the following safe condition:
- activation of an audible and visual ALARM SIGNAL (see 208.6.3.1, 208.6.3.3.2, 208.6.3.3.101);
  - prevention of further air infusion via the arterial and venous bloodlines, even under SINGLE FAULT CONDITION.

NOTE 2 The prevention of further air infusion can typically be accomplished by stopping the blood pump and clamping the venous bloodline.

*Compliance is checked by functional tests taking into account the principles of the test described below.*

NOTE 3 Given numbers in the tests are examples. The MANUFACTURER has to define the values by his RISK MANAGEMENT.

NOTE 4 As a matter of principle, there are two methods for monitoring air infusion:

- a) at an air trap (e.g. at the venous drip chamber) where buoyancy forces act on the air bubbles so that bubbles are prevented from exiting the air trap with a correctly set level; the air bubble monitoring method used here is the method of monitoring the level;
- b) directly at the bloodline (air bubbles are delivered in the fluid stream), where the air volume can be determined by means of the flow velocity.

*There are two different test procedures independent of the air monitoring methods in Note 4.*

- *Continuous air infusion:*

- *Set up the HEMODIALYSIS EQUIPMENT with a standard capillary DIALYZER (e.g. surface area between 1 m<sup>2</sup> and 1.5 m<sup>2</sup>), the recommended EXTRACORPOREAL CIRCUIT and cannulas (e.g. 16 gauge).*
- *Clamp or close the DIALYSIS FLUID lines after priming.*

NOTE 5 This is a worst case condition. If degassed DIALYSIS FLUID is running, gas will be removed by the DIALYZER.

- *Operate the EXTRACORPOREAL CIRCUIT with heparinized blood with defined Hct (e.g. Hct between 0.25 and 0.35, human blood, bovine blood, porcine blood) or an appropriate test fluid.*

NOTE 6 An appropriate test fluid has a viscosity of 3.5 mPa·s at 37 °C and contains a surfactant causing spallation of gas bubbles.

- *Position a storage container for the test fluid at a level of e.g. 100 cm (± 20 cm) from the ground.*
- *Position a collection container for the test fluid at a level of e.g. 100 cm (± 20 cm) from the ground or recirculate the fluid into the storage container.*

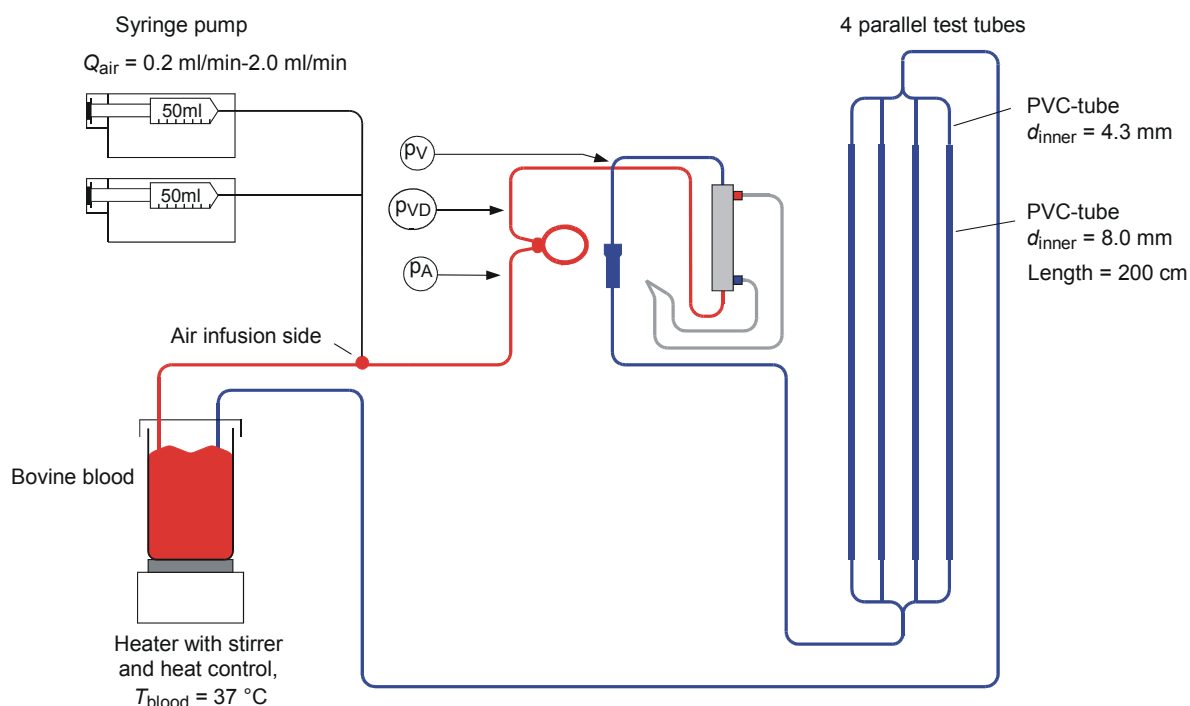
- *Position at least one vertically positioned test tube with diameter of e.g. 8 mm and a length of e.g. 2.0 m in line with a second tube with smaller diameter directly at the venous PATIENT connector in the venous path between the PATIENT connector and collection container (see as an example the set-up in Figure 201.101).*
- *Insert a cannula (e.g. 22 gauge) into the arterial blood tubing in the section of negative pressures close to the connection to the arterial (blood withdrawal) cannula and connect it to a pump capable of controlling air injection under negative pressure condition.*

NOTE 7 A possible method is the use of a small reversible peristaltic pump. This pump is initially primed with test fluid by operating it in reverse mode to avoid uncontrolled injection of air when the blood pump is started. A check valve between needle and pump could be used.

- *Adjust the blood pump speed with a defined pre-pump negative pressure (e.g. between -200 mmHg and -250 mmHg).*
- *Inject air at slowly increasing rates specified by the MANUFACTURER until the air detector alarms.*

NOTE 8 The rationale of this test is based on the assumption that, with the DIALYSIS FLUID line closed, air cannot escape from the EXTRACORPOREAL CIRCUIT and will eventually be pumped to the fluid collection vessel at the same rate as pumped in.

- *Clamp the test tube at both ends immediately after the air detector alarm.*
- *Measure after e.g. 15 min the air volume building at the top of the small diameter test tube.*
- *Calculate the air flow rate by blood flow speed, test tube volume and measured air volume.*
  - *If the HEMODIALYSIS EQUIPMENT allows the DIALYZER to be operated with blood flowing upwards through the DIALYZER and, alternatively with blood flowing downwards through the DIALYZER, separate tests shall be done with both flow directions.*
  - *If RISK ANALYSIS reveals pathways for injecting air post blood pump (e.g., by a level adjust pump) the test shall be repeated by pumping air at the specified rate into the EXTRACORPOREAL CIRCUIT at this point.*



IEC 378/12

**Figure 201.101 – Continuous air infusion test set-up with example dimensions**

- **Bolus air infusion:**

- Set up the HEMODIALYSIS EQUIPMENT with a standard capillary DIALYZER (e.g. surface area between 1 and 1.5 m<sup>2</sup>), the recommended EXTRACORPOREAL CIRCUIT and cannulas (e.g. 16 gauge).
- Clamp or close the DIALYSIS FLUID lines after priming.

NOTE 9 This is a worst case condition. If degassed DIALYSIS FLUID is running, gas will be removed by the DIALYZER.

- Operate the EXTRACORPOREAL CIRCUIT with heparinized blood with defined Hct (e.g. Hct between 0.25 and 0.35, human blood, bovine blood, porcine blood) or an appropriate test fluid.

NOTE 10 An appropriate test fluid has a viscosity of 3.5 mPa·s at 37°C and contains a surfactant causing spallation of gas bubbles.

- Position a storage container for the test fluid at a level of e.g. 100 cm ( $\pm 20$  cm) from the ground.
- Position a collection container for the test fluid at a level of e.g. 100 cm ( $\pm 20$  cm) from the ground or recirculate the fluid into the storage container.
- Position a graduated measuring cylinder or the same test tubes as in the previous test case such that any air that may be pumped through the return (venous) cannula is collected.
- Insert a T-piece with luer-connectors between the blood tubing and the arterial (blood withdrawal) cannula.
- Connect a piece of tubing (e.g. 5 cm long) with a luer connector to the T.

- Prime the EXTRACORPOREAL CIRCUIT and said piece of tubing. Clamp the piece of tubing.
- Adjust the blood pump speed with a defined pre-pump negative pressure (e.g. between 0 mmHg and -250 mmHg) and no pressure alarm arises with the opening of the clamp.
- Open the clamp at the piece of tubing and wait until the air detector activates an ALARM SIGNAL.
- Check the amount of air collected in the graduated measuring cylinder or in the test tube. The amount shall be less than the specified bolus limit.
  - If the HEMODIALYSIS EQUIPMENT allows the DIALYZER to be operated with blood flowing upwards through the DIALYZER and, alternatively with blood flowing downwards through the DIALYZER, separate tests shall be done with both flow directions.
  - If RISK ANALYSIS reveals pathways for injecting air post blood pump (e.g., by a level adjust pump) the test shall be repeated by pumping air at the maximum rate into the EXTRACORPOREAL CIRCUIT at this point.

**\* 201.12.4.4.106 Alarm override modes**

- a) All PROTECTIVE SYSTEMS shall be operational throughout treatment.

NOTE 1 For exceptions, see item b) below.

NOTE 2 Within the meaning of this subclause treatment is considered to have started when the PATIENT's blood is returned to the PATIENT through the EXTRACORPOREAL CIRCUIT, treatment is considered to be finished when the venous needle is disconnected.

- b) The PROTECTIVE SYSTEMS for DIALYSIS FLUID composition and temperature shall be operational before the first contact of DIALYSIS FLUID with blood in the DIALYZER.
- c) During an ALARM CONDITION, temporary override modes may apply individually to the PROTECTIVE SYSTEMS utilizing BLOOD LEAK monitoring (see 201.12.4.4.104.2).
- d) The override time shall not exceed 3 min, but under certain clinical conditions it may be necessary to deactivate the BLOOD LEAK detector completely or partially for unlimited time.
- e) Operation of the override mode shall maintain a visual indication that the PROTECTIVE SYSTEM is being overridden.
- f) Overriding a particular PROTECTIVE SYSTEM (see item b) shall have no effect on any other subsequent ALARM CONDITIONS. Subsequent ALARM CONDITIONS shall achieve the safe condition specified. A remaining ALARM CONDITION shall, after the elapsed override period, re-achieve the safe condition specified.

NOTE 3 Within the meaning of this subclause, override is the means to allow the HEMODIALYSIS EQUIPMENT to function under ALARM CONDITIONS if the OPERATOR consciously selects to temporarily disable the PROTECTIVE SYSTEM. A delayed start is not regarded as an override of the HEMODIALYSIS EQUIPMENT if it does not cause a HAZARD.

*Compliance is checked by inspection of the ACCOMPANYING DOCUMENTS and by functional tests.*

#### **201.12.4.4.107 PROTECTIVE SYSTEMS**

A failure of the PROTECTIVE SYSTEMS required by 201.12.4.4 shall become obvious to the OPERATOR within the following limits:

a) for all PROTECTIVE SYSTEMS except 201.12.4.4.105 (air infusion):

- at least once per day or, if this is not possible, as determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS;

NOTE Acceptable methods of complying with this requirement are for example:

- periodic functional check of the PROTECTIVE SYSTEMS initiated and controlled by the OPERATOR;
- periodic functional check of the PROTECTIVE SYSTEMS initiated by the OPERATOR and controlled by the HEMODIALYSIS EQUIPMENT;
- redundancy of the PROTECTIVE SYSTEMS with self-checking by the HEMODIALYSIS EQUIPMENT;
- periodic functional check of the PROTECTIVE SYSTEMS initiated by the HEMODIALYSIS EQUIPMENT and controlled by the HEMODIALYSIS EQUIPMENT, if the control function of the PROTECTIVE SYSTEM is designed such that it cannot fail simultaneously with the PROTECTIVE SYSTEM by a single failure.

b) for the PROTECTIVE SYSTEM required by 12.4.4.105 (air infusion):

- if an amount of air can be infused to the PATIENT which may cause a HAZARD as a result of a first fault of the air detector, the maximum detection time for this fault is calculated as the fault tolerance time:
  - the volume of the EXTRACORPOREAL CIRCUIT between the air detector and the venous cannula, divided by the highest blood flow;
- in all other cases a) applies.

*Compliance is checked by functional tests and failure simulations.*

#### **201.12.4.4.108 Prevention of contamination by chemicals**

- a) It shall not be possible to treat the PATIENT while the HEMODIALYSIS EQUIPMENT is in the cleaning, sterilization or disinfection mode. Subclauses 4.7 and 11.8 of the general standard apply.
- b) Chemicals (e.g. water, DIALYSIS FLUID, disinfectant or DIALYSIS FLUID CONCENTRATE) shall not flow from the HEMODIALYSIS EQUIPMENT to any supply line, even under SINGLE FAULT CONDITIONS.

*Compliance is checked by functional tests and failure simulations.*

#### **201.12.4.4.109 \*Blood pump(s) and/or SUBSTITUTION FLUID pump(s) reversal**

A method shall be included to prevent inadvertent reversal of the blood and/or SUBSTITUTION FLUID pump(s) during the treatment that may cause a HAZARD.

The applicable HAZARDS (e.g. air infusion via the arterial bloodline) have to be determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS. Human errors have to be taken into account as well as technical failures.

*Compliance is checked by inspection and by functional tests.*

#### **201.12.4.4.110 Selection and change of operation modes**

Inadvertent selection and change of operation modes shall be prevented. Human errors have to be taken into account as well as technical failures.

