STANDARDS FOR IMMUNE EFFECTOR CELL ADMINISTRATION

First Edition
DRAFT
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NOTICE

These Standards are designed to provide minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations.

The Foundation for the Accreditation of Cellular Therapy expressly disclaims any responsibility for setting maximum standards and further expressly disclaims any responsibility, liability, or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance.

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INTRODUCTION

The major objective of the *FACT Standards for Immune Effector Cell Administration* is to promote quality practice in immune effector cell administration. These Standards apply to immune effector cells used to elicit an immune response for therapeutic intent, such as dendritic cells, natural killer cells, T cells, and B cells. This includes, but is not limited to, chimeric antigen receptor T cells (CAR-T cells) and therapeutic vaccines.

The scope of the Standards includes donor selection and management, administration of cells, management of adverse events, and evaluation of clinical outcomes. The Standards require a quality management (QM) program that establishes, maintains, monitors, and implements improvements in the quality of facilities, processes, and performance.

These Standards are intended to be flexible to accommodate various models of patient care and use of cellular therapy products. Requirements for programs that administer immune effector cells on a unit that is not already FACT-accredited are contained fully in the FACT Immune Effector Cell Standards. When immune effector cells are administered on a FACT-accredited blood and marrow transplant (BMT) unit, the program must fully comply with the FACT-JACIE Hematopoietic Cell Therapy Standards and the additional requirements found in the FACT Immune Effector Cell Standards. These additional Standards will be made available to BMT units wishing to pursue this new accreditation, and will eventually be incorporated into the Hematopoietic Cell Therapy Standards also.

These Standards were prepared under the assumption that most programs will not be responsible for collection and processing of immune effector cells. Regardless of where the product comes from, the program must meet clearly defined responsibilities for chain of custody, storage, verification of product identity, and management of adverse events. In so far as a program is responsible for collection of cells, manufacturing of the cellular therapy product, or preparing the product for administration, the collection and processing requirements from the FACT Common Standards apply. These requirements are included in this document.

Standards related to services not provided by accreditation applicants do not apply to the organization. The burden to demonstrate that a requirement is not applicable rests with the applicant.

Since 1996, FACT has been a leader in improving the quality of cellular therapy processes in the fields of hematopoietic progenitor cell (HPC) transplantation, cord blood banking, and regenerative medicine through its program of professional standards and voluntary accreditation. FACT was founded by clinical and laboratory scientists (members of the American Society for Blood and Marrow Transplantation and the International Society for Cellular Therapy, respectively) to be the standard setting and accreditation arm of these societies, in the belief that quality medical and laboratory care would be enhanced through comprehensive, peer-developed professional standards. In addition, the founders sought to minimize unnecessary regulatory burden and to protect an environment of research and development that fosters advancement of the field.

Since the development of the first set of Standards, FACT Standards have been developed by experts active in the field, evidence-based whenever possible, and agreed upon by consensus. For those areas where there are few definitive studies or publications, the Standards Committee weighs the available evidence from preclinical studies and utilizes accepted scientific principles to reach consensus. Minimal standards have always required that there be in place a quality management program and that clinical outcomes be evaluated and reported.

The standards development process includes drafting and review of standards by a committee consisting of experts in the particular area or use of the cellular therapy, publication for peer and public review and comment, committee review of comments, and a final revision process based upon comments received.

ACCREDITATION

The basis for FACT accreditation is documented compliance with the current edition of the applicable set of Standards. Compliance is determined by evaluation of the written information provided by the applicant facility and by on-site inspection. All inspections are conducted by persons qualified by training and experience in cellular therapy who are affiliated with an accredited or applicant facility, have completed inspector training, and have a working knowledge of FACT Standards and of their application to various aspects of the cellular therapy program.

Eligibility for accreditation under the Immune Effector Cell Standards is determined by the FACT Board of Directors, which will review each application for accreditation individually. As eligibility requirements become refined, details will be listed on the FACT website at www.factwebsite.org.

TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

PART A

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PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

For purposes of these Standards, the term *shall* means that the standard is to be complied with at all times. The term *should* indicates an activity that is recommended or advised, but for which there may be effective alternatives. The term *may* is permissive and is used primarily for clarity.

A2 TENETS

Basic tenets for compliance with these Standards include, but are not limited to:

A.2.1 Where applicable laws and regulations include more stringent requirements than these Standards, those laws and regulations supersede the Standards. Conversely, when these Standards are more stringent than applicable laws and regulations, the Standards must be followed.

A2.2 Applicant organizations are responsible for providing verifiable documentation of evidence of compliance with these Standards.

A2.3 Standards related to services not provided by the applicant do not apply to the applicant organization. The burden to demonstrate that a requirement is not applicable rests with the applicant organization.

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

ABO	Major human blood group including erythrocyte antigens, A, B, O
AC	Accompany
AF	Affixed
APP	Advanced Practice Provider/Professional
ASBMT	American Society for Blood and Marrow Transplantation
ASHI	American Society for Histocompatibility and Immunogenetics
AT	Attached
CAR	Chimeric antigen receptor
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CME	Continuing Medical Education
CMS	Centers for Medicare & Medicaid Services
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CNS	Central nervous system
COA	Certificate of Analysis
CRS	Cytokine release syndrome
CTP	Cellular therapy product
DLI	Donor lymphocyte infusion
DNA	Deoxyribonucleic acid
EFI	European Federation for Immunogenetics
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U. S. Food and Drug Administration

GMP	Good Manufacturing Practices
GTP	Good Tissue Practices
GVHD	Graft versus Host Disease
HCT/Ps	Human cells, tissues, or cellular or tissue-based products
HLA	Human leukocyte antigen
IDE	Investigational Device Exemption
IND	Investigational New Drug
ISCT	International Society for Cellular Therapy
MNC	Mononuclear cells
NMDP	National Marrow Donor Program
OSHA	Occupational Safety and Health Administration
QM	Quality management
RBC	Red blood cell
Rh	Rhesus system of human red cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
SCTOD	Stem Cell Therapeutics Outcomes Database
SOP	Standard operating procedure
US	United States
USDA	United States Department of Agriculture
WMDA	World Marrow Donor Association

A4 DEFINITIONS

Accompany: To go, be together with, or be available to the appropriate individual(s) electronically, but not affixed or attached. Written or printed information that must accompany a cellular therapy product must be in a sealed package with, or alternatively, be attached or affixed to, the cellular therapy product container.

Accreditation cycle: The period of time from the awarding of accreditation until its expiration as set, and subject to change, by FACT. At publication of these Standards, this period is three (3) years for FACT-accredited programs.

Advanced practice provider/professional: Physician Assistant, Nurse Practitioner, or other licensed Advanced Practitioner authorized by the applicable legal authority to provide primary patient care with physician oversight. Physician Assistants are formally trained and licensed or certified by the applicable authority to provide diagnostic, therapeutic, and preventive health care services with physician supervision. Advanced Nurse Practitioner includes certified nurse anesthetists, nurse practitioners, certified nurse midwives, and clinical nurse specialists.

Adverse event: Any unintended or unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention that may or may not have a causal relationship with the intervention, medical treatment, or procedure. Adverse reaction is a type of adverse event.

Adverse reaction: A noxious and unintended response suspected or demonstrated to be caused by the collection or infusion of a cellular therapy product or by the product itself.

Affix: To adhere in physical contact with the cellular therapy product container.

Allogeneic: The biologic relationship between genetically distinct individuals of the same species.

Ambulatory setting: An environment of patient care outside of an inpatient hospital.

Apheresis: A medical technology in which the blood of a donor is separated into its component parts, the desired component is removed, and the remaining components are returned to the donor.

Aseptic technique: Practices designed to reduce the risk of microbial contamination of cellular therapy products, reagents, specimens, recipients, and/or donors.

Attach: To fasten securely to the cellular therapy product container by means of a tie tag or comparable alternative. Any information required to be attached to a cellular therapy product container may alternatively be affixed.

Attending physician: The physician who is responsible for the delivery and oversight of care provided to cellular therapy recipients and who meets all qualifications defined in these Standards.

Audit: Documented, systematic evaluation to determine whether approved policies or procedures have been properly implemented and are being followed.

Autologous: Derived from and intended for the same individual.

Available for distribution: The time at which the cellular therapy product may leave the control of the facility.

Biological product deviation: Any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product, if that event meets the following criteria:
Either:

- Represents a deviation from current good manufacturing practice (or current good tissue practices), applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and
    - Occurs in your facility or another facility under contract with you; and
    - Involves a distributed biological product.

Calibrate: To set measurement equipment against a known standard.