*Compliance is checked by inspection and by functional tests.*

#### **201.12.4.4.111 ONLINE HDF and ONLINE HF**

If the HEMODIALYSIS EQUIPMENT is intended for ONLINE HEMOFILTRATION (ONLINE HF) or ONLINE HEMODIAFILTRATION (ONLINE HDF), the MANUFACTURER shall ensure that the HEMODIALYSIS EQUIPMENT shall be capable of producing SUBSTITUTION FLUID that complies with the requirements (e.g. microbiological) for a solution intended for large-volume intravenous applications when the MANUFACTURER'S instructions are followed. This requirement shall also be complied with under SINGLE FAULT CONDITIONS.

*Compliance is checked by inspection and by functional tests.*

### **201.13 HAZARDOUS SITUATIONS and fault conditions**

Clause 13 of the general standard applies, except as follows:

#### **201.13.2.6 \* Leakage of liquid**

*Addition:*

The liquid-carrying parts of the HEMODIALYSIS EQUIPMENT shall be so shielded against the electrical parts that liquid which may leak under normal working pressure does not lead to the PATIENT being exposed to HAZARDS, for example due to short-circuiting of CREEPAGE DISTANCES.

*Compliance is checked by the following test:*

- a) by means of a pipette, drops of potable water are applied to couplings, to seals and to tubings which might rupture, moving parts being in operation or at rest, whichever is least favorable;*

*and in case of doubt in test a):*

- b) by means of a syringe, a jet of an appropriate liquid for the part of the HEMODIALYSIS EQUIPMENT is directed from couplings, from seals and from tubings which might rupture, moving parts being in operation or at rest, whichever is the least favorable.*

*After these procedures, the HEMODIALYSIS EQUIPMENT shall show no signs of wetting of uninsulated electrical parts or of electrical insulation which is liable to be adversely affected by potable water or the selected liquid. In case of doubt, the HEMODIALYSIS EQUIPMENT shall be subjected to the dielectric strength test specified in 8.8.3 of the general standard.*

*The determination of other HAZARDS is checked by inspection of the HEMODIALYSIS EQUIPMENT.*

## **201.14 PROGRAMMABLE ELECTRICAL MEDICAL SYSTEMS (PEMS)**

Clause 14 of the general standard applies, except as follows:

### **201.14.13 \*Connection of PEMS by NETWORK/DATA COUPLING to other equipment**

*Addition:*

Data transfer between NETWORK/DATA COUPLING and HEMODIALYSIS EQUIPMENT shall not cause a HAZARD to the PATIENT under SINGLE FAULT CONDITIONS.

## **201.15 Construction of ME EQUIPMENT**

Clause 15 of the general standard applies, except as follows:

### **201.15.4.1 Construction of connectors**

*Addition:*

#### **201.15.4.1.101 \* Dialysis fluid CONCENTRATE connectors**

The various DIALYSIS FLUID CONCENTRATE supply containers and cleaning solutions should be differentiated by mechanical connections to the DIALYSIS FLUID CONCENTRATE connectors of the HEMODIALYSIS EQUIPMENT or be permanently color marked. (See ISO 13958.)

The HEMODIALYSIS EQUIPMENT shall additionally prevent a mixing of the various DIALYSIS FLUID CONCENTRATES and cleaning solutions which may cause a HAZARD for the PATIENT, by mechanical differentiation of the connectors or by color coding of the connectors.

NOTE 1 The use of various DIALYSIS FLUID CONCENTRATES presents a problem in that connection of the wrong DIALYSIS FLUID CONCENTRATE may cause a HAZARD to the PATIENT. The design of connectors and color coding were recognized as methods to minimize this RISK. There is always the possibility that the OPERATOR will cause a HAZARD by not following the MANUFACTURER's instructions for use.

The MANUFACTURER should make every effort to minimize the possible mix-up in the connection of DIALYSIS FLUID CONCENTRATES.

The following colors shall be used for DIALYSIS FLUID CONCENTRATE connectors:

- connector for acetate shall be white;
- connector for acidic component in bicarbonate dialysis shall be red;
- connector for bicarbonate component in bicarbonate dialysis shall be blue;
- for common usage of one connector for different DIALYSIS FLUID CONCENTRATES, on the HEMODIALYSIS EQUIPMENT the respective colored markings shall be affixed on that connector. For example, a common connector for acetate and acidic DIALYSIS FLUID CONCENTRATE shall be marked white/red.

*Compliance is checked by inspection.*

NOTE 2 ISO 13958 gives requirements for the color coding of DIALYSIS FLUID CONCENTRATE containers.



#### **201.15.4.1.102 \*Connectors for blood pressure transducers**

The connection between blood lines and blood pressure transducers shall have an equivalent safety according to ISO 594-2, as stipulated by ISO 8638.

Any potential HAZARDS to the PATIENT, such as air infusion, cross contamination and blood loss, shall be taken into account in the MANUFACTURER'S RISK MANAGEMENT PROCESS.

*Compliance is checked by functional tests and inspection of the RISK MANAGEMENT FILE.*

### **201.16 \* ME SYSTEMS**

Clause 16 of the general standard applies, except as follows:

#### **201.16.1 General requirements for the ME SYSTEMS**

*Addition:*

ME SYSTEMS have not yet been examined comprehensively with regard to the whole field of dialysis in this particular standard. Application of RISK MANAGEMENT with consideration of ME SYSTEMS is therefore also recommended for MANUFACTURERS of HEMODIALYSIS EQUIPMENT, since definite identification of a particular MANUFACTURER of the complete ME SYSTEM is often not possible in a dialysis clinic. (See IEC 60601-1, Annex A, Clause A.4, Subclauses 4.2 and 16.1.)

#### **201.16.2 ACCOMPANYING DOCUMENTS of an ME SYSTEM**

d) advice to the RESPONSIBLE ORGANIZATION

*Addition:*

- a listing of RISKS and measures in case of a connection of HEMODIALYSIS EQUIPMENT to CENTRAL DELIVERY SYSTEMS or other fluid-carrying central systems (increased LEAKAGE CURRENTS).

*Compliance is checked by inspection of the ACCOMPANYING DOCUMENTS.*

#### **201.16.6.3 PATIENT LEAKAGE CURRENT**

*Addition:*

NOTE Possible methods for reducing PATIENT LEAKAGE CURRENTS are the utilization of conductive rings in central water supply systems or ensuring that all connection points of the dialysis unit have the same potential and are PROTECTIVELY EARTHED (see ISO 11197).

#### **201.16.9.1 \* Connection terminals and connectors**

*Addition:*

- The connectors on the CENTRAL DELIVERY SYSTEM shall be permanently color marked. See 201.15.4.1.101.
- The color markings shall be affixed such that the OPERATOR can easily assign the DIALYSIS FLUID CONCENTRATE to the appropriately color-marked DIALYSIS FLUID CONCENTRATE container or the CENTRAL DELIVERY SYSTEM (see 201.15.4.1.101).

*Compliance is checked by inspection and testing.*

## **201.17 Electromagnetic compatibility of ME EQUIPMENT and ME SYSTEMS**

Clause 17 of the general standard applies.

## **202 Electromagnetic compatibility – Requirements and tests**

IEC 60601-1-2:2007 applies except as follows:

### **202.3.18**

#### **LIFE-SUPPORTING ME EQUIPMENT OR ME SYSTEM**

*Addition:*

NOTE HEMODIALYSIS EQUIPMENT is not considered to be LIFE-SUPPORTING EQUIPMENT or a LIFE-SUPPORTING SYSTEM as defined in 3.18 of IEC 60601-1-2:2007, since a premature termination of the dialysis treatment is not likely to lead to serious injury or death of a PATIENT

## **208 General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems**

IEC 60601-1-8:2006 applies except as follows:

### **208.4 \*General requirements**

*Addition:*

If the INTENDED USE of the HEMODIALYSIS EQUIPMENT includes the intensive care or surgery environment, it is acceptable to implement additional ALARM SYSTEMS deviating from IEC 60601-1-8:2006 in the following subclauses:

- 6.1.2 ALARM CONDITION priority;
- 6.3.2.2 Characteristics of visual ALARM SIGNALS;
- 6.3.3.1 Characteristics of auditory ALARM SIGNALS.

If additional ALARM SYSTEMS deviating from IEC 60601-1-8:2006 are implemented,

- a) the ALARM SYSTEM according to IEC 60601-1-8:2006 shall be the factory default;
- b) only the RESPONSIBLE ORGANIZATION shall be able to change the ALARM SYSTEM.

Compliance is checked by functional tests

NOTE 1 Table AA.1 of Annex AA shows possible ALARM CONDITION priorities according to IEC 60601-1-8:2006 6.1.2 adapted for HEMODIALYSIS EQUIPMENT needs.

If the INTENDED USE of the HEMODIALYSIS EQUIPMENT does not include the intensive care or surgery environment, the following clauses of IEC 60601-1-8:2006 are not mandatory:

- 6.1.2 ALARM CONDITION priority;
- 6.3.2.2 Characteristics of visual ALARM SIGNALS;
- 6.3.3.1 Characteristics of auditory ALARM SIGNALS.

NOTE 2 7.8.1 Colors of indicator lights of the general standard applies, but the urgency of the response of the OPERATOR can have other than PATIENT centric causes.

### **208.5.2.1 Instructions for use**

*Addition:*

NOTE 101 In the listing and description of every possible ALARM CONDITION only these conditions need to be written with a remaining HAZARD beside the safe state of the HEMODIALYSIS EQUIPMENT.

### **208.6.3 Generation of ALARM SIGNALS**

#### **208.6.3.1 \*General**

*Addition:*

Unless otherwise specified by this particular standard, ALARM SIGNALS shall be activated both visually and audibly. The visual alarm shall remain activated for the entire duration of the ALARM CONDITION, whereas it is allowed to pause the audible alarm for the amount of time specified in 208.6.3.3.101 b).

*Compliance is checked by functional tests.*

#### **208.6.3.3.2 \*Volume of auditory ALARM SIGNALS and INFORMATION SIGNALS**

*Addition:*

In the initial setting by the MANUFACTURER the HEMODIALYSIS EQUIPMENT shall generate a sound pressure level of at least 65 dB(A) at a distance of 1 m.

*Compliance is checked by measuring the A-rated sound pressure level with instruments meeting the requirements for measuring instruments of Class 1 according to IEC 61672-1 and free field conditions as specified in ISO 3744.*

#### **208.6.3.3.101 \*Special characteristics of auditory ALARM SIGNALS for HEMODIALYSIS EQUIPMENT**

Audible ALARM SIGNALS shall meet the following requirements:

- a) If the HEMODIALYSIS EQUIPMENT enables the OPERATOR to set the audible alarm volume to lower values, a minimum value shall be defined. This minimum value may only be changed by the RESPONSIBLE ORGANIZATION. If the RESPONSIBLE ORGANIZATION can reduce the audible alarm volume to zero, there shall be an alternative means to notify the OPERATOR under SINGLE FAULT CONDITION.
- b) If it is possible to pause the audible ALARM SIGNAL, the alarm AUDIO PAUSED period shall not exceed 3 min.  
  
Exception: for ALARM SIGNALS as described in 201.12.4.4.101 (DIALYSIS FLUID composition) or 201.12.4.4.102 (DIALYSIS FLUID and SUBSTITUTION FLUID temperature) the alarm AUDIO PAUSED period shall not exceed 10 min.
- c) If during an alarm AUDIO PAUSED period another alarm occurs requiring the immediate response by the OPERATOR to prevent any HAZARD, then the AUDIO PAUSED period shall be interrupted.

*Compliance is checked by functional tests.*

## **210 Process requirements for the development of PHYSIOLOGIC CLOSED-LOOP CONTROLLERS**

IEC 60601-1-10:2007 applies except as follows:

### **Annex A – General guidance and rationale**

#### **A.2 Rationale for particular clauses and subclauses**

##### **Definition 210.3.20 PHYSIOLOGIC CLOSED-LOOP CONTROLLERS**

*Addition:*

Physiological parameters are, for example, blood temperature, blood pressure, pulse and hematocrit. The controller in the control circuit compares the physiological parameter with a reference value and, using the resulting difference, varies a control signal that takes effect on the variable quantities, such as ULTRAFILTRATION flow, conductivity and temperature.

## **211 \* Requirements for MEDICAL ELECTRICAL EQUIPMENT and MEDICAL ELECTRICAL SYSTEMS used in the HOME HEALTHCARE ENVIRONMENT**

IEC 60601-1-11:2010 applies except as follows:

### **211.6 Classification of ME EQUIPMENT and ME SYSTEMS**

*Addition:*

Besides the PERMANENTLY INSTALLED connection to SUPPLY MAINS, other means of preventing connection to a non-grounded outlet can be used, such as a unique MAINS PLUG connector that is normally not used in the HOME HEALTHCARE ENVIRONMENT.

## **Annexes**

The annexes of the general standard apply, except as follows:

**Annex G**  
(normative)

**Protection against HAZARDS of ignition  
of flammable anesthetic mixtures**

Annex G of the general standard does not apply.

## **Annex AA** (informative)

### **Particular guidance and rationale**

#### **AA.1 General guidance**

Clause A.1 of the general standard applies.

#### **AA.2 Rationale for particular clauses and subclauses**

The following are rationales for specific clauses and subclauses in this particular standard, with clause and subclause numbers parallel to those in the body of the document.

##### **Subclause 201.3.8 APPLIED PART**

The PATIENT is in direct contact with the HEMODIALYSIS EQUIPMENT and the ME SYSTEM via fluids. It is also important to consider the parts of the ME SYSTEM or non-ME SYSTEM coming into direct or indirect contact with the PATIENT via the OPERATOR, in order to determine the PATIENT LEAKAGE CURRENTS.

##### **Subclause 201.3.202 BLOOD LEAK**

Blood appears in the DIALYSIS FLUID compartment only if there is a pressure gradient from the blood compartment to the DIALYSIS FLUID compartment and a rupture in the semi-permeable membrane in the DIALYZER.

A BLOOD LEAK can also be accompanied by back-contamination caused by backfiltration.

The BLOOD LEAK detector detects a rupture of the semi-permeable membrane only if the blood volume entering the DIALYSIS FLUID exceeds the detection value of the BLOOD LEAK detector.