Cellular therapy: The administration of products with the intent of providing effector cells in the treatment of disease or support of other therapy.

Cellular therapy product: Somatic cell-based product (e.g., mobilized HPC, mononuclear cells, cord blood cells, mesenchymal stromal cells, T cells) that is procured from a donor and intended for processing and administration.

Circular of Information: An extension of container labels that includes the use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

Clinical Program: An integrated medical team housed in a defined location that includes a Clinical Program Director and demonstrates common staff training, protocols, procedures, quality management systems, clinical outcome analysis, and regular interaction among clinical sites.

Collection: Any procedure for procuring and labeling a cellular therapy product regardless of technique or source.

Collection Facility: An entity providing the service of cellular therapy product collection.

Competency: Ability to adequately perform a specific procedure or task according to direction.

Complaint: Any written, oral, or electronic communication about a problem associated with a cellular therapy product or with a service related to the collection, processing, storage, distribution, or administration of a cellular therapy product.

Cord blood: The whole blood, including HPC, collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.

Corrective action: Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence.

Courier: An individual trained and competent in transport or shipping of cellular therapy products.

Critical: The quality of any element employed in cellular therapy product manufacturing to potentially change the identity, purity, potency, or safety of the cellular therapy product if altered or omitted. "Element" includes, but is not limited to, materials, equipment, personnel, documents, or facilities. For example, DMSO is a critical reagent because omitting it from the freezing medium will cause loss of cells during freezing and thawing.

Current Good Tissue Practice: The methods used in, and the facilities and controls used for, the manufacture of cellular therapy products to prevent the introduction or transmission of communicable diseases, including all steps in collection, donor screening and testing, processing, storage, labeling, packaging, and distribution.

Current Good Manufacturing Practice: The set of current practices followed by entities producing drug and biologic products, including cellular therapy products, to ensure that the products produced meet specific requirements for identity, strength, quality, and purity. In the US, cGMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act (21USC351). Cellular therapy products that are extensively manipulated or that are used for non-homologous purposes are examples of products controlled under cGMP regulations. Similar requirements are delineated by the European Union as EU-GMP, and other countries such as United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

Cytokine release syndrome: A reaction from the release of cytokines from cells targeted by an antibody or immune effector cells.

Designee: An individual with appropriate education, experience, or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility.

Distribution: Any transportation or shipment of a cellular therapy product that has been determined to meet release criteria or urgent medical need requirements.

Donor: A person who is the source of cells or tissue for a cellular therapy product.

Donor advocate: An individual distinct from the cellular therapy recipient's primary treating physician whose main obligation is to protect the interests, well-being, and safety of the donor. The donor

advocate may help the donor understand the process, the procedures, and the potential risks and benefits of donation.

Donor lymphocyte infusion (DLI): A type of therapy given to a patient who has already received a cellular therapy from the same donor. The donor lymphocytes may kill remaining cancer cells, facilitate full donor chimerism, or provide a source of antigen specific immunity. The DLI cell source may be whole blood, bone marrow, mononuclear cells collected by apheresis with or without mobilization, cord blood, or cellular subsets purified from these source products. The active cell type may include T lymphocytes, NK cells, or B lymphocytes. May also be referred to as donor leukocyte infusion.

Electronic record: A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer.

Critical electronic record: Electronic record system under facility control that is used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

Eligible: An allogeneic cellular therapy product donor for whom all the donor screening and testing have been completed in accordance with applicable laws and regulations and who has been determined to be free of risk factor(s) for relevant communicable diseases.

Errors and Accidents: Any unforeseen or unexpected deviations from applicable regulations, standards, or established specifications that may affect the safety, purity, or potency of a cellular therapy product.

Establish and maintain: A process to define, document in writing (including electronically), implement, follow, review, and, as needed, revise on an ongoing basis.

Exceptional release: Removal of a product that fails to meet specified criteria from quarantine or in-process status for distribution through a defined approval process.

Expansion: Growth of one or more cell populations in an *in vitro* culture system.

Extracorporeal photopheresis: An apheresis technique in which the patient's blood is collected into a specialized instrument, centrifuged, and separated into a leukocyte-depleted fraction (which is returned to the patient unmanipulated) and mononuclear "buffy coat" enriched plasma. The mononuclear cell-enriched fraction is incubated with 8-methoxypsoralen in the presence of ultraviolet A (UVA) radiation, and, upon completion of the procedure, reinfused into the patient.

Facility: A location where activities covered by these Standards are performed, including but not limited to determination of donor eligibility or suitability, product collection, processing, storage, distribution, issue, or administration.

Fellow: A physician who is in a training program in a medical specialty after completing residency, usually in a hospital or academic setting.

Fresh: A cellular therapy product that has never been cryopreserved.

Human cells, tissues, or cellular or tissue-based products (HCT/Ps): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

Immune effector cell: A cell that has been induced to differentiate into a form capable of eliciting a specific immune response.

Ineligible: An allogeneic cellular therapy product donor for whom all the donor screening and testing has been completed in accordance with the applicable laws and regulations and who has identified risk factor(s) for relevant communicable diseases.

Institutional Review Board or Ethics Committee: A Board or Committee established by an institution in accordance with the regulations of the relevant governmental agency to review biomedical and behavioral research that involves human subjects and is conducted at or supported by that institution.

ISBT 128: A global standard for the identification, labeling, and information transfer of human blood, cell, tissue, and organ products.

Key position: A job category with responsibilities that significantly affect the provision of service or product safety and quality.

Label: Written, printed, or graphic material affixed to, attached to, or accompanying a cellular therapy product container or package. Labels must contain the information as defined by applicable standards, laws, and regulations.

Labeling: The process of creating and applying the cellular therapy product label, including confirmation of the presence and accuracy of the required information as defined in these Standards.

**Late Effect:* A health problem that occurs months or years after a disease is diagnosed or after treatment has been administered. Late effects may be caused by the primary disease or its treatment, and may include physical, mental, or social problems and/or secondary cancers.

Licensed health care professional: An individual who has completed a prescribed program of health-care related study and has been certified, registered, or licensed by the applicable authority in the jurisdiction in which he or she is performing services to perform duties within the scope of practice of that certificate, registration, or license.

Manipulation: An ex vivo procedure(s) that selectively removes, enriches, expands, or functionally alters the cellular therapy product.

Minimally Manipulated: Processing that does not alter the relevant biological characteristics of cells or tissues. For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

More than minimally manipulated: Processing that does alter the relevant biological characteristics of cells or tissues. For structural tissue, processing that does alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. Products that are more than minimally manipulated are referred to as Advanced Therapy Medicinal Products in the European Union.

Unmanipulated: A cellular therapy product as obtained at collection and not subjected to any form of processing.

Manufacturing: Activity that includes, but is not limited to, any or all steps in the recovery, processing, packaging, labeling, storage, or distribution of any human cellular or tissue-based product, and/or the screening and testing of a cell or tissue donor.

Marrow collection: Harvest of bone marrow for transplantation to achieve hematopoietic reconstitution in the recipient or for further cellular therapy product manufacture. This does not include marrow aspirations intended for diagnostic purposes.

Materials management: An integrated process for planning and controlling all steps in the acquisition and use of goods or supply items (materials) used for the collection or processing of cellular therapy products to determine whether these materials are of adequate quality and quantity and available when needed. The materials management system combines and integrates the material selection, vendor evaluation, purchasing, expediting, storage, distribution, and disposition of materials.

Microbial: Related to infectious agents including bacterial and fungal organisms.

Negative selection: The manipulation of a cellular therapy product such that a specific cell population(s) is reduced.

New patient: An individual undergoing the specified type of cellular therapy (allogeneic, autologous, or syngeneic) for the first time in the Clinical Program, whether or not that patient was previously treated by that Clinical Program.

Orientation: An introduction to guide one in adjusting to new surroundings, employment, or activity.

Outcome analysis: The process by which the results of a therapeutic procedure are formally assessed.

Partial label: The minimum essential elements that must be affixed to all cellular therapy product containers at all times.

Physician-in-training: A physician in one of the postgraduate years of clinical training. Can be referred to as resident, fellow, registrar, or other designation, depending on the setting. The length of training varies according to the specialty.

Policy: A document that defines the scope of an organization, explains how the goals of the organization will be achieved, and/or serves as a means by which authority can be delegated.

Positive selection: The manipulation of a cellular therapy product such that a specific cell population(s) is enriched.

Potency: The therapeutic activity of a product as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

Preparative (conditioning) regimen: The treatment(s) used to prepare a patient for cellular therapy (e.g., chemotherapy, monoclonal antibody therapy, radiation therapy).