##### **Subclause 201.3.210 HEMODIALYSIS EQUIPMENT**

The type of HD, HDF and HF equipment can be classified as HEMODIALYSIS EQUIPMENT with or without preparation of DIALYSIS FLUID. HEMODIALYSIS EQUIPMENT with preparation of DIALYSIS FLUID usually requires a water treatment system (RO system) and may also be connected to a CENTRAL DELIVERY SYSTEM.

The HDF HEMODIALYSIS EQUIPMENT can also be used for performing the HD or HF treatment procedures. The treatment procedure is then defined by the accessories and the setting parameters.

##### **Subclause 201.3.213 and 201.3.214 ONLINE HDF and ONLINE HF**

According to the state of art, the SUBSTITUTION FLUID is produced from the DIALYSIS FLUID produced by the HEMODIALYSIS EQUIPMENT. The process comprises microbiological filtering and delivery into the EXTRACORPOREAL CIRCUIT.

### **Subclause 201.3.215 PROTECTIVE SYSTEM**

See: POLASCHEGG HD, LEVIN N. Hemodialysis machines and monitors. Winchester J, Koch R, Lindsay R, Ronco C, Horl W, editors. *Replacement of Renal Function by Dialysis*, 5th Edition. Kluwer Academic Publishers, 2004: pp.323 – 447 (page 342). The authors point out that HEMODIALYSIS EQUIPMENT comprises redundancy or PROTECTIVE SYSTEMS in addition to control systems. A HAZARD to the PATIENT is only possible if the control system and the PROTECTIVE SYSTEM both fail. The likelihood for failure for any of these systems is less than  $10^{-4}$ / treatment resulting in a combined likelihood of less than  $10^{-8}$  per treatment (4 h to 6 h). This observation was made by the first author in the mid-1980s based on quality feedback data from ~ 3,000 HEMODIALYSIS EQUIPMENTS and is corroborated by the low number of serious accidents caused by HEMODIALYSIS EQUIPMENT malfunction in the US where accident reports are published by the FDA.

### **Subclause 201.3.218 ULTRAFILTRATION**

In HF or HDF treatment, ULTRAFILTRATION should not be confused with the reduction in the PATIENT's weight (NET FLUID REMOVAL), because in this procedure, the volume equivalent to the SUBSTITUTION FLUID flow also flows across the DIALYZER membrane.

ULTRAFILTRATION rate = NET FLUID REMOVAL rate + SUBSTITUTION FLOW rate.

### **Subclause 201.4.3 ESSENTIAL PERFORMANCE**

The following general philosophy for the definition of test procedures for ESSENTIAL PERFORMANCE items was applied.

When defining the test procedures, it was the opinion of the committee that a safety standard for HEMODIALYSIS EQUIPMENT should not duplicate what is common knowledge in test laboratories, for example:

- selection of a suitable method of measurement (e.g. flow measurement by flow meter or by volume and time);
- the use of instruments with sufficient accuracy;
- the use of calibrated instruments.

Therefore the test procedures contain only the basic information needed for testing HEMODIALYSIS EQUIPMENT.

#### **Subclause 201.4.3.101 Additional ESSENTIAL PERFORMANCE requirements**

The ESSENTIAL PERFORMANCE for HEMODIALYSIS EQUIPMENT was determined with the following aspects taken into account: on one hand, all parameters required for the therapeutic effectiveness of the procedure should be included; on the other hand, definition of more parameters than necessary should be avoided, because the ESSENTIAL PERFORMANCE has to be complied with even under the irradiation conditions of the ELECTROMAGNETIC COMPATIBILITY - EMC immunity test. The observation and documentation of a great number of ESSENTIAL PERFORMANCE features would cause impractically high time and cost expenditures during the EMC test. The list of ESSENTIAL PERFORMANCE features defined here is a compromise between these two contrary aspects. (See IEC 60601-1-2.)

Since a standard cannot describe all possible special procedures modifying or expanding the classical dialysis procedure, this clause involves merely standard HEMODIALYSIS EQUIPMENT. If

special procedures require further parameters for therapeutic effectiveness or if parameters that are defined as ESSENTIAL PERFORMANCE in this standard are not required, the list of ESSENTIAL PERFORMANCE features should be adjusted to the HEMODIALYSIS EQUIPMENT concerned by the MANUFACTURER. The MANUFACTURER should list ESSENTIAL PERFORMANCES and appropriate rationales.

Comment to Note: If peristaltic pumps are used, the blood flow may considerably decrease in case of high negative pressures on the suction side.

#### **Subclause 201.4.3.107 DIALYSIS FLUID composition**

Due to the complexity of determining the DIALYSIS FLUID composition, a simple solution practical for all kind of HEMODIALYSIS EQUIPMENT was not found to date. Ideas for determining the DIALYSIS FLUID composition are:

- measurement by ion sensitive electrodes. However, the standard laboratory methods used for blood analysis are not accurate enough for measurement of absolute values in DIALYSIS FLUID;
- measurement of the dilution by adding a dye to the DIALYSIS FLUID CONCENTRATE. The adsorption is measured before and after mixing;
- theoretical calculation of conductivity, based on the known composition of the DIALYSIS FLUID CONCENTRATE. Create a systematic matrix of settings, e.g.:
  - highest sodium with lowest bicarbonate;
  - lowest sodium with highest bicarbonate;
  - highest sodium with highest bicarbonate;
  - lowest sodium with lowest bicarbonate;
- compare measured and theoretical values or the relative differences or ratios between the elements of the matrix;
- measurement of conductivity and pH in order to separate the sodium from the bicarbonate.

#### **Subclause 201.7.9.2.2 Warnings and safety notices (6<sup>th</sup> dash)**

Because of counter current flow in the DIALYZER, backfiltration of DIALYSIS FLUID takes place in at least one part of the DIALYZER even in low flux DIALYZERS (ULTRAFILTRATION coefficient < 10 ml/(h mmHg) ). If high-flux DIALYZERS are used, backfiltration cannot be avoided even by high ULTRAFILTRATION rates acceptable for fluid removal from the PATIENT.

The effect of backfiltration through an intact DIALYZER membrane is limited to the increased backtransport of larger molecules from the DIALYSIS FLUID to the blood. DIALYSIS FLUID does not contain such substances intentionally. In case of bacterial contamination the DIALYSIS FLUID contains endotoxins and other bacterial cell debris. Intact endotoxin molecules are too large to pass through the membrane but they split into smaller components. The molecular weight of Lipid A, the active component causing pyrogenic reactions has a molecular weight of ~ 2,000 mass units and will readily diffuse even through low flux membranes. Other molecules causing adverse cell reactions in blood have even lower molecular weight.

Backfiltration only contributes less than 50 % to backtransport even for high-flux membranes under unfavorable conditions. Considering that bacterial and endotoxin contamination is scaled by orders of magnitudes, a factor of 2 is not relevant. “Avoiding” backfiltration by increasing TMP or ULTRAFILTRATION cannot be regarded as a sufficient measure to prevent backtransport. It is therefore necessary to avoid contamination of DIALYSIS FLUID by bacteria by appropriate means.



The effect of backfiltration through structural leaks in the DIALYZER is usually limited to the amount not detected by the BLOOD LEAK detector. Because of the pulsating flow produced by a peristaltic blood pump, back and forward ULTRAFILTRATION will alternate in the DIALYZER. During the backfiltration phase, bacteria may enter into the blood stream undetected. Assuming that the back flow is 1 ml/min (three times larger than the typical sensitivity of a BLOOD LEAK detector) the hypothetical contamination of blood is 100 CFU/min – 200 CFU/min, if water for dialysis or DIALYSIS FLUID is according to EuPharm or AAMI guidelines respectively. It is extremely unlikely that a small leak below the detection limit of the BLOOD LEAK detector persists in a DIALYZER. Usually small leaks close by clotting within a few minutes.

#### **Subclause 201.7.9.2.2 Warnings and safety notices (9<sup>th</sup> dash)**

Hemolysis may be caused by excessive shear which is the result of high blood flow through a narrow passage, especially when flow becomes turbulent. Static pressure (–600 mmHg to +1000 mmHg) does not cause hemolysis. Elevated pressures measured in the EXTRACORPOREAL CIRCUIT indicate increased flow resistance which may cause subclinical hemolysis. Acute hemolysis has been reported to be caused by obstructions in the blood tubing system downstream of the blood pump but upstream of the pressure monitor. Such obstructions are not detected by the VENOUS PRESSURE monitor. For a review of accident reports see:

POLASCHEGG, HD, LEVIN, N. Hemodialysis machines and monitors. Winchester, J., Koch, R., Lindsay, R., Ronco, C., Horl, W., editors. *Replacement of Renal Function by Dialysis*, 5th Edition. Kluwer Academic Publishers, 2004: pp 323 – 447 (pp 328-332)

#### **Subclause 201.7.9.2.5 ME EQUIPMENT description (7<sup>th</sup> dash, item c))**

For Kt/V, applicable standards are e.g. K/DOQI guidelines and the European Best Practice Guidelines for Hemodialysis

#### **Subclause 201.7.9.2.12 Cleaning, disinfection and sterilization (2<sup>nd</sup> dash)**

This description of the test procedure should at least include:

- the recommended type of disinfectant;
- the required concentration of disinfectant in the container;
- the resulting concentration of disinfectant in the HEMODIALYSIS EQUIPMENT;
- the required minimum time of the disinfection phase (if not automatically set by the HEMODIALYSIS EQUIPMENT);
- the required minimum rinse phase (if not automatically set by the HEMODIALYSIS EQUIPMENT).

#### **Subclause 201.7.9.3.1 General (3<sup>rd</sup> and 4<sup>th</sup> dashes)**

Proposal for typical operating conditions of chronic HD treatments with HEMODIALYSIS EQUIPMENT to compare different features:

- dialyzing time: 4 h plus preparation time and post treatment operation;
- DIALYSIS FLUID flow: 500 ml/min;
- blood flow: 300 ml/min;
- ULTRAFILTRATION flow: 0.5 l/h;
- DIALYSIS FLUID temperature: 37 °C;
- chemical and/or heat disinfection according to the MANUFACTURER'S specification.

#### **Subclause 201.7.9.3.1 General (5<sup>th</sup> dash)**

Where systems with anticoagulant solution-delivering equipment are concerned, it should be considered that the following HAZARDS may occur, if a system / PROTECTIVE SYSTEM fails:

- fluid flow from the EXTRACORPOREAL CIRCUIT via the arterial PATIENT CONNECTION with the blood delivery equipment not running;
- HAZARD caused by improperly dosing the anticoagulant solution;
- air infusion via the arterial PATIENT CONNECTION, because the anticoagulant pump doses upstream of the blood pump (wrong delivery rate or delivery while the blood pump is not running).

#### **Subclause 201.7.9.3.1 General (11<sup>th</sup> dash)**

The flow through the BLOOD LEAK detector depends on the treatment type. In HD and ONLINE HDF it is the DIALYSIS FLUID flow plus the ULTRAFILTRATION flow. In “sequential” therapy it is the ULTRAFILTRATION flow. In HF it is the filtrate flow plus the ULTRAFILTRATION flow.

#### **Subclause 201.8.3 Classification of APPLIED PARTS**

Compliance with TYPE CF APPLIED PART requirements for HEMODIALYSIS EQUIPMENT that is provided with a permanent water connection and/or connection to CENTRAL DELIVERY SYSTEM, can be achieved with high technical expenditures only. For that reason, an exception rule has been established for the use of HEMODIALYSIS EQUIPMENT with TYPE B APPLIED PARTS on PATIENTS with central venous catheter with atrial location.

The goal of the exception rule is to protect the PATIENT under NORMAL CONDITIONS and under SINGLE FAULT CONDITIONS from LEAKAGE CURRENTS with the same effectiveness as HEMODIALYSIS EQUIPMENT with TYPE CF APPLIED PART. Two sources of LEAKAGE CURRENTS have to be distinguished;

##### **1) LEAKAGE CURRENTS originating from the HEMODIALYSIS EQUIPMENT.**

These LEAKAGE CURRENTS could flow through the central venous catheter with atrial location via the heart of the PATIENT to the grounded PATIENT bed, chair or other means. Under NORMAL CONDITIONS these LEAKAGE CURRENTS flow to earth via the PROTECTIVE EARTH CONDUCTOR of the HEMODIALYSIS EQUIPMENT. Under SINGLE FAULT CONDITIONS (PROTECTIVE EARTH CONDUCTOR of the HEMODIALYSIS EQUIPMENT is interrupted) the LEAKAGE CURRENTS need to be minimized by other means.

If ME-EQUIPMENT complies with these special LEAKAGE CURRENT limits in NORMAL CONDITIONS, but does not comply in SINGLE FAULT CONDITIONS (i.e. with the PROTECTIVE EARTH CONDUCTOR interrupted), an external POTENTIAL EQUALIZATION CONDUCTOR may be used for reducing the LEAKAGE CURRENTS to the necessary lower levels.

The external POTENTIAL EQUALIZATION CONDUCTOR has to be protected against unintentional disconnection (unintentional disconnection of the plug). Intentional disconnection of the plug without use of TOOLS may be possible.

##### **2) LEAKAGE CURRENTS originating from other electrical equipment and ME EQUIPMENT set up in the PATIENT ENVIRONMENT.**

These LEAKAGE CURRENTS could flow through the body of the PATIENT via the heart and the central venous catheter with atrial location to the earth via the HEMODIALYSIS EQUIPMENT. Under NORMAL CONDITIONS these LEAKAGE CURRENTS flow to earth via the PROTECTIVE EARTH CONDUCTOR of the external equipment.

Under SINGLE FAULT CONDITIONS (PROTECTIVE EARTH CONDUCTOR of the external equipment is interrupted) and if the HEMODIALYSIS EQUIPMENT has a TYPE CF APPLIED PART, the isolation barrier between the APPLIED PART and the rest of the HEMODIALYSIS EQUIPMENT would prevent these LEAKAGE CURRENTS from reaching the PATIENT.

If the HEMODIALYSIS EQUIPMENT has a TYPE B APPLIED PART, these LEAKAGE CURRENTS need to be minimized by other means.

Since measures that have to be applied to non-HEMODIALYSIS EQUIPMENT are not subject to this particular standard, the normative requirement of this particular standard is that information has to be provided in the ACCOMPANYING DOCUMENTS for the OPERATOR (201.7.9.2.5, 8<sup>th</sup> dash and 201.7.9.2.2, 14<sup>th</sup> dash) and for the RESPONSIBLE ORGANIZATION (201.7.9.2.6, 3<sup>rd</sup> dash and 201.7.9.2.2, 14<sup>th</sup> dash).

Remarks for the use of central venous catheters:

- Microshock by catheter LEAKAGE CURRENT is a hypothetical risk that cannot be excluded. The likelihood of such a shock occurring is limited.
- Only central venous catheters with the venous tip in the right atrium are relevant.
- This limits the catheters at risk to permanent catheters inserted through an upper limb (jugular or subclavian vein). The tip of non-permanent catheters or femoral catheters is usually not placed into the atrium.
- Side holes in the venous limb will also distribute electrical current to the body outside the heart (Jonsson P, Stegmayr B, Polaschegg HD. Central dialysis catheter LEAKAGE CURRENT distribution. *Nephrol Dial Transplant* 2007;22:vi519) although most catheters today have no side holes in the return (venous) lumen.
- The withdrawal (arterial) lumen is electrically isolated or only connected with a high resistance to ground. (Jonsson P, Stegmayr BG. Current leakage in hemodialysis machines may be a safety risk for patients. *Artif Organs* 2000;24:977-81)
- If the catheter tip is placed in the right atrium as recommended for permanent catheters, the catheter will normally not touch the atrium wall because this may cause flow problems. The requirements for CF based on the risk of microshock were established based on measurements with metal electrodes in direct touch with the atrium.
- With the catheter not in direct contact with the myocard the current density on the myocard surface will be very much reduced because the current is distributed over a larger surface area. Starmer et al. (Starmer CF, McIntosh HD, Whalen RE. Electrical hazards and cardiovascular function. *N Engl J Med* 1971;284:181-6) report that ~ 500  $\mu$ A were required for fibrillation when applied to a circular surface with 2.5 mm diameter. When the surface area was increased to 2.5 cm in diameter the current required for fibrillation increased to more than 3000  $\mu$ A
- In order to create a serious HAZARD:
  - the catheter tip must be placed in the right atrium and
  - touch the atrium wall (by mistake) and
  - the patient must be in touch with a current source

#### **Subclause 201.8.7.4.7 aa) Measurement of the PATIENT LEAKAGE CURRENT**

“Typical treatment mode with no alarms activated” means e.g. that a heater is on during measurement. If valves can block the current path between the heater and the PATIENT, these valves should be in open condition.

### **Subclause 201.8.11.2 MULTIPLE SOCKET-OUTLETS**

An example is a HEMODIALYSIS EQUIPMENT which has a MULTIPLE SOCKET-OUTLET. One socket is intended for an external heater which is switched off by the HEMODIALYSIS EQUIPMENT in case of temperature ALARM CONDITION. The other socket is intended for a reading light and is not switched off in case of ALARM CONDITIONS. It could cause a safety HAZARD if the heater were unintentionally connected into the socket for the reading light. This has to be prevented, e.g. by mechanically incompatible sockets.

### **Subclause 201.11.6.6 Cleaning and disinfection of ME EQUIPMENT and ME SYSTEMS**

The surface of the HEMODIALYSIS EQUIPMENT should be designed in such a way that there are no gaps and corners at the surface, where microorganisms may remain after surface disinfection.

The following is an example how disinfection efficiency and disinfectant residuals can be tested.

#### **a) Testing of disinfection efficiency**

##### **1) Chemical disinfection**

The disinfection efficiency test consists of the following steps:

- (1) It has to be shown that in the disinfection phase the fluid in the HEMODIALYSIS EQUIPMENT really reaches the intended concentration of disinfectant. The goal of this test is to verify the correct function of the hydraulic components and of the software in the disinfection process. The test is done by taking a sample of fluid from the HEMODIALYSIS EQUIPMENT at different locations of the DIALYSIS FLUID circuit and measuring the disinfectant concentration of these samples.
- (2) It has to be shown that the contact time of the disinfectant in the HEMODIALYSIS EQUIPMENT is as intended. Using colored test liquid instead of disinfectant, it is checked by visual inspection in each section of the fluid path that the contact time is as expected.
- (3) It has to be shown that all internal tubing is included in the disinfection process. This is done by performing a normal disinfection, but using a colored test liquid instead of real disinfectant. Then it is checked by visual inspection that in the disinfection phase all parts of the fluid system are filled with colored liquid. No tubes or containers should be only partly filled, or filled with a liquid that is considerably lighter in color. Such test liquids are e.g. "Methylene blue" or "Fluorescein".

An alternative method is measuring the conductivity of a conductive fluid.

- (4) It has to be shown by a "quantitative suspension test" that in the worst case condition that is acceptable according to the OPERATOR's manual (lowest concentration, shortest time), the disinfectant concentration and disinfection time deactivate the microorganisms to the necessary degrees. This test includes several types of microorganisms.

The following set of microorganisms is considered to cover the typical chemical disinfection methods in HEMODIALYSIS EQUIPMENT. For validation of a specific chemical disinfection method the relevant subset (at least 4) is chosen:

- pseudomonas aeruginosa;
- staphylococcus aureus;
- bacillus subtilis spores;
- candida albicans;
- aspergillus niger;

- enterococcus hirae.

ATCC strains are recommended.

This step 4 can be done in one of three ways:

- a) A disinfection is performed on the HEMODIALYSIS EQUIPMENT, inserting a known number of microorganisms per ml of fluid, and it is checked that the number of microorganisms is reduced to the necessary degree. The necessary degree is determined by relevant standards, e.g.  $10^5$  for the bacteria (EN 1040) and  $10^4$  for the yeast (EN 1275). The test can be done either with each type of microorganism separately or with a mixture of some microorganism types. The relevant subset of microorganisms indicated above is used (at least 4).
- b) A laboratory test (in test tubes) is performed, including all of the above types of microorganisms, and using the same conditions (disinfectant concentration, temperature and time) as in the HEMODIALYSIS EQUIPMENT.
- c) By literature, e.g. the validation data of the disinfectant.

## **2) Heat disinfection**

The MANUFACTURER identifies which of the relevant microorganisms is the most heat resistive.

The following highly heat-resistive microorganism can be used: bacillus subtilis spores.

This identified type is added to the pool of at least 4 of the microorganisms indicated above and a heat disinfection is performed in the HEMODIALYSIS EQUIPMENT.

It has to be shown that in the heat disinfection phase the fluid in the HEMODIALYSIS EQUIPMENT really reaches the intended temperature for the necessary time. The goal of this test is to verify the correct function of the involved components and of the software in the disinfection process. The test is done by measuring the temperature in the HEMODIALYSIS EQUIPMENT at different locations of the DIALYSIS FLUID circuit over the time.

## **3) Combination of chemical and heat disinfection**

The temperature and the concentration distribution within the HEMODIALYSIS EQUIPMENT are verified over the time of the disinfection procedure.

### **b) Testing of disinfectant residuals**

It has to be shown that the rinsing process after disinfection reduces the disinfectant concentration to an acceptable level. As a standard the "Lethal dose" [LD <50] should be used as the reference limit. The test is done in the following way:

A normal disinfection and rinse are performed, but a colored test liquid (e.g. Methylene blue or Fluorescein) is used instead of disinfectant. Then it is checked that in the rinse phase all parts of the fluid system are filled with colored liquid. No tubes or containers should be only partly filled, or filled with a liquid that is considerably lighter in color.

After rinsing, no parts of the fluid system should show traces of the colored liquid. The remaining concentration of the colored liquid can be measured photometrically.

Using a color test liquid results in higher sensitivity of the measurement than using real disinfectant but does not cover the effect of diffusion of disinfectant into plastic.

An alternative method is conductivity measurement as follows: Increase the conductivity level within the fluid and take samples from the most critical parts of the HEMODIALYSIS EQUIPMENT for analysis.

#### **Subclause 201.11.8 Interruption of the power supply / SUPPLY MAINS to HEMODIALYSIS EQUIPMENT**

The following items are examples for additional measures which may be necessary;

- stopping of the DIALYSIS FLUID flow to the DIALYZER;
- interruption of any SUBSTITUTION FLUID flow;
- reduction of ULTRAFILTRATION to its minimum value;
- clamping of the venous blood line.

#### **Clause 201.12 Accuracy of controls and instruments and protection against hazardous outputs**

The preceding second edition of this particular standard (IEC 60601-2-16:1998) usually did not specify any definite values for the necessary ALARM LIMITS of the PROTECTIVE SYSTEMS. It was up to the MANUFACTURER to define the deviation from the value that presented a HAZARD which had to be detected by the PROTECTIVE SYSTEM and justified in the MANUFACTURER'S RISK MANAGEMENT PROCESS.

The objective of the present third edition of this particular standard is to reach an agreement between the MANUFACTURERS and other interested organizations as to that part of the RISK MANAGEMENT PROCESS that is applicable to all systems and to describe the result in the present standard. It is intended to avoid any unnecessary redundant work on the part of the MANUFACTURER and to facilitate a uniform evaluation by the testing agencies.

When preparing this particular standard, the committee took "typical" HEMODIALYSIS EQUIPMENT for the treatment of acute or chronic renal failures as a basis. If the properties of a HEMODIALYSIS EQUIPMENT deviate from the "typical" values, the MANUFACTURER should define and justify the ALARM LIMITS in the MANUFACTURER'S RISK MANAGEMENT PROCESS.

#### **Subclause 201.12.4.4.101 Composition of the DIALYSIS FLUID**

The requirement for a PROTECTIVE SYSTEM is also applicable to human errors (e.g. mistaking of DIALYSIS FLUID CONCENTRATES) and also refers to Clause 15 (Construction of ME EQUIPMENT) and Clause 16 (ME SYSTEMS).

In acetate treatment, it is considered to be appropriate if the PROTECTIVE SYSTEM is designed such that it prevents a deviation beyond the following limits:

- conductivity of final DIALYSIS FLUID                      12 mS/cm – 16 mS/cm
- sodium in DIALYSIS FLUID                                       $\pm 5$  % from set point

Additionally in bicarbonate treatment:

- bicarbonate in DIALYSIS FLUID                                 $\pm 25$  % from set point

If other components can be added individually, additionally:

- other electrolytes in DIALYSIS FLUID                         $\pm 20$  % from set point

Where HEMODIAFILTRATION without buffer (special form of HDF where the buffer is given to the PATIENT not as part of the DIALYSIS FLUID but as part of the SUBSTITUTION FLUID) and other special

procedures are concerned, the technical safety requirements should be defined in the scope of the MANUFACTURER'S RISK MANAGEMENT PROCESS.

#### **Subclause 201.12.4.4.102 DIALYSIS FLUID and SUBSTITUTION FLUID temperature**

Long-term application of DIALYSIS FLUID temperatures above body temperature will result in a positive thermal energy balance for the PATIENT, which is associated with physiological reactions. Increased body temperature leads to increased perfusion of the skin and in consequence frequently to clinically relevant blood pressure drop. Temperatures above 46 °C cause hemolysis.

Decrease of body temperature results in discomfort and trembling. The tolerance limits of the body are some tenths of a °C.

Increasing the temperature above 42 °C for a short time is permitted to enable e.g. the measurement of recirculation by temperature measurement. A short-term increase is uncritical because it doesn't lead to perturbation of the energy balance of the body.

Blood damage (thermal hemolysis) occurs when blood is heated to more than 46 °C for a prolonged time. Blood temperatures up to 46 °C in the EXTRACORPOREAL CIRCUIT have been used for hyperthermia treatment. Low temperatures have no adverse effect on blood. Historically blood has been dialyzed at 5 °C.

The DIALYZER is a very efficient heat exchanger and any temperature gradient will change the thermal energy balance of the PATIENT. A prolonged positive thermal energy balance is known to cause hypotension while a prolonged large negative balance will be uncomfortable for the PATIENT and cause shivering.

To avoid high positive energy balances that may cause hypotension, the maximum DIALYSIS FLUID temperature is limited to 42 °C or less.

No adverse effects besides PATIENT discomfort are known for low DIALYSIS FLUID temperatures. Ventricular fibrillation has been reported after cooling of the heart to less than 33 °C by rapid infusion of large amounts (>5 l) of cold (4 °C) blood. In HEMODIALYSIS cooling to 33 °C would take > 15 min even assuming high blood flow, low DIALYSIS FLUID temperature (10 °C) and low body weight (50 kg).

#### **Subclause 201.12.4.4.103 NET FLUID REMOVAL**

The direction of a fluid balancing error is an essential factor: insufficient removal is un-hazardous in case of chronic dialysis, if it is detected and corrected before the PATIENT is discharged. Excessive removal is hazardous. Hyperhydration (fluid supplied) can be hazardous and depends on the initial situation.

Monitoring of the following limits by the PROTECTIVE SYSTEM is usually considered to be appropriate for 4 h of dialysis:

- a) the NET FLUID REMOVAL is within  $\pm 0.1$  l/h of the set point, and
- b) the target NET FLUID REMOVAL is to be kept within  $\pm 400$  ml at any time during the treatment.

Safe limits for an acceptable NET FLUID REMOVAL error cannot be derived from physiological data, however, the medical industry has many years of experience with fluid balancing systems. The limits given in 201.12.4.4.103 are derived from this experience.

TMP monitoring is not considered to be an adequate protection against fluid balancing errors in the case of high-flux DIALYZERS. (However, TMP monitoring can improve the safety and performance in a different way, e.g. with regard to the detection of a secondary membrane, interdialytic hyperuremia, undetected membrane rupture, "rescuing" the DIALYZER if heparinization is inadequate.)

Possible sources of fluid balancing errors which should be covered by a PROTECTIVE SYSTEM are, for example: leaks at connectors (including SUBSTITUTION FLUID), errors in the balancing system (e.g. flow meter, balancing chamber).