Preventive action: Action taken to eliminate the cause and prevent occurrence of a potential discrepancy or other undesirable situation.

Procedure: A document that describes in detail the process or chronological steps taken to accomplish a specific task; work instructions; a procedure is more specific than a policy.

Process: A goal-directed, interrelated series of actions, events, or steps.

Process control: The standardization of processes in order to produce predictable output.

Process development: The series of procedures performed in order to develop a final process that achieves the required results.

Processing: All aspects of manipulation, cryopreservation, packaging, and labeling of cellular therapy products regardless of source, including microbial testing, preparation for administration or storage, and removal from storage. Processing does not include collection, donor screening, donor testing, storage, or distribution.

Processing Facility: A location where cellular therapy product processing activities are performed in support of the Clinical Program. A Processing Facility may be part of the same institution as the Clinical Program or may be part of another institution and perform these functions through contractual agreement.

Product sample: A representative quantity of product removed from the cellular therapy product; an aliquot.

***Products*: The ISBT 128 Cellular Therapy Class product database name and definition (format: type of cells, comma, source of cells) for products collected from marrow, peripheral blood, and cord blood are as follows:

Subcategory 1: The type of cells at collection (HPC, NC, or MNC). If product is collected for infusion without further manipulation, there is no name change. HPCs may be further manipulated, and retain the class name HPC if they are used as a source of hematopoietic progenitor cells; the modification (such as cryopreservation) is added into the product description as an attribute.

HPC, APHERESIS: A cell product containing hematopoietic progenitor cells obtained by apheresis.

HPC, CORD BLOOD: A cell product containing hematopoietic progenitor cells obtained from cord blood.

HPC, MARROW: A cell product containing hematopoietic progenitor cells obtained from bone marrow.

HPC, WHOLE BLOOD: A cell product containing hematopoietic progenitor cells obtained from whole blood.

MNC, APHERESIS: A cell product containing mononuclear cells obtained by apheresis.

MNC, UMBILICAL CORD TISSUE: A cell product containing mononuclear cells derived from umbilical cord tissue.

NC, CORD BLOOD: A cell product containing nucleated cells obtained from cord blood.

NC, MARROW: A cell product containing nucleated cells obtained from bone marrow.

NC, WHOLE BLOOD: A cell product containing nucleated cells obtained from whole blood.

CONCURRENT PLASMA, APHERESIS: Plasma collected from the donor as part of an apheresis cell collection procedure, intended for use in further processing of that cellular therapy product.

Subcategory 2: After enumeration or manufacture/processing of a collected product, the product class is identified by the target cell population thought to be present in the product.

DC, APHERESIS: A cell product containing dendritic cells obtained by apheresis.

DC, CORD BLOOD: A cell product containing dendritic cells obtained from cord blood.

DC, MARROW: A cell product containing dendritic cells obtained from bone marrow.

DC, WHOLE BLOOD: A cell product containing dendritic cells obtained from whole blood.

INVESTIGATIONAL PRODUCT: A product for an investigational study that is accompanied by appropriate identifying study information. This class may be used for a specific product that may be part of a blinded comparison study. Products labeled as Investigational Product may include different doses or may include an active product or a placebo.

MALIGNANT CELLS, APHERESIS: A cell product containing malignant cells obtained by apheresis.

MALIGNANT CELLS, MARROW: A cell product containing malignant cells obtained from marrow.

MALIGNANT CELLS, WHOLE BLOOD: A cell product containing malignant cells obtained from whole blood.

MSC, CORD BLOOD: A cell product containing mesenchymal stromal cells derived from cord blood.

MSC, MARROW: A cell product containing mesenchymal stromal cells derived from bone marrow.

MSC, WHARTON'S JELLY: A cell product containing mesenchymal stromal cells derived from Wharton's jelly.

NK CELLS, APHERESIS: A cell product containing natural killer cells obtained by apheresis.

NK CELLS, CORD BLOOD: A cell product containing natural killer cells obtained from cord blood.

NK CELLS, MARROW: A cell product containing natural killer cells obtained from bone marrow.

NK CELLS, WHOLE BLOOD: A cell product containing natural killer cells obtained from peripheral blood.

T CELLS, APHERESIS: A cell product containing T cells obtained by apheresis.

T CELLS, CORD BLOOD: A cell product containing T cells obtained from cord blood.

T CELLS, MARROW: A cell product containing T cells obtained from bone marrow.

T CELLS, WHOLE BLOOD: A cell product containing T cells obtained from peripheral blood.

Proficiency test: A test to evaluate the adequacy of testing methods and equipment and the competency of personnel performing testing.

Protocol: A written document describing steps of a treatment or procedure in sufficient detail such that the treatment or procedure can be reproduced repeatedly without variation.

Purity: Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

Qualification: The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

Qualified person: A person who has received training, is experienced, and has documented competence in the task assigned.

Quality: Conformance of a product or process with pre-established specifications or standards.

Quality assurance: The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected individually and collectively.

Quality assessment: The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

Quality audit: A documented, independent inspection and review of a facility's quality management activities to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

Quality control: A component of a quality management program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of cellular therapy products, including testing and product release.

Quality improvement: The actions, planned and performed, to implement changes designed to improve the quality of a product or process.

Quality management: The integration of quality assessment, assurance, control, and improvement in cellular therapy activities.

Quality management plan: A written document that describes the systems in place to implement the quality management program.

Quality management program: An organization's comprehensive system of quality assessment, assurance, control, and improvement. A quality management program is designed to prevent, detect, and correct deficiencies that may adversely affect the quality of the cellular therapy product or increase the risk of communicable disease introduction or transmission. May also be referred to by other terms.

Quality Unit: The personnel responsible for Quality Management. Under good manufacturing practices, the quality unit must be independent from manufacturing, facility, and medical oversight and have final authority and oversight for the release of cellular therapy products.

Quarantine: The identification or storage of a cellular therapy product in a physically separate area clearly identified for such use, or through use of other procedures such as automated designation to prevent improper release of that product. Also refers to segregated storage of

products known to contain infectious disease agents to reduce the likelihood of cross-contamination.

Record: Documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed.

Release: Removal of a product from quarantine or in-process status when it meets specified criteria.

Release criteria: The requirements that must have been met before a cellular therapy product may leave the control of the Collection or Processing Facility.

Safety: Relative freedom from harmful effects to persons or products.

Shipping: The physical act of transferring a cellular therapy product within or between facilities. During shipping the product leaves the control of trained personnel at the distributing or receiving facility.

Standard Operating Procedures (SOP) Manual: A compilation of policies and procedures with written detailed instructions required to perform procedures. The SOP Manual may be in electronic or paper format.

Standards: The current edition of the *FACT Standards for Immune Effector Cell Administration*, which may be referred to herein as "Standards" or "FACT Standards."

Storage: Holding a cellular therapy product for future processing, distribution, or administration.

Suitable: Donor or recipient suitability refers to issues that relate to the general health or medical fitness of the donor or recipient to undergo the collection procedure or therapy.

Syngeneic: The biologic relationship between identical twins.

Target cell population: A cell population that is expected to be affected by an action or that is believed to be mainly responsible for a given activity.

Time of collection: The time of day at the end of the cellular therapy product collection procedure.

Trace: To follow the history of a process, product, or service by review of documents.

Track: To follow a process or product from beginning to end.

Transport: The physical act of transferring a cellular therapy product within or between facilities. During transportation the product does not leave the control of trained personnel at the transporting or receiving facility.

Unique: Being the only one of its kind or having only one use or purpose.

Unique identifier: A numeric or alphanumeric sequence used to designate a given cellular therapy product with reasonable confidence that it will not be used for another purpose.

Unplanned deviation: The action of departing from an established course or accepted standard without intent.

Urgent medical need: A situation in which no comparable cellular therapy product is available and the recipient is likely to suffer death or serious morbidity without the cellular therapy product.

Validation: Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications.

Variance: A planned deviation from recommended practice or standard operating procedure approved as the best course of action when adherence to the established course or accepted standard was not feasible or possible.

Verification: The confirmation of the accuracy of something or that specified requirements have been fulfilled.

Verification typing: HLA typing performed on an independently collected sample with the purpose of verifying concordance of that typing assignment with the initial HLA typing assignment. Concordance does not require identical levels of resolution for the two sets of typing but requires the two assignments be consistent with one another.

Viability: Living cells as defined by dye exclusion, flow cytometry, or progenitor cell culture.

Written: Documentation in human readable form.