#### **Subclause 201.12.4.4.104.1 a) Extracorporeal blood loss to the environment**

Monitoring of the VENOUS PRESSURE is not always suitable for detecting a blood loss in time, in case the venous puncture cannula slips out. The VENOUS PRESSURE is determined mainly by the hydraulic resistance of the venous puncture cannula, particularly with today's usual high blood flow rates of up to 500 ml/min. A VENOUS PRESSURE ALARM SYSTEM is, hence, not able to always detect whether or not the puncture cannula slips out.

If dialysis is performed in the single-needle mode with only one blood pump ("single-needle single pump", "SN click-clack"), the VENOUS PRESSURE measurement is an integral part of the control system. An error in this control system (e.g. pressure sensor stuck to low value) might lead to the upper changeover point of the VENOUS PRESSURE never being reached. As a result, the pressure becomes too high, the tubing system may burst, and the PATIENT may lose a great amount of blood. This may require a PROTECTIVE SYSTEM which is independent of the control system, e.g. monitoring of the phase duration by an independent microprocessor.

Inherent safe design is e.g. a pump rotor that is spring-mounted so smoothly that bursting of the tubing is not possible. However, in this case the HAZARD of hemolysis may exist.

Other measures for prevention of overpressure are holders for the EXTRACORPOREAL CIRCUIT lines and the DIALYZER which make kinking sufficiently unlikely.

Blood loss to the environment caused by disconnections or faults in the EXTRACORPOREAL CIRCUIT cannot be prevented by any PROTECTIVE SYSTEM. The PROTECTIVE SYSTEM should be designed so that blood loss is detected and major blood loss is prevented. Most reported cases of fatal blood loss are caused by blood access cannulas slipping from the fistula or graft. This cannot be prevented by the HEMODIALYSIS EQUIPMENT. Traditionally, VENOUS PRESSURE monitors have been used for protection of blood loss to the environment. These sensors detect a drop of the pressure in the return bloodline. In case of a bloodline rupture or disconnection of the bloodline from the blood access device (cannula or central venous catheter) the pressure will drop considerably because of the high flow resistance in the blood access device. When the venous cannula slips from a fistula the pressure change is usually too low to be detected by the VENOUS PRESSURE monitor. The pressure drops only by the amount of the fistula pressure which is typically 5 mmHg – 20 mmHg. To avoid frequent nuisance alarms caused by PATIENT movement the difference between the actual VENOUS PRESSURE and the lower pressure ALARM LIMIT is usually adjusted to 10 mmHg – 20 mmHg.



Monitors employing pressure pulses or other parameters may offer greater sensitivity but may also require up to a minute to detect the fault condition and switch off the blood pump. With high blood flow this may cause blood losses of 500 ml, which are usually not fatal for adults.

The effects of hemorrhage are described by:

GUYTON AC. Circulatory Shock and Physiology of Its Treatment. Guyton AC, editor, *Textbook of Medical Physiology*, Eight Edition. W.B. Saunders Company, 1991: pp 263-71

#### **Subclause 201.12.4.4.104.1 c) Extracorporeal blood loss to the environment**

As alarm reaction, the stopping of an occluding blood pump is considered as sufficient. The additional closing of the safety clamp adds only little value because a rupture will occur most likely at the point of highest pressure, which normally is between blood pump and DIALYZER. In this case “retrograde” blood loss via the venous bloodline is negligible compared to the direct blood loss through the arterial bloodline.

If staff is not present (e.g. home PATIENT) or delayed for a long period in the case of venous puncture cannula slippage, the blood loss from the venous access (backwards) may become hazardous to the PATIENT.

#### **Subclause 201.12.4.4.104.2 BLOOD LEAK to the DIALYSIS FLUID**

An acceptable method of complying with this requirement is, for example, a PROTECTIVE SYSTEM utilizing a BLOOD LEAK detector.

BLOOD LEAKS of less than 0.35 ml/min blood (with an Hct of 32 %) are not considered to present a HAZARD.

Historically, BLOOD LEAK sensitivity has been specified in milligrams of hemoglobin per liter (mgHb/l) of DIALYSIS FLUID, probably because of the established spectrophotometric tests for determination of hemoglobin. Specification in mgHb, however, requires calculation to determine the quantity of blood lost, which is the parameter of interest to the practitioner. The threshold limits of 55 mg Hb/l were translated to 0.35 ml/min of blood, respectively. Calculations were based on the assumption of 14 grams Hb/100 ml blood in normal subjects, a Hct of 46 % (0.46) in normal subjects, a hematocrit possibly as low as 25 % (0.25) in typical HEMODIALYSIS PATIENTS, and a DIALYSIS FLUID flow rate of 500 ml/min.

#### **Subclause 201.12.4.4.104.3 Extracorporeal blood loss due to coagulation**

In this case, an independent PROTECTIVE SYSTEM is not required because the degree of harm is limited to the blood loss in the EXTRACORPOREAL CIRCUIT.

At the time of writing of this standard there are no scientific publications available about coagulation of blood as a function of the stopping time of the extracorporeal blood flow. A maximum alarm delay time of three minutes has been proven by experience to be appropriate.

#### **Subclause 201.12.4.4.105 Air infusion**

At the time of writing of this standard there was not enough scientific literature to define a safe ALARM LIMIT in this particular standard. In *Replacement of renal function by dialysis*, 5th ed.,

chapter 14, Polaschegg and Levin consider the continuous infusion of air of less than 0.03 ml/(kg min) and infusion of a bolus of 0.1 ml/kg not to be a HAZARD.

If there is no air in the tubing system with the HEMODIALYSIS EQUIPMENT being used as intended, the presence of air presents already a first fault, and it may be improbable that an independent second fault (e.g. failure of the air detector) occurs during the same treatment. In this case, the air detector would not need to be SINGLE FAULT SAFE. This has to be determined by RISK MANAGEMENT.

If air is permanently present in the tubing system with the HEMODIALYSIS EQUIPMENT being used as intended, e.g. if a partially filled drip chamber is used, air in the system is the NORMAL CONDITION (not a first fault). If a normal operating mode (not a technical failure) can lead to infuse this air to the PATIENT, the air detector has to be SINGLE FAULT SAFE.

An air detector is SINGLE FAULT SAFE, if, for example:

- a) it is designed with two channels and each channel is tested prior to each treatment; or
- b) it is designed with one channel and is tested periodically during the treatment, with the test interval having to be shorter than the fault tolerance time. The fault tolerance time is the shortest time required by an air bubble to move from the air detector to the PATIENT CONNECTION.

A SINGLE FAULT SAFE method to stop the blood flow to the PATIENT is for example as follows:

- a) it is completely designed with two channels (e.g. stopping of the pumps and closing of the clamps) and both channels are tested; or
- b) the blood pump(s) and all pumps delivering in the direction of the PATIENT are turned off via two channels and even a mechanical failure (e.g. breakage of a rotor spring) cannot cause a loss of occlusion.

If air, accumulated in the EXTRACORPOREAL CIRCUIT can reach the PATIENT by expansion even if the blood pump is stopped by an air detector alarm, an additional clamp has to be provided to prevent air infusion into the PATIENT.

This is typically the case when the air detector is positioned downstream of the DIALYZER.

No additional clamp is typically required if the air detector is positioned downstream of the blood pump but upstream of the DIALYZER and, if a leak in the negative pressure section of the EXTRACORPOREAL CIRCUIT is the only pathway for ingress of air.

Where HEMODIALYSIS EQUIPMENT is concerned which can raise or lower the level in the drip chamber by means of an electrically operated air pump, a malfunction of this air pump may cause air in the tubing system. If this air pump is able to build up a pressure that is higher than the occlusion pressure of the venous clamp, the venous clamp no longer presents a safe switch off path. In this case, the air pump has also to be switched off in a SINGLE FAULT SAFE manner. In addition, it should be noted that the air pump might be able to press air into the PATIENT via the arterial bloodline when the blood flow is stopped (e.g. because of an alarm) and that this air would not be detected by the air detector.

In case of single-needle procedures, it should be noted that, owing to the compressed air present in the system, the actual blood flow can be temporarily higher than the set blood flow. This should be taken into consideration when the scanning interval of the air detector and the fault tolerance time are determined.

In case of a failure of the power supply, air in the EXTRACORPOREAL CIRCUIT under pressure may also generate flows in direction of the venous and/or arterial PATIENT CONNECTION. In this case, air has to be prevented from reaching the PATIENT.

At least the following potential sources of air should be considered in the RISK ANALYSIS:

- air in the drip chamber;
- residual air in the bloodline;
- residual air in the DIALYZER;
- air in the monitor lines leading to the pressure transducers;
- air entering the system in the recirculation path of a single needle treatment;
- air entering the EXTRACORPOREAL CIRCUIT.

Non-dissolved air can appear in bulk and in the form of bubbles of different sizes.

The physical principle used for any air detector and electronic delay or dead times should be taken into account in the RISK ANALYSIS. Today ultrasonic air detectors are used almost exclusively for the detection of air in the EXTRACORPOREAL CIRCUIT. Some of these air detectors are positioned on the partially air-filled venous drip chamber. They are usually designed as level detectors, which means that they will generate an alarm if the level decreases or if the drip chamber is filled with foam.

Other air detectors are positioned directly on the blood tubing and are usually capable of detecting single bubbles with volumes much lower than the volumes believed to cause a HAZARD. The important parameter of the air detector is the accumulated volume of these single bubbles. In order to avoid nuisance alarms the number of detected bubbles is integrated with a time function.

#### **Subclause 201.12.4.4.106 Alarm override modes**

It should not be possible to deactivate the BLOOD LEAK detector inadvertently. Possible solutions might, for example, be two independent actions on the OPERATOR's part and automatic restart on commencement of the next treatment. Deactivation of the BLOOD LEAK detector should not increase the RISK of blood loss to a higher degree than necessary. An acceptable method is to design the BLOOD LEAK detector such that it is not only possible to switch it off completely but also to reduce its sensitivity and that this reduction will be automatically cancelled again on commencement of the next treatment.

#### **Subclause 201.12.4.4.109 Blood pump(s) and/or SUBSTITUTION FLUID pump(s) reversal**

Example of a HAZARD caused by human error:

In case of mains power failure in a dialysis unit it is very likely that the staff is under high stress and therefore human error is relative likely. In this situation the HAZARD of air infusion via the arterial bloodline (if applicable) by wrong blood pump direction can be avoided e.g. by:

- a) prevention of wrong hand cranking direction by
  - a unidirectional cranking mechanism or
  - a clearly marked arrow on the pump(s); or
- b) avoidance of hand cranking by continuation of the blood flow with battery power.

Example of a HAZARD caused by a technical fault:

A technical fault could cause the blood pump(s) and/or SUBSTITUTION FLUID pump(s) to rotate in the wrong direction. This can be avoided e.g. by:

- a) wiring a DC motor with electromechanical commutation such that no random hardware failure can reverse the direction of the current; or
- b) implementation of a PROTECTIVE SYSTEM independent of the motor control system, which stops the motor in case of wrong direction.

#### **Subclause 201.13.2.6 Leakage of liquid**

The test considers that fluid may flow out under normal working pressure. Although its performance and reproduction is difficult, the test specified in this particular standard is considered to be suitable for this type of equipment.

#### **Subclause 201.14.13 Connection of PEMS by NETWORK/DATA COUPLING to other equipment**

A method proven to reduce RISK for the transfer of HEMODIALYSIS EQUIPMENT settings via a network is the explicit test of the data transferred, performed by the OPERATOR and confirmation by the OPERATOR before these settings become effective in the HEMODIALYSIS EQUIPMENT.

#### **Subclause 201.15.4.1.101 DIALYSIS FLUID CONCENTRATE connectors**

DIALYSIS FLUID CONCENTRATES may be used in the form of powder or fluid. For DIALYSIS FLUID CONCENTRATES in the form of powder and "DIALYSIS FLUID ions for sodium chloride (powdered)", constructional features preventing their misuse are usually provided in the HEMODIALYSIS EQUIPMENT designs. Liquid DIALYSIS FLUID CONCENTRATES are taken either from containers or from CENTRAL DELIVERY SYSTEMS, which are not prevented from being misused by constructional features.

At least the following DIALYSIS FLUID CONCENTRATE types should be taken into consideration in the RISK MANAGEMENT PROCESS:

- acetate DIALYSIS FLUID CONCENTRATE;
- acid DIALYSIS FLUID CONCENTRATE for use with bicarbonate DIALYSIS FLUID CONCENTRATE without sodium chloride;  
NOTE 1 With 35X, 36.83X, 45X dilution.
- acid DIALYSIS FLUID CONCENTRATE for use with bicarbonate DIALYSIS FLUID CONCENTRATE with sodium chloride;  
NOTE 2 With 35X, 36.83X, 45X dilution.
- bicarbonate DIALYSIS FLUID CONCENTRATE without sodium chloride;  
NOTE 3 Can be supplied as liquid or powder.
- bicarbonate DIALYSIS FLUID CONCENTRATE with sodium chloride;
- sodium chloride;  
NOTE 4 Can be supplied as liquid or powder.
- concentrates complementary to sodium and bicarbonate;  
NOTE 5 Used for mixing systems with separate sodium and bicarbonate concentrate supplies.  
NOTE 6 Can be supplied as liquid or powder.

#### Subclause 201.15.4.1.102 Connectors for blood pressure transducers

An internal transducer protector placed between the internal pressure transducer and the connection to the external transducer protector is one method of preventing HEMODIALYSIS EQUIPMENT contamination.

#### Subclause 201.16 ME SYSTEMS

A ME SYSTEM for dialysis can comprise one or more types of HEMODIALYSIS EQUIPMENT and one or more of the following:

- water treatment system;
- discharge (drain);
- data transfer;
- CENTRAL DELIVERY SYSTEM;
- staff call system.

NOTE Since TOUCH CURRENTS of other equipment exist in the PATIENT ENVIRONMENT (e.g. dialysis chairs), a POTENTIAL EQUALIZATION CONDUCTOR could be necessary for such equipment.

The water treatment systems and the CENTRAL DELIVERY SYSTEMS are usually set up at a location that is remote from the HEMODIALYSIS EQUIPMENT and cannot be connected via a MULTIPLE SOCKET-OUTLET. HAZARDS have to be minimized via the installation, by applying the supply lines, for example, to the same potential as the HEMODIALYSIS EQUIPMENT.

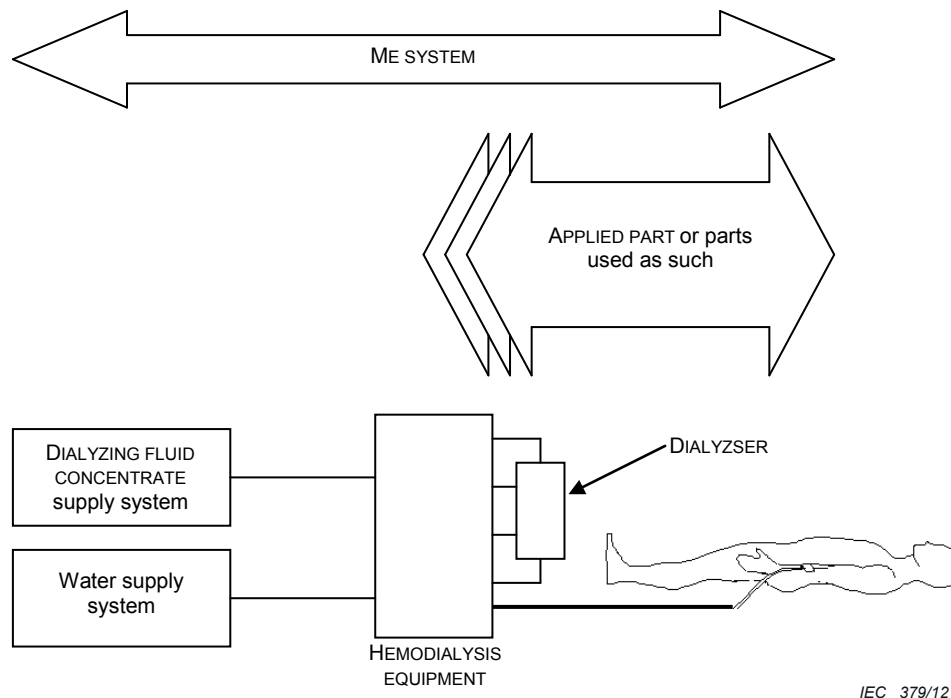


**Figure AA.1 – Example of the HEMODIALYSIS ME SYSTEM**

For HEMODIALYSIS EQUIPMENT with TYPE CF APPLIED PARTS the following item should be considered:

The bloodlines of the EXTRACORPOREAL CIRCUIT are not considered to be insulating. It should be assumed that conducting solutions in and around the tubing establish an electrical contact to the PATIENT.

An EXTRACORPOREAL CIRCUIT or DIALYSIS FLUID circuit is considered isolating if:

- a) the material is electrically isolating, and
- b) the circuit is built such that a rupture is sufficiently unlikely.

Point a) is tested by applying 1,500 V AC to the relevant segments of the circuit, filled with 0.9 % NaCl. A conductive foil is wrapped over the tube over a length of 10 cm. No breakthrough between foil and fluid should occur over 1 min.

Point b) is demonstrated by the MANUFACTURER of the circuit by RISK MANAGEMENT which includes the interface between HEMODIALYSIS EQUIPMENT and circuit and the manufacturing process.

#### **Subclause 201.16.9.1 Connection terminals and connectors**

According to the state of technology, the PROTECTIVE SYSTEM for "composition of the DIALYSIS FLUID" is based on the measurement of the conductivity or the volumetric admixture. Depending on the operating mode (acetate, bicarbonate), an incorrect DIALYSIS FLUID CONCENTRATE is frequently detected via the conductivity or the volumetric admixture.

Additional measures besides color coding of the CENTRAL DELIVERY SYSTEM may be required by RISK MANAGEMENT in case of DIALYSIS FLUID CONCENTRATES which, although they deliver a conductivity within the expected range, are hazardous for the treatment type concerned in their composition (e.g. acid DIALYSIS FLUID CONCENTRATE 45X ratio for acetate dialysis).

In such cases, the RESPONSIBLE ORGANIZATION should initiate the appropriate measures which are equivalent to color coding with the pertinent operating mode, such as disabling the operating mode of acetate dialysis or mechanically coding the HEMODIALYSIS EQUIPMENT and the DIALYSIS FLUID CONCENTRATE container.

#### **Subclause 208.4 General requirements**

IEC 60601-1-8 is written from the view of intensive care or surgery environments and adds in the clause 6.1.2 ALARM CONDITION priority a very PATIENT centric view of potential results of failure to respond to the cause of ALARM CONDITIONS. HEMODIALYSIS EQUIPMENT is mainly used in a chronic ambulant approach. The PATIENTS normally do not have life threatening status, ALARM CONDITIONS mostly arise from technical causes and the therapy has in most cases of problems the chance to go to a safe state, which only loses time for PATIENT and OPERATORS, but which is one of the most important issues in a timely exact planned schedule of subsequent following shifts. The environment in a normal chronic HEMODIALYSIS clinic is dominated by the HEMODIALYSIS EQUIPMENT, in many cases from one MANUFACTURER. Normally other ME EQUIPMENT will not be used continuously beside the HEMODIALYSIS EQUIPMENT in the PATIENT ENVIRONMENT.

In this ambulatory environment the alarm categories need completely different priorities than in an environment where the PATIENTS have life threatening status and the therapy is life-supporting. In the ambulatory environment subclause 6.1.2 ALARM CONDITION priority with Table 1 would not mirror the needed priorities.

Even in the critical care environments the HEMODIALYSIS EQUIPMENT is not life-supporting and most alarm situations would not be a HAZARD for PATIENT and OPERATOR and the alarm priority will

be low. In some cases OPERATORS from chronic hemodialysis support and operate the HEMODIALYSIS EQUIPMENT in the intensive care environment.

For HEMODIALYSIS EQUIPMENT not used in intensive care environments the actual used – over years of operation optimized – ALARM SYSTEMS should not be worsened by the need of applying IEC 60601-1-8:2006.

Because of these reasons this standard only requires the complete implementation of IEC 60601-1-8:2006 for HEMODIALYSIS EQUIPMENT with INTENDED USE in the intensive care environment. For this environment Table AA.1 shows how possible ALARM CONDITION priorities according to IEC 60601-1-8:2006 could be adapted for HEMODIALYSIS EQUIPMENT needs. If the HEMODIALYSIS EQUIPMENT is intended to be used in both environments the ALARM SYSTEM according to IEC 60601-1-8:2006 has to be implemented and selectable by the RESPONSIBLE ORGANIZATION, but ALARM SYSTEMS with deviation from subclauses 6.1.2 ALARM CONDITION priority, 6.3.2.2 Characteristics of visual ALARM SIGNALS, 6.3.3.1 Characteristics of auditory ALARM SIGNALS are allowed for additional implementation.

This particular standard does not mandatorily require for HEMODIALYSIS EQUIPMENT with a screen that the visual alarm has to be indicated by an indicator light that is independent of the screen, since there may be applications where it is appropriate if the alarm is indicated on the screen. In large-size dialysis units, however, it is probably more appropriate to provide an indicator light that can be seen from a far distance and is installed at an up-raised position, so that the HEMODIALYSIS EQUIPMENT activating the ALARM SIGNAL can be readily located.

**Table AA.1 – Possible ALARM CONDITION priorities according to 6.1.2 of IEC 60601-1-8:2006, adapted for hemodialysis equipment needs.**

| ALARM CONDITION                                                                                                   | ALARM CONDITION priority                                                                  |
|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Different reasons (e.g. pressures, technical faults)                                                              |                                                                                           |
| Reasons that lead to a stop of the blood system                                                                   | LOW PRIORITY, yellow                                                                      |
| Blood loss due to coagulation in the extracorporeal system                                                        |                                                                                           |
| Blood pump stop alarm (201.12.4.4.104.3), as escalation of above alarm                                            | MEDIUM PRIORITY, yellow flashing                                                          |
| Mains off – battery running system, before battery goes down                                                      |                                                                                           |
| Possible blood loss out of the puncture side or open catheter, following accidental needle or catheter disconnect |                                                                                           |
| Detectable by low VENOUS PRESSURE                                                                                 | HIGH PRIORITY, red flashing                                                               |
| PHYSIOLOGICAL ALARM CONDITIONS, if not specified in other standards                                               |                                                                                           |
| Physiological alarms, e.g. non invasive blood pressure limit alarm                                                | HIGH PRIORITY, red flashing<br>Possible: escalation with two different limits.            |
| Treatment deviation, influence on prescription                                                                    |                                                                                           |
| E.g. balancing alarms, long lasting bypass of DIALYZING FLUID                                                     | LOW PRIORITY, yellow                                                                      |
| Technical information                                                                                             |                                                                                           |
| Technical faults, but blood system is running, e.g. short bypass of dialysate                                     | INFORMATION SIGNAL, e.g. green flashing<br>Alternative is the use of LOW PRIORITY, yellow |

An ALARM SIGNAL activated in case of extracorporeal blood loss to the environment (see 201.12.4.4.104.1) is one example of a HIGH PRIORITY ALARM SIGNAL that requires immediate response by the OPERATOR. If the blood flow is stopped for an extended period of time (201.12.4.4.104.3), this is an example for a MEDIUM PRIORITY ALARM SIGNAL. In most other ALARM CONDITIONS the PROTECTIVE SYSTEM puts the HEMODIALYSIS EQUIPMENT in a state, which is safe for the PATIENT, at least temporarily, and therefore such an ALARM SIGNAL is indicated by a LOW PRIORITY ALARM SIGNAL. Other ALARM SIGNALS should be determined by the MANUFACTURER'S RISK MANAGEMENT PROCESS.

#### **Subclause 208.6.3.1 General**

If the OPERATOR is allowed to configure the contents of the screen, the MANUFACTURER has to use constructive measures (and not notes in the instructions for use) to ensure that the alarms are indicated under any and all circumstances.



#### **Subclause 208.6.3.3.2 Volume of auditory ALARM SIGNALS and INFORMATION SIGNALS**

It is intended to prevent the OPERATOR from misusing the volume adjustment function for silencing alarms, since such a silencing could not be terminated automatically. The RESPONSIBLE ORGANIZATION, however, should have the possibility of adjusting the alarm volume to a reasonable value depending on the sound level on site.

#### **Subclause 208.6.3.3.101 Special characteristics of auditory ALARM SIGNALS for HEMODIALYSIS EQUIPMENT**

There are alarms which do not present any HAZARD if they are paused for more than 3 min, but where elimination of the cause of the alarm often takes more than 3 min, e.g. in case of a conductivity alarm caused by an empty DIALYSIS FLUID CONCENTRATE container. In this case, the PATIENT's state will not aggravate during the alarm AUDIO PAUSED period and the activated bypass mode.

#### **Subclause 211 Requirements for MEDICAL ELECTRICAL EQUIPMENT and MEDICAL ELECTRICAL SYSTEMS used in the HOME HEALTHCARE ENVIRONMENT**

Besides the PERMANENTLY INSTALLED connection to SUPPLY MAINS, other means of preventing connection to a non-grounded outlet can be used, such as a unique MAINS PLUG connector that is normally not used in the HOME HEALTHCARE ENVIRONMENT. This allows the PATIENT OPERATOR to disconnect and remove the device without the problem of reconnecting it to another SUPPLY MAINS socket-outlet with improper PROTECTIVE EARTH CONNECTION. If a unique SUPPLY MAINS socket-outlet connector is used, it has to be installed and tested by the RESPONSIBLE ORGANIZATION.

**Annex BB**  
(informative)

**Examples of HAZARDS, foreseeable sequences of events, and HAZARDOUS SITUATIONS  
in HEMODIALYSIS EQUIPMENT**

Table BB.1 is not intended to be a complete RISK ANALYSIS and is provided partially and for example only. Given HARM levels do not apply to all PATIENT groups. Risk assessment is the responsibility of each MANUFACTURER.