**A portion of the definition that can be located in the National Cancer Institute at the National Institutes of Health's NCI Dictionary of Cancer Terms: http://www.cancer.gov/dictionary?CdrID=390292.*

***These definitions are as of the date of publication and use the current terminology as found in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.*

CLINICAL PROGRAM STANDARDS

PART B

PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

B1.1 The Clinical Program shall consist of an integrated medical team that includes a Clinical Program Director housed in a defined location(s).

B1.1.1 The Clinical Program shall demonstrate common staff training, protocols, procedures, quality management systems, clinical outcome analysis, and regular interaction among all clinical sites.

B1.2 The Clinical Program shall use a cell collection process and processing facilities that meet FACT Standards with respect to their interactions with the Clinical Program.

B1.2.1 If cellular therapy products are received directly by the Clinical Program from a third-party manufacturer, the following responsibilities shall be defined at a minimum:

B1.2.1.1 Chain of custody of cellular therapy products.

B1.2.1.2 Cellular therapy product storage.

B1.2.1.3 Verification of cellular therapy product identity.

B1.2.1.4 Management of adverse events.

B1.3 The Clinical Program shall abide by all applicable laws and regulations.

B1.3.1 The Clinical Program shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

B1.4 The Clinical Program shall have a designated team that includes a Clinical Program Director, a Quality Manager, and a minimum of one (1) additional physician trained and/or experienced in cellular therapy. The designated team shall have been in place for at least twelve (12) months preceding initial accreditation.

B1.5 The Clinical Program shall administer cellular therapy products to a minimum of five (5) new recipients during the twelve (12) month period immediately preceding accreditation and to a minimum average of five (5) new recipients per year within the accreditation cycle.

B2: CLINICAL UNIT

B2.1 A clinical unit of adequate space, design, and location shall be identified for the treatment of patients needing inpatient care related to the cellular therapy.

B2.2 There shall be a designated outpatient care area that protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient

isolation; confidential examination and evaluation; and administration of intravenous fluids, medications, or blood products.

B2.3 When preparative regimens, cellular therapy product administration, or initial post-administration care are provided in an ambulatory setting, there shall be a designated area with appropriate location and adequate space and design to minimize the risk of airborne microbial contamination.

B2.4 Facilities used by the Clinical Program shall be maintained in a clean, sanitary, and orderly manner.

B2.5 There shall be provisions for prompt evaluation and treatment by a physician who specializes in the therapeutic disease area available on a 24-hour basis.

B2.6 There shall be written guidelines for communication, patient monitoring, and prompt transfer or triage of patients to an intensive care unit, emergency department, or equivalent when appropriate.

B2.7 There shall be attending physician oversight if general medical physicians or APPs provide care to cellular therapy patients. The scope of responsibility of general medical physicians or APPs shall be defined.

B2.8 There shall be a pharmacy providing 24-hour availability of medications needed for the care of cellular therapy patients.

B2.8.1 Pharmacies shall have access to formularies adequate to treat cytokine release syndrome and other expected complications of immune effector cell administration.

B2.9 If HLA matching of the recipient and the cellular therapy product is required, Clinical Programs shall use HLA testing laboratories that are capable of carrying out DNA–based intermediate and high resolution HLA typing and are appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or other accrediting organizations providing histocompatibility services appropriate for the types of cellular therapy patients.

B2.10 There shall be an intensive care unit or equivalent coverage available.

B2.11 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

B2.12 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological hazards.

B3: PERSONNEL

B3.1 CLINICAL PROGRAM DIRECTOR

B3.1.1 The Clinical Program Director shall be a physician appropriately licensed or certified to practice medicine in the jurisdiction in which the Clinical Program is located and shall have achieved specialist certification in the applicable therapeutic disease area. A physician trained prior to requirements for specialty training may serve as the Clinical Program Director if he/she has documented experience in the applicable therapeutic disease area extending over ten (10) years.

B3.1.2 The Clinical Program Director shall have two (2) years of experience as an attending physician responsible for the direct clinical management of patients in the applicable therapeutic disease area in the inpatient and outpatient settings.

B3.1.3 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and applicable laws and regulations.

B3.1.4 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of patients and donors, and cell collection and processing, whether internal or contracted services.

B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program.

B3.1.5.1 The Clinical Program Director or designee shall be responsible for verifying the knowledge and skills of members of the Clinical Program once per accreditation cycle, at minimum.

B3.1.6 The Clinical Program Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

B3.2 ATTENDING PHYSICIANS

B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be specialist certified or trained in the therapeutic disease area.

B3.2.1.1 There shall be at least one attending physician who has achieved specialist certification in the applicable therapeutic disease area.

B3.2.2 Attending physicians shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.3.1 Attending physicians shall each have had a minimum total of one year of supervised training in the management of patients in the applicable therapeutic disease area in both inpatient and outpatient settings.

B3.3.2 Clinical Program Directors and attending physicians shall have received specific training and maintain competency in each of the following areas:

B3.3.2.1 Indications for cellular therapy.

B3.3.2.2 Selection of suitable recipients and appropriate treatments.

B3.3.2.3 Donor selection, evaluation, and management (when applicable).

B3.3.2.4 Donor and recipient informed consent (when applicable).

B3.3.2.5 Cellular therapy product administration and patient management.

B3.3.2.6 Adverse events associated with cellular therapy.

B3.3.2.7 Management of anticipated complications of cellular therapy, including, but not limited to, cytokine release syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, renal and hepatic failure, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, and nausea and vomiting.

B3.3.2.8 Monitoring and management of pain.

B3.3.2.9 Evaluation of post-treatment cellular therapy outcomes.

B3.3.2.10 Evaluation of late effects of cellular therapy.

B3.3.2.11 Documentation and reporting for patients on investigational protocols.

B3.3.3 If applicable to the cellular therapy product, specific clinical training and competency required for physicians in Clinical Programs requesting accreditation for allogeneic cellular therapy shall include:

B3.3.3.1 Identification, evaluation, and selection of cell source, including use of donor registries.

B3.3.3.2 Donor eligibility determination.

B3.3.3.3 Methodology and implications of human leukocyte antigen (HLA) typing.

B3.3.3.4 Management of patients receiving ABO incompatible cellular therapy products.

B3.3.4 The attending physicians shall be knowledgeable in the following procedures:

B3.3.4.1 Cellular therapy product collection.

B3.3.4.2 Cellular therapy product processing.

B3.3.4.3 Cellular therapy product cryopreservation.

B3.3.4.4 Cellular therapy product administration.

B3.4 PHYSICIANS-IN-TRAINING

B3.4.1 Physicians-in-training shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure and shall be appropriately supervised.

B3.4.2 Physicians-in-training shall receive specific training and develop competency in therapeutic-related skills, including but not limited to those listed in B3.3.2 and B3.3.3.

B3.5 ADVANCED PRACTICE PROVIDERS/PROFESSIONALS

B3.5.1 APPs shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licenses.

B3.5.2 APPs shall have received specific training and maintain competency in the therapeutic-related skills that they routinely practice including but not limited to those listed in B3.3.2 and B3.3.3.

B3.5.3 APPs shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

B3.6 CLINICAL PROGRAM TEAM

B3.6.1 Clinical Programs treating pediatric patients shall have a team trained in the management of pediatric patients.

B3.6.2 If marrow is utilized in the cellular therapy product, the Clinical Program shall have access to licensed physicians who are trained and competent in marrow collection and a process for marrow collection that meets these Standards.

B3.6.3 If mononuclear cells derived from peripheral blood by apheresis are utilized in the cellular therapy product, the Clinical Program shall have access to personnel who

are trained and competent in cellular therapy product collection by apheresis and utilize a process for apheresis collection that meets these Standards.

B3.7 NURSES

B3.7.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients in the therapeutic disease area.

B3.7.2 Clinical Programs treating pediatric patients shall have nurses formally trained and experienced in the management of pediatric patients in the therapeutic disease area.

B3.7.3 Training and competency shall include:

B3.7.3.1 Administration of preparative regimens, if applicable.

B3.7.3.2 Administration of cellular therapy products.

B3.7.3.3 Care interventions to manage cellular therapy complications, including, but not limited to, cytokine release syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, renal and hepatic failure, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.

B3.7.3.4 Recognition of cellular therapy complications and emergencies requiring rapid notification of the clinical team.

B3.7.4 There shall be written policies for all relevant nursing procedures, including, but not limited to:

B3.7.4.1 Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.3.

B3.7.4.2 Care of immunocompromised patients.

B3.7.4.3 Administration of preparative regimens.

B3.7.4.4 Administration of cellular therapy products.