**Table BB.1 – Hazardous situation list following ISO 14971:2007, Annex E**

| HAZARD                    | Foreseeable sequence of events                                     | HAZARDOUS SITUATION                                              | Harm                               | Reference Standard                                                                           |
|---------------------------|--------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------|
| Multiple HAZARDS possible | Venous needle punctures vascular access                            | Extracorporeal blood flow into intertissue through venous needle | Hematoma                           |                                                                                              |
|                           | Delivery rate or amount of heparin too high                        | Heparin concentration too high inside blood volume               | Excessive bleeding                 | - IEC 60601-2-16 (this standard): 201.11.8                                                   |
|                           | Blood flow was stopped too long                                    | Coagulation of extracorporeal blood                              | Blood loss                         | - IEC 60601-2-16: 201.7.9.2.5; 201.7.9.3.1; 201.11.8; 201.12.4.4.104.3                       |
|                           | Interruption of power supply too long                              |                                                                  |                                    | - IEC 60601-1, 3ed:2005: 7.9.2.4                                                             |
|                           | High ultrafiltration rate over membrane in relation to blood flow  | Increasing hematocrit may block fibers of dialyzer               |                                    | - IEC 60601-2-16: 201.11.8; 201.7.9.3.1; 201.12.4.4.104.3                                    |
|                           | Venous needle slips out                                            | Extracorporeal blood is pumped to environment                    |                                    | - IEC 60601-2-16: 201.12.4.4.104.3                                                           |
|                           | Connector of disposable behind arterial blood pump opened or leaks |                                                                  |                                    | - IEC 60601-2-16: 201.7.9.2.2, 7th dash; 201.7.9.3.1, 2nd bullet, 6th dash; 201.12.4.4.104.1 |
|                           | Pressure higher than disposal resist leading to rupture            |                                                                  |                                    | - IEC 60601-2-16: 201.7.9.2.2, 3rd dash; 201.12.4.4.104.1                                    |
|                           | Post-blood pump heparin pump syringe plunger slipped out           |                                                                  |                                    | - EC 60601-2-16: 201.12.4.4.104.1                                                            |
|                           |                                                                    |                                                                  | - IEC 60601-2-16: 201.12.4.4.104.1 |                                                                                              |

| HAZARD | Foreseeable sequence of events                                                                               | HAZARDOUS SITUATION                           | Harm                                   | Reference Standard                                                                                                         |
|--------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
|        | Dialyzer membrane or fiber broken                                                                            | Blood leaks into dialysis fluid               |                                        | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 7th dash; 201.12.4.4.104.2                                                      |
|        | Unintended Blood flow reversal and air in the system                                                         | Air infused over arterial branch              | Air infusion                           | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 2nd dash; 201.12.4.4.109                                                        |
|        | Level regulator pump pumps air into arterial pressure monitor pre-arterial blood pump                        |                                               |                                        | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 2nd dash; 201.12.4.4.109                                                        |
|        | Air sucked into blood side before blood pump (material damage or unintentional opening of the infusion port) | Air infused over venous branch                |                                        | - IEC 60601-2-16: 201.7.9.2.2, 8th dash; 201.7.9.3.1, 2nd bullet, 2nd dash; 201.12.4.4.105; 201.12.4.4.106; 201.12.4.4.107 |
|        | Level regulator pump pumps air into arterial and/or venous pressure monitor post arterial blood pump         |                                               |                                        | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 2nd dash; 201.12.4.4.105, 201.12.4.4.106, 201.12.4.4.107                        |
|        | Substitution pump pumps air into venous branch                                                               |                                               |                                        | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 2nd dash; 201.12.4.4.105; 201.12.4.4.106; 201.12.4.4.107                        |
|        | Improper function of ultrasonic air detector caused by coagulum or ultrasound gel                            |                                               |                                        | - IEC 60601-2-16: 201.7.9.2.2, 10th dash                                                                                   |
|        | Air entering the system in the recirculation path of single needle treatment                                 |                                               |                                        | - IEC 60601-2-16: 201.7.9.2.2, 11th dash                                                                                   |
|        | Blood line kinked (specially dialyzer input)                                                                 | Red blood cells exposed to high sheer forces. | Hemolysis                              | - IEC 60601-2-16: 201.7.9.2.2, 9th dash                                                                                    |
|        | Reduced blood flow by high negative arterial pre-pump pressure                                               | Reduced effectiveness of dialysis             | Prescribed dialysis dose not delivered | - IEC 60601-2-16: 201.7.9.2.2, 13th dash                                                                                   |
|        | Insufficient degassing of dialysis fluid                                                                     |                                               |                                        |                                                                                                                            |
|        | Insufficient flow of fresh dialysis fluid                                                                    |                                               |                                        | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet,4th dash                                                                         |
|        | Blood flow too low by technical defect                                                                       |                                               |                                        | - IEC 60601-2-16: 201.4.3.101                                                                                              |
|        | Dialysis fluid bypassing dialyzer                                                                            |                                               |                                        | - IEC 60601-2-16: 201.4.3.101                                                                                              |

| HAZARD                    | Foreseeable sequence of events                                                                                 | HAZARDOUS SITUATION                                                                        | Harm                                        | Reference Standard                                                                                                |
|---------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
|                           | Effective dialysis time too low by technical defect                                                            |                                                                                            |                                             | - IEC 60601-2-16: 201.4.3.101                                                                                     |
|                           | Substitution fluid flow too low by technical defect                                                            |                                                                                            |                                             | - IEC 60601-2-16: 201.4.3.101                                                                                     |
| Biological                | Blood of the previous PATIENT is flown into the pressure inlet connection of the machine                       | Pyrogens/ endotoxins/bacteria/viruses may contaminate the blood directly (Cross infection) | Virus/bacterial infection/ Pyrogen reaction | - IEC 60601-2-16: 201.15.4.102                                                                                    |
|                           | Disinfection procedure of machine internally and externally has inadequately removed viruses contamination     |                                                                                            |                                             | - IEC 60601-1:2005 (3ed): 7.9.2.12, 11.6.6<br>- IEC 60601-2-16: 201.7.9.2.12 1st, 2nd, 3rd dash; 201.11.6.6       |
|                           | Infusion of contaminated dialysis fluid into blood from dialysis fluid side in online HDF/HF systems           | Pyroxenes/ endotoxins/bacteria may contaminate the blood directly                          |                                             | - IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 14th dash; 201.12.4.4.111                                              |
|                           | Contaminated surface of enclosure                                                                              | Skin contamination with bacteria                                                           | Bacterial infection                         | - IEC 60601-2-16: 201.7.9.2.2, 1st dash                                                                           |
| Chemical                  | Treatment of PATIENT when machine is in disinfection mode                                                      | Blood contamination with toxins                                                            | Poisoning / allergy                         | - IEC 60601-2-16: 201.12.4.4.108                                                                                  |
|                           | Dialysis fluid system has been inadequately rinsed out from disinfectant                                       |                                                                                            |                                             | - IEC 60601-2-16: 201.11.6.6                                                                                      |
|                           | OPERATOR uses disinfectant canister instead of BIC concentrate or acid/acetate concentrate canister to machine |                                                                                            |                                             | - IEC 60601-1:2005 (3ed): 15.4.1<br>- IEC 60601-2-16: 201.15.4.1.101                                              |
|                           | Toxic materials comes in contact with dialysis fluid                                                           |                                                                                            |                                             | - IEC 60601-1:2005 (3ed): 11.7<br>- IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 13th dash                            |
| Biological                | Returning fluid into central water/concentrate supply                                                          | Blood contamination with toxins                                                            | Poisoning/ allergy                          | - IEC 60601-2-16: 201.12.4.4.108                                                                                  |
| Multiple HAZARDS possible | Dialyzing / substitution fluid temperature too low                                                             | Blood is cooled directly (infusion) or via dialyzer                                        | Cooling heart until cardiac arrest          | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.7.9.3.1, 2nd bullet, 4th dash; 201.12.4.4.102; 201.11.8 |

| HAZARD | Foreseeable sequence of events                                                          | HAZARDOUS SITUATION                                                                                 | Harm                        | Reference Standard                                                                                                                       |
|--------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
|        | Dialyzing / substitution fluid temperature too high                                     | Blood is heated directly (infusion) or via dialyzer                                                 | Hemolysis                   | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.7.9.2.6, 4th dash; 201.7.9.3.1, 2nd bullet, 4th dash; 201.12.4.4.102; 201.11.8 |
|        | Dialysis fluid composition lower than prescribed                                        | Blood is dialyzed or infused (HDF-Online) with too low composition (NaCl) of dialysis fluid         | Hyponatremia                | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.4.3.101; 201.7.9.3.1, 2nd bullet, 3rd dash                                     |
|        | Dialysis fluid composition lower than 120 mmol/l                                        |                                                                                                     | Hemolysis                   | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.101                                                                     |
|        | Dialysis fluid composition higher than prescribed                                       | Blood is dialyzed or infused (HDF-Online) with too high composition (NaCl) of dialysis fluid        | Hypernatremia               | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.4.3.101; 201.7.9.3.1, 2nd bullet, 3rd dash                                     |
|        | Dialysis fluid composition higher than 160 mmol/l                                       |                                                                                                     |                             | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.101                                                                     |
|        | Dialysis fluid bicarbonate composition too low                                          | Blood is dialyzed or infused (HDF-Online) with too low composition (bicarbonate) of dialysis fluid  | Acidosis                    | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.101                                                                     |
|        | Acid concentrate instead of acetate concentrate when acetate dialysis has been selected |                                                                                                     |                             | - IEC 60601-2-16: 201.7.9.2.5, 2nd dash; 201.12.4.4.101; 201.15.4.1.101; 201.16.9.1                                                      |
|        | Acid concentrate instead of BIC concentrate when BIC dialysis has been selected         |                                                                                                     |                             | - IEC 60601-2-16: 201.7.9.2.5, 2nd dash; 201.12.4.4.101; 201.15.4.1.101; 201.16.9.1                                                      |
|        | Acetate concentrate instead of BIC concentrate when BIC dialysis has been selected      |                                                                                                     |                             | - IEC 60601-2-16: 201.7.9.2.5, 2nd dash; 201.12.4.4.101; 201.15.4.1.101; 201.16.9.1                                                      |
|        | Acetate dialysis instead of BIC dialysis                                                |                                                                                                     | Hyperacetatemia             | - IEC 60601-2-16: 201.12.4.4.110                                                                                                         |
|        | Dialysis fluid bicarbonate composition too high                                         | Blood is dialyzed or infused (HDF-Online) with too high composition (bicarbonate) of dialysis fluid | Alkalosis                   | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.101                                                                     |
|        | Acetate concentrate instead of acid concentrate when BIC dialysis has been selected     |                                                                                                     |                             | - IEC 60601-2-16: 201.7.9.2.5, 2nd dash; 201.12.4.4.101; 201.15.4.1.101; 201.16.9.1                                                      |
|        | Substitution bolus volume too high                                                      | Blood volume increased                                                                              | Extracellular volume change | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.103                                                                     |
|        | Priming or returning volume too high by technical faults                                |                                                                                                     |                             | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.103                                                                     |

| HAZARD      | Foreseeable sequence of events                                  | HAZARDOUS SITUATION                           | Harm                        | Reference Standard                                                                                                                                                  |
|-------------|-----------------------------------------------------------------|-----------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             | Inlet dialysis fluid flow to dialyzer higher than outlet flow   |                                               |                             | - IEC 60601-2-16: 201.12.4.4.103; 201.7.9.2.2; 201.7.9.2.5; 201.7.9.3.1                                                                                             |
|             | Substitution volume higher than ultrafiltration volume          |                                               |                             | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.103                                                                                                |
|             | Dry weight not achieved                                         | Insufficient removal of blood water           | Interdialytic overhydration | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.103                                                                                                |
|             | Substitution bolus volume too low                               | Insufficient increase of PATIENT blood volume | Extracellular volume change | - IEC 60601-1:2005 (3ed): 12.4.3                                                                                                                                    |
|             | Ultrafiltration volume to high                                  | Excessive removal of blood water              |                             | - IEC 60601-1:2005 (3ed): 12.4.3<br>- IEC 60601-2-16: 201.12.4.4.103                                                                                                |
|             | Ultrafiltration rate greater than set rate                      |                                               |                             | - IEC 60601-1-10:2007: Clause 4<br>- IEC 60601-2-16: 201.12.4.4.103; 201.7.9.2.2; 201.7.9.2.5; 201.7.9.3.1; 201.11.8                                                |
|             | Dialysis fluid loss from balanced system                        |                                               |                             | - IEC 60601-2-16: 201.12.4.4.103                                                                                                                                    |
|             | Ultrafiltration volume higher than substitution volume          |                                               |                             | - IEC 60601-2-16: 201.12.4.4.103                                                                                                                                    |
| Operational | Restoring of data/instructions after power interruption wrong   | Incorrect treatment                           | Multiple harms possible     | - IEC 60601-2-16: 201.11.8                                                                                                                                          |
|             | Faulty treatment data/instructions from PATIENT card or network |                                               |                             | - IEC 60601-1:2005 (3ed): 14.13<br>- IEC 60601-2-16: 201.14.13                                                                                                      |
|             | Faulty treatment instruction(s) on screen from network          |                                               |                             | - IEC 60601-1:2005 (3ed): 14.13<br>- IEC 60601-2-16: 201.14.13                                                                                                      |
| Information | Periodical maintenance has not been carried out                 |                                               |                             | - IEC 60601-1:2005 (3ed): 7.9.2.13                                                                                                                                  |
|             | Expected service life is elapsed                                |                                               |                             | - IEC 60601-1:2005 (3ed): 4.4                                                                                                                                       |
|             | Markings or user information missing or wrong                   |                                               |                             | - IEC 60601-1:2005 (3ed): 7.1; 7.2; 7.4; 7.5; 7.6; 7.9.2<br>- IEC 60601-1-8:2006; 5.2; 6.1; 6.2<br>- IEC 60601-1-10:2007; 5.1; 5.2<br>- IEC 60601-2-16: 201.7.9.2.2 |

| HAZARD      | Foreseeable sequence of events                                              | HAZARDOUS SITUATION | Harm           | Reference Standard                                                                                                                |
|-------------|-----------------------------------------------------------------------------|---------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------|
|             | Service information missing or wrong                                        |                     |                | - IEC 60601-1:2005 (3ed): 7.3; 7.7; 7.9.2.13; 7.9.3                                                                               |
|             | OPERATOR response missing or wrong (USE ERROR)                              |                     |                | - IEC 60601-2-16: 201.7.9.2.6                                                                                                     |
|             |                                                                             |                     |                | - IEC 60601-1:2005 (3ed): 7.8; 7.9.2.8; 7.9.2.9; 7.9.2.10; 7.9.2.11; 7.9.2.14; 9.2.3.1; 12.1; 12.2; 12.4.2                        |
|             |                                                                             |                     |                | - IEC 60601-1-8:2006; 6.1.2; 6.3.1; 6.3.2.1                                                                                       |
|             |                                                                             |                     |                | - IEC 60601-1-10:2007; 6.1; 6.2; 6.3; 6.4                                                                                         |
|             |                                                                             |                     |                | - IEC 60601-2-16: 201.7.9.2.2; 201.7.9.2.6; 201.7.9.2.14; 201.7.9.3.1; 208.4; 208.6.3.1; 208.6.3.3.2; 208.6.3.3.3; 201.12.4.4.110 |
| Operational | Alarm override                                                              | Leakage current     | Electric shock | - IEC 60601-2-16: 201.12.4.4.106                                                                                                  |
|             | Failure of protective systems                                               |                     |                | - IEC 60601-2-16: 201.12.4.4.107                                                                                                  |
| Electrical  | Reduced insulation                                                          |                     |                | - IEC 60601-1:2005 (3ed): 8.5; 8.6; 8.7; 8.8; 13.1.3; 13.2.2                                                                      |
|             | Reduced CREEPAGE DISTANCES and air clearance                                |                     |                | - IEC 60601-2-16: 201.8.3; 201.8.7.4.7; 201.11.6.3                                                                                |
|             | Internal or external leaks that reduce CREEPAGE DISTANCES and air clearance |                     |                | - IEC 60601-1:2005 (3ed): 8.9; 13.2.6                                                                                             |
|             | Rapid aging of insulation                                                   |                     |                | - IEC 60601-2-16: 201.13.2.6                                                                                                      |
|             | Touching ACCESSIBLE PARTS                                                   |                     |                | - IEC 60601-1:2005 (3ed): 8.9                                                                                                     |
|             | Ingress of fluid into the device                                            |                     |                | - IEC 60601-1:2005 (3ed): 11.1; 11.6.6                                                                                            |
|             |                                                                             |                     |                | - IEC 60601-1:2005 (3ed): 4.8; 4.9; 5.9.2; 7.9.2.7; 8.4; 8.5; 8.10; 8.11; 9.2.2.4                                                 |
|             |                                                                             |                     |                | - IEC 60601-2-16: 201.7.9.2.6; 201.8.11.2                                                                                         |
|             |                                                                             |                     |                | - IEC 60601-1:2005 (3ed): 11.6                                                                                                    |
|             |                                                                             |                     |                | - IEC 60601-2-16: 201.11.6.3                                                                                                      |