B3.7.4.5 Administration of blood products.

B3.7.5 There shall be an adequate number of nurses experienced in the care of patients in the applicable therapeutic disease area.

B3.7.6 There shall be a nurse/patient ratio satisfactory to manage the severity of the patients' clinical status.

B3.8 PHARMACISTS

B3.8.1 Pharmacists shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure.

B3.8.2 Training shall include:

B3.8.2.1 An overview of patient care, including cytokine release syndrome and neurological toxicities.

B3.8.2.2 Recognition of medications that require adjustment for organ dysfunction.

B3.8.3 Pharmacists should be involved in the development and implementation of guidelines or SOPs related to the pharmaceutical management of transplant recipients.

B3.8.4 Designated transplant pharmacists shall participate in ten (10) hours of educational activities annually at a minimum.

B3.8.4.1 Continuing education shall include, but is not limited to, activities related to cytokine release syndrome and neurological toxicities resulting from cellular therapies.

B3.9 CONSULTING SPECIALISTS

B3.9.1 The Clinical Program shall have access to certified or trained consulting specialists and/or specialist groups from key disciplines who are capable of assisting in the management of patients requiring medical care, including, but not limited to:

B3.9.1.1 Surgery.

B3.9.1.2 Pulmonary medicine.

B3.9.1.3 Intensive care.

B3.9.1.4 Gastroenterology.

B3.9.1.5 Nephrology.

B3.9.1.6 Infectious disease.

B3.9.1.7 Cardiology.

B3.9.1.8 Pathology.

B3.9.1.9 Psychiatry.

B3.9.1.10 Radiology.

B3.9.1.11 Radiation therapy.

B3.9.1.12 Transfusion medicine.

B3.9.1.13 Neurology.

B3.9.1.14 Ophthalmology.

B3.9.1.15 Obstetrics/Gynecology.

B3.9.1.16 Dermatology.

B3.9.2 A Clinical Program treating pediatric patients shall have consultants, as defined in B3.8.1, qualified to manage pediatric patients.

B3.10 QUALITY MANAGER

B3.10.1 There shall be a Clinical Program Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Clinical Program.

B3.10.2 The Clinical Program Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy and/or quality management annually at a minimum.

B3.11 SUPPORT SERVICES STAFF

B3.11.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in the provision of pre-cellular therapy product administration patient evaluation, treatment, and post-administration follow-up and care. Designated staff shall include the following as applicable to the cellular therapy product:

B3.11.1.1 Dietary staff capable of providing dietary consultation regarding the nutritional needs of the cellular therapy recipient, including enteral and parenteral support, and appropriate dietary advice to avoid food-borne illness.

B3.11.1.2 Social Services staff.

B3.11.1.3 Psychology Services staff.

B3.11.1.4 Physical Therapy staff.

B3.11.1.5 Data Management staff sufficient to comply with B9.

B4: QUALITY MANAGEMENT

B4.1 There shall be an overall Quality Management Program that incorporates key performance data from clinical, collection, and processing facility quality management.

B4.1.1 The Clinical Program Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established, documented, and maintained.

B4.1.2 The Clinical Program Director shall annually review the effectiveness of the Quality Management Program.

B4.2 The Clinical Program shall establish and maintain a written Quality Management Plan.

B4.2.1 The Clinical Program Director or designee shall be responsible for the Quality Management Plan.

B4.2.2 The Clinical Program Director or designee shall review and report to staff quality management activities, at a minimum, quarterly.

B4.2.3 The Clinical Program Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Clinical Program.

B4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions and functions within the cellular therapy program, including clinical, collection, and processing activities, as applicable.

B4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

B4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Clinical Program. Personnel requirements shall include at a minimum:

B4.4.1 A current job description for all staff.

B4.4.2 A system to document the following for all staff:

B4.4.2.1 Initial qualifications.

B4.4.2.2 New employee orientation.

B4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

B4.4.2.4 Competency for each critical function performed.

B4.4.2.5 Continued competency at least annually.

B4.4.2.6 Continuing education.

B4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

B4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.

B4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

B4.5.2.1 Policies, protocols, and Standard Operating Procedures.

B4.5.2.2 Worksheets.

B4.5.2.3 Forms.

B4.5.2.4 Labels.

B4.5.3 The document control policy shall include:

B4.5.3.1 A standardized format for policies, procedures, worksheets, and forms.

B4.5.3.2 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

B4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

B4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

B4.5.3.5 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), effective date, and archival date.

B4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

B4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.

B4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.

B4.5.4 There shall be a process for the regular review and assessment of records to identify recurring problems, potential points of failure, or need for process improvement.

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the clinical care of the recipient and/or donor.

B4.6.1 Agreements shall include the responsibility of the third-party facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

B4.6.2 Agreements shall be dated and reviewed on a regular basis.

B4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

B4.7.1 Safety endpoints and the criteria for cellular therapy product efficacy and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

B4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product and/or recipient type shall be evaluated.

B4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:

B4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.

B4.7.3.2 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration.

B4.7.4 Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, and/or product, shall be provided in a timely manner to entities involved in the collection, processing, and/or distribution of the cellular therapy product.

B4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Clinical Program's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

B4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

B4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.

B4.8.3 Audits shall include, at a minimum:

B4.8.3.1 Periodic audit of the accuracy of data elements included in the applicable CIBMTR Cellular Therapy forms.

B4.8.3.2 Annual audit of safety endpoints and immune effector cellular therapy toxicity management.

B4.8.3.3 Annual audit of donor screening and testing.

B4.8.3.4 Annual audit of management of cellular therapy products with positive microbial culture results.

B4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

B4.9.1 Notification of the recipient.

B4.9.2 Recipient follow-up and outcome analysis.

B4.9.3 Follow-up of the donor, if relevant.

B4.9.4 Reporting to regulatory agencies if appropriate.

B4.9.5 Criteria for the administration of cellular therapy products with positive microbial culture results.

B4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, serious adverse events, and complaints, including the following activities at a minimum:

B4.10.1 Detection.

B4.10.2 Investigation.

B4.10.2.1 A thorough investigation shall be conducted by the Clinical Program in collaboration with the Collection Facility and Processing Facility, as appropriate.

B4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.

B4.10.3 Documentation.

B4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.

B4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Clinical Program Director or designee and the Quality Manager.

B4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.

B4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products, if applicable.

B4.10.4 Reporting.

B4.10.4.1 When it is determined that a cellular therapy product was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws and regulations.

B4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

B4.10.5 Corrective and preventive action.

B4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

B4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

B4.10.6 There shall be a defined process to obtain feedback from patients or legally authorized representatives.

B4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the

donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

B4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Clinical Program's operations are interrupted.

B5: POLICIES AND PROCEDURES

B5.1 The Clinical Program shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:

B5.1.1 Recipient evaluation, selection, and treatment.

B5.1.2 Donor and recipient confidentiality.

B5.1.3 Donor and recipient consent.

B5.1.4 Donor screening, testing, eligibility determination, selection, and management.

B5.1.5 Preparation of the recipient prior to cellular therapy product administration.

B5.1.6 Administration of blood products.

B5.1.7 Administration of cellular therapy products, including products under exceptional release.

B5.1.8 Duration and conditions of cellular therapy product storage and indications for disposal.

B5.1.9 Hygiene and use of personal protective equipment.

B5.1.10 Disposal of medical and biohazard waste.

B5.1.11 Emergency and disaster plan, including the Clinical Program response.

B5.1.12 Management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system disease.

B5.2 The Clinical Program shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.

B5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

B5.3.1 A clearly written description of the objectives.

B5.3.2 A description of equipment and supplies used.

B5.3.3 Acceptable end-points and the range of expected results.

B5.3.4 A stepwise description of the procedure.

B5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

B5.3.6 Age-specific issues where relevant.

B5.3.7 A reference section listing appropriate literature.

B5.3.8 Documented approval of each procedure by the Clinical Program Director or designated physician prior to implementation and every two years thereafter.

B5.3.9 Documented approval of each procedural modification by the Clinical Program Director or designated physician prior to implementation.

B5.3.10 Reference to current version of orders, worksheets, reports, labels, and forms.

B5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

B5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

B5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

B5.7 Variances shall be pre-approved by the Clinical Program Director and reviewed by the Quality Manager.

B6: ALLOGENEIC AND AUTOLOGOUS DONOR SELECTION, EVALUATION, AND MANAGEMENT

B6.1 AUTOLOGOUS AND RECIPIENT-SPECIFIC ALLOGENEIC CELLULAR THERAPY PRODUCTS

B6.1.1 There shall be written criteria for allogeneic and autologous donor selection, evaluation, and management by trained medical personnel.