| HAZARD     | Foreseeable sequence of events                                                                                               | HAZARDOUS SITUATION                  | Harm                                  | Reference Standard                                                                                           |
|------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------|
|            | Components are used outside of its specified current ratings                                                                 |                                      |                                       | - IEC 60601-1:2005 (3ed): 13.2.3                                                                             |
|            | Exchange of parts                                                                                                            |                                      |                                       | - IEC 60601-1:2005 (3ed): 15.2                                                                               |
|            | Mechanical parts of the housing                                                                                              |                                      |                                       | - IEC 60601-1:2005 (3ed): 15.3                                                                               |
|            | Overheating transformer                                                                                                      |                                      |                                       | - IEC 60601-1:2005 (3ed): 15.5                                                                               |
|            | Drain connected to central water supply                                                                                      |                                      |                                       | - IEC 60601-1:2005 (3ed): 15.4.1                                                                             |
|            | Concentrate connected to central water supply                                                                                |                                      |                                       | - IEC 60601-1:2005 (3ed): 15.4                                                                               |
|            | ME-System within/ outside the PATIENT ENVIRONMENT                                                                            |                                      |                                       | - IEC 60601-1:2005 (3ed): 16.1; 16.2; 16.3; 16.4; 16.5; 16.6; 16.9<br>- IEC 60601-2-16: 201.16.2; 201.16.6.3 |
|            | Treatment with atrial catheter with Type B device                                                                            | PATIENT leakage current              | Electric shock                        | - IEC 60601-1:2005 (3ed): 8.7<br>- IEC 60601-2-16: 201.7.9.2.5; 201.8.3                                      |
|            | Magnetic and electric fields cause disruption of proper operation through interference from other equipment and power supply | Incorrect treatment                  | Multiple harms                        | - IEC 60601-1-2:2007<br>- IEC 60601-2-16: 202.3.18                                                           |
|            | Magnetic and electric fields cause disruption of proper operation through interference to other equipment and power supply   |                                      | Multiple harms to PATIENTS and others | - IEC 60601-1-2:2007                                                                                         |
| Chemical   | Escape of chemical substances                                                                                                | Contact with chemicals               | Body harm                             | - IEC 60601-1:2005 (3ed): 7.9.2.4; 11.6.4                                                                    |
|            | High pressure fluid ejection                                                                                                 |                                      |                                       | - IEC 60601-1:2005 (3ed): 9.7                                                                                |
| Thermal    | Hot external or internal components                                                                                          | Contact with high temperature fluids | Body harm                             | - IEC 60601-1:2005 (3ed): 11.1; 11.6.4; 11.6.6                                                               |
|            | High pressure fluid ejection                                                                                                 |                                      |                                       | - IEC 60601-1:2005 (3ed): 9.7                                                                                |
| Mechanical | Finger into roller pump                                                                                                      | Crushing/Shearing/Limb breaking      | Bruise/ Sprain/Cut/Fractures          | - IEC 60601-1:2005 (3ed): 5.9.2; 9.2.2.4.4                                                                   |
|            | Limb between moving parts                                                                                                    |                                      |                                       | - IEC 60601-1:2005 (3ed): 9.2.2.2; 16.7                                                                      |
|            | Foot under the base                                                                                                          |                                      |                                       |                                                                                                              |
|            | Machine on inclined plane                                                                                                    |                                      |                                       | - IEC 60601-1:2005 (3ed): 9.4                                                                                |
|            | Displacement of machine                                                                                                      |                                      |                                       |                                                                                                              |



| HAZARD  | Foreseeable sequence of events                              | HAZARDOUS SITUATION | Harm                                  | Reference Standard                                             |
|---------|-------------------------------------------------------------|---------------------|---------------------------------------|----------------------------------------------------------------|
|         | Sharp parts                                                 | Cutting             | Body harm                             | - IEC 60601-1:2005 (3ed): 9.3                                  |
|         | Whole in housing with moving parts behind                   |                     |                                       | - IEC 60601-1:2005 (3ed): 5.9.2                                |
| Thermal | Components are used outside of it specified current ratings | Fire                | Multiple harms to PATIENTS and others | - IEC 60601-1:2005 (3ed): 4.8; 4.9; 13.1.2; 13.2.3; 13.2.13    |
|         | Ingress of water into the device leads to short cut current |                     |                                       | - IEC 60601-1:2005 (3ed): 11.6<br>- IEC 60601-2-16: 201.11.6.3 |
|         | Defect control of heater                                    |                     |                                       | - IEC 60601-1:2005 (3ed): 13.2.4; 13.2.5; 13.2.13; 15.4.2      |
|         | Impaired cooling                                            |                     |                                       | - IEC 60601-1:2005 (3ed): 13.2.7                               |
|         | Interruption and short circuit of motor capacitors          |                     |                                       | - IEC 60601-1:2005 (3ed): 13.2.9                               |
|         | Defects of battery                                          |                     |                                       | - IEC 60601-1:2005 (3ed): 15.4.3.1                             |
|         | Incorrect polarity of battery connection                    |                     |                                       | - IEC 60601-1:2005 (3ed): 15.4.3.2                             |
|         | Overcharging battery                                        |                     |                                       | - IEC 60601-1:2005 (3ed): 15.4.3.3                             |
|         | Excessive current from battery                              |                     |                                       | - IEC 60601-1:2005 (3ed): 15.4.3.5                             |
|         | Overheating transformer                                     |                     |                                       | - IEC 60601-1:2005 (3ed): 15.5                                 |

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<sup>2)</sup> Second edition, withdrawn and replaced by IEC 60601-2-16:2008.

## Index of defined terms used in this particular standard

|                                                   |                          |
|---------------------------------------------------|--------------------------|
| ACCESSIBLE PART .....                             | IEC 60601-1:2005, 3.2    |
| ACCESSORY .....                                   | IEC 60601-1:2005, 3.3    |
| ACCOMPANYING DOCUMENT .....                       | IEC 60601-1:2005, 3.4    |
| ALARM CONDITION.....                              | IEC 60601-1-8:2006, 3.1  |
| ALARM LIMIT .....                                 | IEC 60601-1-8:2006, 3.3  |
| ALARM SIGNAL .....                                | IEC 60601-1-8:2006, 3.9  |
| ALARM SYSTEM.....                                 | IEC 60601-1-8:2006, 3.11 |
| APPLIED PART.....                                 | IEC 60601-1:2005, 3.8    |
| ARTERIAL PRESSURE .....                           | 201.3.201                |
| AUDIO PAUSED.....                                 | IEC 60601-1-8:2006, 3.13 |
| BASIC SAFETY.....                                 | IEC 60601-1:2005, 3.10   |
| BLOOD LEAK .....                                  | 201.3.202                |
| CENTRAL DELIVERY SYSTEM.....                      | 201.3.203                |
| CLASS I.....                                      | IEC 60601-1:2005, 3.13   |
| CREEPAGE DISTANCE .....                           | IEC 60601-1:2005, 3.19   |
| DIALYZER .....                                    | 201.3.204                |
| DIALYSIS FLUID .....                              | 201.3.205                |
| DIALYSIS FLUID CONCENTRATE .....                  | 201.3.206                |
| EARTH LEAKAGE CURRENT .....                       | IEC 60601-1:2005, 3.25   |
| ESSENTIAL PERFORMANCE .....                       | IEC 60601-1:2005, 3.27   |
| EXTRACORPOREAL CIRCUIT .....                      | 201.3.207                |
| HAZARD .....                                      | IEC 60601-1:2005, 3.39   |
| HAZARDOUS SITUATION.....                          | IEC 60601-1:2005, 3.40   |
| HEMODIAFILTRATION (HDF) .....                     | 201.3.208                |
| HEMODIALYSIS (HD) .....                           | 201.3.209                |
| HEMODIALYSIS EQUIPMENT .....                      | 201.3.210                |
| HEMOFILTRATION (HF) .....                         | 201.3.211                |
| HIGH PRIORITY.....                                | IEC 60601-1-8:2006, 3.22 |
| INFORMATION SIGNAL .....                          | IEC 60601-1-8:2006, 3.23 |
| INTENDED USE .....                                | IEC 60601-1:2005, 3.44   |
| INTERNAL ELECTRICAL POWER SOURCE .....            | IEC 60601-1:2005, 3.45   |
| LEAKAGE CURRENT .....                             | IEC 60601-1:2005, 3.47   |
| LIFE-SUPPORTING ME EQUIPMENT or ME SYSTEM.....    | IEC 60601-1-2:2007, 3.18 |
| LOW PRIORITY .....                                | IEC 60601-1-8:2006, 3.27 |
| MAINS PLUG .....                                  | IEC 60601-1:2005, 3.50   |
| MANUFACTURER .....                                | IEC 60601-1:2005, 3.55   |
| MECHANICAL HAZARD .....                           | IEC 60601-1:2005, 3.61   |
| MEDICAL ELECTRICAL EQUIPMENT (ME EQUIPMENT) ..... | IEC 60601-1:2005, 3.63   |
| MEDICAL ELECTRICAL SYSTEM (ME SYSTEM).....        | IEC 60601-1:2005, 3.64   |

|                                                    |                           |
|----------------------------------------------------|---------------------------|
| MEDIUM PRIORITY .....                              | IEC 60601-1-8:2006, 3.28  |
| MULTIPLE SOCKET-OUTLET.....                        | IEC 60601-1:2005, 3.67    |
| NET FLUID REMOVAL .....                            | 201.3.212                 |
| NETWORK/DATA COUPLING .....                        | IEC 60601-1:2005, 3.68    |
| NORMAL CONDITION .....                             | IEC 60601-1:2005, 3.70    |
| ONLINE HDF.....                                    | 201.3.213                 |
| ONLINE HF.....                                     | 201.3.214                 |
| OPERATOR .....                                     | IEC 60601-1:2005, 3.73    |
| PATIENT.....                                       | IEC 60601-1:2005, 3.76    |
| PATIENT CONNECTION .....                           | IEC 60601-1:2005, 3.78    |
| PATIENT ENVIRONMENT.....                           | IEC 60601-1:2005, 3.79    |
| PATIENT LEAKAGE CURRENT.....                       | IEC 60601-1:2005, 3.80    |
| PHYSIOLOGIC CLOSED-LOOP CONTROLLER.....            | IEC 60601-1-10:2007, 3.20 |
| PHYSIOLOGICAL ALARM CONDITION .....                | IEC 60601-1-8:2006, 3.31  |
| POTENTIAL EQUALIZATION CONDUCTOR .....             | IEC 60601-1:2005, 3.86    |
| PROCESS .....                                      | IEC 60601-1:2005, 3.89    |
| PROGRAMMABLE ELECTRICAL MEDICAL SYSTEM (PEMS)..... | IEC 60601-1:2005, 3.90    |
| PROTECTIVE EARTH CONDUCTOR .....                   | IEC 60601-1:2005, 3.93    |
| PROTECTIVE EARTH CONNECTION .....                  | IEC 60601-1:2005, 3.94    |
| PROTECTIVELY EARTHED .....                         | IEC 60601-1:2005, 3.96    |
| PROTECTIVE SYSTEM.....                             | 201.3.215                 |
| RESPONSIBLE ORGANIZATION .....                     | IEC 60601-1:2005, 3.101   |
| RISK .....                                         | IEC 60601-1:2005, 3.102   |
| RISK ANALYSIS.....                                 | IEC 60601-1:2005, 3.103   |
| RISK MANAGEMENT .....                              | IEC 60601-1:2005, 3.107   |
| RISK MANAGEMENT FILE.....                          | IEC 60601-1:2005, 3.108   |
| SINGLE FAULT CONDITION .....                       | IEC 60601-1:2005, 3.116   |
| SINGLE FAULT SAFE.....                             | IEC 60601-1:2005, 3.117   |
| SUBSTITUTION FLUID .....                           | 201.3.216                 |
| SUPPLY MAINS .....                                 | IEC 60601-1:2005, 3.120   |
| TOOL .....                                         | IEC 60601-1:2005, 3.127   |
| TOUCH CURRENT .....                                | IEC 60601-1:2005, 3.129   |
| TRANSMEMBRANE PRESSURE (TMP) .....                 | 201.3.217                 |
| TYPE B APPLIED PART .....                          | IEC 60601-1:2005, 3.132   |
| TYPE CF APPLIED PART .....                         | IEC 60601-1:2005, 3.134   |
| ULTRAFILTRATION .....                              | 201.3.218                 |
| USE ERROR .....                                    | IEC 62366:2007, 3.21      |
| VENOUS PRESSURE .....                              | 201.3.219                 |

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