B6.1.1.1 Written criteria shall include criteria for the selection of allogeneic donors who are minors or elderly.

B6.1.1.2 Written criteria shall include criteria for the selection of allogeneic donors when more than one donor is available and suitable.

B6.1.2 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

B6.1.2.1 The risks and benefits of the procedure.

B6.1.2.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

B6.1.2.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.

B6.1.2.4 Alternative collection methods.

B6.1.2.5 Protection of medical information and confidentiality.

B6.1.3 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

B6.1.4 Family members and legally authorized representatives should not serve as interpreters or translators.

B6.1.5 The donor shall have an opportunity to ask questions.

B6.1.6 The donor shall have the right to refuse to donate.

B6.1.6.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

B6.1.7 Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

B6.1.7.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

B6.1.8 In the case of a minor donor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.

B6.1.9 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.

B6.1.10 The donor shall be informed of the policy for cellular therapy product discard, including actions taken when an intended recipient no longer requires the cellular therapy product.

B6.1.11 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

B6.1.12 There shall be criteria and evaluation policies and procedures in place to protect the safety of donors during the process of cellular therapy product collection.

B6.1.12.1 Any abnormal finding shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

B6.1.12.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

B6.1.12.3 Autologous donors shall be tested as required by applicable laws and regulations.

B6.1.12.4 The risks of donation shall be evaluated and documented.

B6.1.13 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to preparation for collection and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

B6.1.14 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.

B6.1.15 The Clinical Program shall inform collection staff and the Processing Facility of donor test results or if any testing was not performed.

B6.1.16 There shall be a written order from a physician specifying, at a minimum, timing and goals of collection and processing.

B6.1.17 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the collection staff prior to collection.

B6.1.18 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the recipient's physician.

B6.1.19 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.

B6.1.20 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated.

B6.1.21 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.

B6.1.22 For allogeneic products containing red blood cells sufficient to cause a transfusion reaction, donors and recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

B6.1.23 When relevant, a red cell antibody screen shall be performed on allogeneic recipients.

B6.1.24 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.

B6.1.25 When appropriate for the cellular therapy product, the medical history for allogeneic donors shall include at least the following:

B6.1.25.1 Vaccination history.

B6.1.25.2 Travel history.

B6.1.25.3 Blood transfusion history.

B6.1.25.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.

B6.1.25.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.1.25.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

B6.1.25.7 Questions to identify a past history of malignant disease.

B6.1.25.8 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.

B6.1.26 Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests required by applicable laws and regulations:

B6.1.26.1 Human immunodeficiency virus, type 1.

B6.1.26.2 Human immunodeficiency virus, type 2.

B6.1.26.3 Hepatitis B virus.

B6.1.26.4 Hepatitis C virus.

B6.1.26.5 Treponema pallidum (syphilis).

B6.1.27 If required by applicable laws and regulations, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:

B6.1.27.1 Human T cell lymphotropic virus I.

B6.1.27.2 Human T cell lymphotropic virus II.

B6.1.27.3 West Nile Virus.

B6.1.27.4 Trypanosoma cruzi (Chagas Disease).

B6.1.28 Blood samples for testing for evidence of clinically relevant infection shall be drawn and tested within timeframes required by applicable laws and regulations.

B6.1.28.1 For viable, lymphocyte rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in European Union member states.

B6.1.29 Allogeneic donors shall be tested for CMV (unless previously documented to be positive).

B6.1.30 Additional tests shall be performed as required to assess the possibility of transmission of other infectious and non-infectious diseases.

B6.1.31 Allogeneic donors and recipients shall be tested for HLA loci determined by the Clinical Program Director to be of importance to the cellular therapy product by a laboratory accredited by ASHI, EFI, or other appropriate organization.

B6.1.31.1 DNA high resolution molecular typing shall be used for Class II typing, if indicated.

B6.1.31.2 Verification typing shall be performed on the selected allogeneic donor using an independently collected sample. Results shall be confirmed prior to collection.

B6.1.31.3 When relevant to the cellular therapy product, there shall be a policy for anti-HLA antibody testing for mismatched donors and recipients.

B6.1.32 Allogeneic donor eligibility, as defined by applicable laws and regulations, shall be determined by a physician after history, exam, medical record review, and testing. The donor eligibility determination shall be documented in the recipient's medical

record before the recipient is prepared for administration and before the allogeneic donor begins the mobilization regimen, if applicable.

B6.1.33 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

B6.1.34 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of the rationale for his/her selection by the administering physician, urgent medical need documentation, and the informed consent of the donor and the recipient.

B6.1.35 Allogeneic donor eligibility shall be communicated in writing to the Collection and Processing Facilities.

B6.1.36 There shall be a policy covering the creation and retention of allogeneic donor records.

B6.1.36.1 Allogeneic donor records shall include donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

B6.2 ALLOGENEIC CELLULAR THERAPY PRODUCTS MANUFACTURED FOR MULTIPLE RECIPIENTS

B6.2.1 At the time of selection for administration, the Clinical Program shall request all technical data from the cellular therapy product manufacturing facility regarding the product after processing prior to cryopreservation, including at a minimum:

B6.2.1.1 Total count of relevant cell.

B6.2.1.2 Viability and/or potency, if applicable.

B6.2.1.3 Microbial cultures from the cellular therapy product after processing prior to cryopreservation.

B6.2.1.4 ABO group and Rh type, if applicable.

B6.2.1.5 All HLA Class I and II typing results.

B6.2.1.6 Communicable disease testing results performed on the donor.

B6.2.1.7 Final donor eligibility determination and risks of communicable and/or genetic diseases, disclosed by the donor medical and genetic screening or clinical chart review, and the results of any investigation or further testing performed.

B6.2.1.8 The method of processing.

B6.2.1.9 Any variances in collection, processing, testing, cryopreservation, storage, and/or transport or shipping procedures that may influence the integrity and/or quality of the cellular therapy product.

B6.2.1.10 Physical characteristics of the cellular therapy product, including at a minimum the number and type of bags or compartments used for storage.

B7: RECIPIENT CARE

B7.1 Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional familiar with the proposed therapy.

B7.1.1 The Clinical Program shall provide information regarding the risks and benefits of the proposed cellular therapy.

B7.2 The attending physician shall verify the availability and suitability of a donor or cellular therapy product prior to initiating the recipient for cellular therapy.

B7.2.1 The Clinical Program shall notify the Processing Facility prior to requesting a cellular therapy product from a cord blood bank, registry, or other facility.

B7.3 Records shall be made concurrently with each step of recipient care in such a way that all steps may be accurately traced.

B7.3.1 Records shall identify the person immediately responsible for each significant step, including dates and times (where appropriate) of various steps.

B7.4 There shall be a policy addressing safe administration of the preparative regimen, if applicable.

B7.4.1 The treatment orders shall include the patient height and weight, specific dates of administration, daily doses (if appropriate), and route of administration of each agent.

B7.4.2 Preprinted orders or electronic equivalent shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.

B7.6 There shall be a policy addressing safe administration of cellular therapy products.

B7.6.1 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.

B7.6.2 There shall be documentation in the recipient's medical record of the administered cellular therapy product unique identifier, initiation and completion times of administration, and any adverse events related to administration.

B7.6.3 There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.

B7.6.3.1 There shall be a process for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.

B7.6.3.2 Communication to, as relevant, clinical staff, intensive care units, emergency departments, and pharmacies shall be timely.

B7.6.3.3 The Clinical Program shall have written guidelines for management of complications, including the use of cytokine-blocking agents and corticosteroid administration.

B7.6.4 A circular of information for cellular therapy products shall be available to staff.

B7.7 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC CELLULAR THERAPY

B7.7.1 Allogeneic recipients should be assessed regularly for evidence of acute GVHD using an established staging and grading system.

B7.7.2 Allogeneic recipients should be assessed regularly for evidence of chronic GVHD using an established staging and grading system.

B8: CLINICAL RESEARCH

B8.1 Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved under institutional policies and applicable laws and regulations.

B8.1.1 Those Clinical Programs utilizing investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a process for tracking, inventory, and secured storage of investigational drugs.

B8.2 Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and applicable laws and regulations, including audits; approvals by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse events.

B8.3 For clinical research, informed consent shall be obtained from each research subject or legally authorized representative, in language he or she can understand, and under circumstances that minimize the possibility of coercion or undue influence.

B8.3.1 The research subject or legally authorized representative shall be given the opportunity to ask questions and to have his/her questions answered to his/her satisfaction, and to withdraw from the research without prejudice.

B8.3.2 Informed consent for a research subject shall contain the following elements at a minimum and comply with applicable laws and regulations:

B8.3.2.1 An explanation of the research purposes, a description of the procedures to be followed, and the identification of investigational procedures.

B8.3.2.2 The expected duration of the subject's participation.

B8.3.2.3 A description of the reasonably expected risks, discomforts, benefits to the subject and others, and alternative procedures.

B8.3.2.4 A statement of the extent to which confidentiality will be maintained.

B8.3.2.5 An explanation of the extent of compensation for injury.

B8.4 There shall be a process in place to address the disclosure of any issues that may represent a conflict of interest in clinical research.

B9: DATA MANAGEMENT

B9.1 The Clinical Program shall collect all the data elements included in the applicable CIBMTR Cellular Therapy forms.

B9.2 The Clinical Program shall define staff responsible for collecting data and, as appropriate, reporting data to institutional repositories and CIBMTR.

B10: RECORDS

B10.1 Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years by the Clinical Program, or longer in accordance with applicable laws and regulations, or by a defined program or institutional policy.

B10.1.1 Employee records shall be maintained in a confidential manner and as required by applicable laws and regulations.

B10.2 Patient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration, whichever requires the longest maintenance period.

B10.3 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

B10.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

B10.4.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

B10.4.2 The Clinical Program shall furnish outcome data, in so far as they concern the safety, purity, or potency of the cellular therapy product involved, to other facilities involved in the collection or processing of the cellular therapy product.

COLLECTION STANDARDS

PART C

C1	General
C2	Collection Activities
C3	Personnel
C4	Quality Management
C5	Policies and Procedures
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PART C: COLLECTION STANDARDS

C1: GENERAL

C1.1 These Standards apply to the collection activities of all cellular therapy products collected from living donors.

C1.2 Collected cellular therapy products shall be distributed to cell processing facilities that meet the Standards with respect to their role in the cellular therapy product manufacturing process.

C1.3 Collection shall comply with applicable laws and regulations.

C1.3.1 If required by applicable laws and regulations, collections shall be performed in a facility licensed, registered, or accredited as required by the appropriate governmental authority for the activities performed.

C2: COLLECTION ACTIVITIES

C2.1 There shall be appropriate designated areas for collection of cellular therapy products, for collected products, and for storage of supplies, reagents, and equipment.

C2.1.1 The collection area shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

C2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

C2.1.3 There shall be a process for confidential donor examination and evaluation.

C2.2 There shall be adequate lighting, ventilation, and access to sinks during collection to prevent the introduction, transmission, or spread of communicable disease.

C2.3 Environmental conditions shall be controlled to protect the safety and comfort of patients, donors, and personnel.

C2.4 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled, monitored, and recorded, when appropriate, for air quality and surface contaminates.

C2.5 There shall be adequate equipment and materials for the procedures performed.

C2.6 There shall be access to an intensive care unit and/or emergency services.

C2.7 The facility in which collection is performed shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

C2.8 There shall be a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, or radiological hazards.

C3: PERSONNEL

C3.1 MEDICAL DIRECTOR OF COLLECTION ACTIVITIES

C3.1.1 There shall be a Medical Director who is a licensed or certified physician with postgraduate training in the methods required for cell collection and/or the therapeutic disease area.

C3.1.2 The Medical Director or designee shall be responsible for the following elements:

C3.1.2.1 All technical procedures.

C3.1.2.2 Performance of the collection procedure.

C3.1.2.3 Supervision of staff.

C3.1.2.4 Administrative operations.

C3.1.2.5 The medical care of donors undergoing cell collection.

C3.1.2.6 Pre-collection evaluation of donors at the time of donation.

C3.1.2.7 Care of any complications resulting from the collection procedure.

C3.1.2.8 The Quality Management Program, including compliance with these Standards and other applicable laws and regulations.

C3.1.3 The Medical Director shall have at least one year experience in performing and/or supervising cellular therapy product collection procedures.

C3.1.4 The Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy product collection and/or the therapeutic disease area annually at a minimum.

C3.2 QUALITY MANAGER

C3.2.1 There shall be a Quality Manager for collection activities to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the collection activities.

C3.2.2 The Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy, cell collection, and/or quality management annually at a minimum.

C3.3 STAFF

C3.3.1 The number of trained collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage.

C3.3.2 For collection activities involving pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.

C4: QUALITY MANAGEMENT

C4.1 The Medical Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

C4.1.1 The Medical Director or designee shall annually review the effectiveness of the Quality Management Program. Documentation of the review findings shall also be provided to the Clinical Program Director, as applicable.

C4.2 Collection activities shall be performed in compliance with a written Quality Management Plan.

C4.2.1 The Medical Director or designee shall be responsible for the Quality Management Plan as it pertains to collection activities.

C4.2.2 The Medical Director or designee shall review and report to staff on quality management activities, at a minimum, quarterly.

C4.2.3 The Medical Director or designee shall not have oversight of his/her own work if this person also performs other tasks related to cellular therapy product collection.

C4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions and functions required for collection.

C4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

C4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position required for cellular therapy product collection. Personnel requirements shall include at a minimum:

C4.4.1 A current job description for all staff.

C4.4.2 A system to document the following for all staff:

C4.4.2.1 Initial qualifications.

C4.4.2.2 New employee orientation.

C4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

C4.4.2.4 Competency for each critical function performed.

C4.4.2.5 Continued competency at least annually.

C4.4.2.6 Continuing education.

C4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

C4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.

C4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

C4.5.2.1 Policies and Standard Operating Procedures.

C4.5.2.2 Worksheets.

C4.5.2.3 Forms.

C4.5.2.4 Labels.

C4.5.3 The document control policy shall include:

C4.5.3.1 A standardized format for policies, procedures, worksheets, forms, and labels.

C4.5.3.2 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

C4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

C4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

C4.5.3.5 A system for document change control that includes a description of the change, the signature of the approving individual(s), approval date, effective date, and archival date.

C4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

C4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.

C4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.

C4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product or clinical care of the donor.

C4.6.1 Agreements shall include the responsibility of the facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

C4.6.2 Agreements shall be dated and reviewed on a regular basis.

C4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

C4.7.1 Criteria for cellular therapy product safety, product efficacy, and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

C4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product shall be evaluated.

C4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the collection activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

C4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

C4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.

C4.8.3 Audits shall include the following annually at a minimum:

C4.8.3.1 Documentation of proper donor eligibility determination prior to start of the collection procedure.

C4.8.3.2 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

C4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

C4.9.1 Notification of the recipient's physician.

C4.9.2 Investigation of cause.

C4.9.3 Follow-up of the donor, if relevant.

C4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, severe adverse events, and complaints, including the following activities at a minimum:

C4.10.1 Detection.

C4.10.2 Investigation.

C4.10.2.1 A thorough investigation shall be conducted by the collection staff in collaboration with the Processing Facility and Clinical Program, as appropriate.

C4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.

C4.10.3 Documentation.

C4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.

C4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Medical Director or designee and the Quality Manager.

C4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.

C4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products.

C4.10.4 Reporting.

C4.10.4.1 When it is determined that a cellular therapy product was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws.

C4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

C4.10.5 Corrective and preventive action.

C4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

C4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

C4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event collection operations are interrupted.

C4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities.

C4.13.1 Qualification plans shall be reviewed and approved by the Medical Director or designee.

C4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.

C4.14.1 Critical procedures shall include at least the following: collection procedures, labeling, storage, and distribution.

C4.14.2 Each validation shall include:

C4.14.2.1 An approved validation plan, including conditions to be validated.

C4.14.2.2 Acceptance criteria.

C4.14.2.3 Data collection.

C4.14.2.4 Evaluation of data.

C4.14.2.5 Summary of results.

C4.14.2.6 Review and approval of the validation plan, results, and conclusion by the Medical Director or designee and the Quality Manager or designee.

C4.14.3 Changes to a process shall include evaluation of risk to confirm that they do not create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.

C5: POLICIES AND PROCEDURES

C5.1 Policies and/or procedures addressing critical aspects of operations and management in addition to those required in C4 shall be established and maintained. These documents shall include all elements required by these Standards and shall address at a minimum:

C5.1.1 Donor and recipient confidentiality.

C5.1.2 Donor consent.

C5.1.3 Donor screening, testing, eligibility determination, and management.

C5.1.4 Cellular therapy product collection.

C5.1.5 Prevention of mix-ups and cross-contamination.

C5.1.6 Labeling (including associated forms and samples).

C5.1.7 Cellular therapy product expiration dates.

C5.1.8 Cellular therapy product storage.

C5.1.9 Release and exceptional release.

C5.1.10 Transportation and shipping including methods and conditions to be used for distribution to external facilities.

C5.1.11 Critical reagent and supply management.

C5.1.12 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.

C5.1.13 Recalls of equipment, supplies, and reagents.

C5.1.14 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.

C5.1.15 Hygiene and use of personal protective attire.

C5.1.16 Disposal of medical and biohazard waste.

C5.1.17 Emergency and disaster plan, including the collection staff response.

C5.2 A Standard Operating Procedures Manual for collection activities shall be maintained, including a listing of all current Standard Operating Procedures, including title, identifier, and version.

C5.3 Standard Operating Procedures required in C5.1 shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

C5.3.1 A clearly written description of the objectives.

C5.3.2 A description of equipment and supplies used.

C5.3.3 Acceptable end-points and the range of expected results.

C5.3.4 A stepwise description of the procedure.

C5.3.5 Age-specific issues where relevant.

C5.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.

C5.3.7 A reference section listing appropriate literature.

C5.3.8 Documented approval of each procedure by the Medical Director prior to implementation and every two years thereafter.

C5.3.9 Documented approval of each procedural modification by the Medical Director or designee prior to implementation.

C5.3.10 Reference to a current version of orders, worksheets, reports, labels, and forms.

C5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

C5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

C5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

C5.7 Variances shall be pre-approved by the Medical Director and reviewed by the Quality Manager.

C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

C6.1 There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.

C6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION

C6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

C6.2.1.1 The risks and benefits of the procedure.

C6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

C6.2.1.3 The rights of the donor and legally authorized representative of the donor who is a minor to review the results of such tests according to applicable laws and regulations.

C6.2.1.4 Protection of medical information and confidentiality.

C6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

C6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.

C6.2.4 The donor shall have an opportunity to ask questions.

C6.2.5 The donor shall have the right to refuse to donate.

C6.2.5.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

C6.2.6 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

C6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health professional overseeing care of the recipient.

C6.2.7 In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.

C6.2.8 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.

C6.2.9 Documentation of consent shall be available to the collection staff prior to the collection procedure.

C6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

C6.3.1 There shall be criteria and evaluation policies and procedures in place to protect the safety of donors during the process of cellular therapy product collection.

C6.3.1.1 The collection staff shall confirm that any abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

C6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

C6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

C6.3.2 The risks of the cellular therapy product collection procedure shall be evaluated and documented.

C6.3.3 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to cellular therapy product collection and, as applicable, within seven (7) days prior to preparation of the recipient for administration.

C6.3.4 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.

C6.3.5 The Clinical Program shall inform collection and processing staff of donor test results or if any testing was not performed.

C6.3.6 There shall be written order from a physician specifying, at a minimum, timing and goals of collection.

C6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the recipient's physician. Collection staff shall document review of these donor safety issues.

C6.3.8 There shall be written documentation of issues of donor health that pertain to the safety of the collection procedure available to the collection staff. Collection staff shall document review of these issues prior to collection.

C6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.

C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

C6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated.

C6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.

C6.4.3 Collection staff shall comply with B6.1.25 through B6.1.25.8 when primarily responsible for donor screening for transmissible disease.

C6.4.4 Collection staff shall comply with B6.1.26 through B6.1.30 when primarily responsible for infectious and non-infectious disease testing of donors.

C6.4.5 Collection staff shall comply with B6.1.22, B6.1.23, and B6.1.31 through B6.1.31.3 when primarily responsible for testing for the selection of allogeneic donors.

C6.4.6 Collection staff shall confirm that allogeneic donor eligibility, as defined by applicable laws and regulations, is determined by a physician after history, exam, medical record review, and testing before collection.

C6.4.7 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

C6.4.8 Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.

C6.4.9 Allogeneic donor eligibility shall be communicated in writing to the Processing Facility.

C6.5 There shall be a policy covering the creation and retention of donor records including at a minimum:

C6.5.1 Donor identification including at least name and date of birth.

C6.5.2 Age, gender, and medical history, and, for allogeneic donors, behavioral history.

C6.5.3 Consent to donate.

C6.5.4 Results of laboratory testing.

C6.5.5 Allogeneic donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

C7.1 LABELING OPERATIONS

C7.1.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

C7.1.1.1 Stocks of unused labels representing different products shall be stored in a controlled manner to prevent errors.

C7.1.1.2 Obsolete labels shall be restricted from use.

C7.1.2 The labeling operation for pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Medical Director or designee to confirm accuracy regarding identity, content, and conformity.

C7.1.3 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Medical Director or designee.

C7.1.4 A system for label version control shall be employed.

C7.1.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

C7.1.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

C7.1.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

C7.1.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

C7.1.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

C7.1.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process to verify the information or two (2) qualified staff members.

C7.1.8 Labeling elements required by applicable laws and regulations shall be present.

C7.1.9 All data fields on labels shall be completed.

C7.1.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

C7.1.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

C7.1.12 The label shall be validated as reliable for storage under the conditions in use.

C7.2 PRODUCT IDENTIFICATION

C7.2.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

C7.2.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

C7.2.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

C7.2.1.3 Supplementary identifiers shall not obscure the original identifier.

C7.2.1.4 The facility associated with each identifier shall be noted on the label.

C7.2.2 Cellular therapy products shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

C7.3 LABEL CONTENT

C7.3.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

C7.3.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

C7.3.3 Labeling at the end of collection shall occur before the cellular therapy product is removed from the proximity of the donor.

C7.3.4 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.

C7.3.5 For allogeneic cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after the use of the product.

C8: PROCESS CONTROLS

C8.1 Collection of cellular therapy products shall be performed according to written procedures.

C8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.

C8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products.

C8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.

C8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.

C8.3 Equipment for the collection procedure shall conform to applicable laws and regulations.

C8.4 There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

C8.5 Collection procedures shall include a process for assessing the quality of cellular therapy products to confirm product safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.

C8.5.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to confirm products meet predetermined release specifications.

C8.5.2 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.

C8.6 Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection.

C8.7 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures when required.

C8.8 Cellular therapy products shall be packaged in closed sterile containers appropriate for the product collected.

C8.9 Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood.

C8.10 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

C8.10.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

C9: CELLULAR THERAPY PRODUCT STORAGE

C9.1 Cellular therapy products stored before distribution shall be stored in a manner to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of products.

C9.2 Collection policies or procedures shall include the duration and conditions of short-term storage prior to distribution to a Processing Facility or Clinical Program.

C10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

C10.1 Procedures for transportation and shipping of the cellular therapy product shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

C10.2 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

C10.3 The cellular therapy product shall be transported and/or shipped to the Processing Facility in a validated container at a temperature defined in a Standard Operating Procedure.

C10.3.1 Cellular therapy products that are transported and/or shipped from the collection site to the Processing Facility shall be transported and/or shipped in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.

C10.4 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping procedure and in compliance with C7.3.4 and C7.3.5.

C10.5 There shall be a record of the date and time of cellular therapy product distribution.

C11: RECORDS

C11.1 GENERAL REQUIREMENTS

C11.1.1 A records management system shall be established and maintained to facilitate the review of records.

C11.1.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C11.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the receiving institution shall be informed of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C11.1.2 Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.

C11.1.3 Records shall be accurate, legible, and indelible.

C11.1.4 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and their recipients and donors, shall be established and followed in compliance with applicable laws and regulations.

C11.2 Collection records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years, or longer in accordance with applicable laws and regulations, or a defined program or institution policy.

C11.2.1 Employee records shall be maintained in a confidential manner, as required by applicable laws and regulations.

C11.3 Records to allow tracking and tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include: product identity, unique numeric or alphanumeric identifier, and collection date and time; and donor and recipient identification as far as known.

C11.4 Patient and donor records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever requires the longest maintenance period.

C11.5 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

C11.6 ELECTRONIC RECORDS

C11.6.1 There shall be a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the cellular therapy program that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

C11.6.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

C11.6.3 There shall be a means by which access to electronic records is limited to authorized individuals.

C11.6.4 The critical electronic record system shall maintain unique identifiers.

C11.6.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

C11.6.6 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record systems are not available. The alternative system shall be validated and collection staff shall be trained in its use.

C11.6.7 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

C11.6.7.1 A method shall be established or the system shall provide for review of data before final acceptance.

C11.6.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

C11.6.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

C11.6.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:

C11.6.9.1 Training and continued competency of personnel in systems use.

C11.6.9.2 Monitoring of data integrity.

C11.6.9.3 Back-up of the electronic records system on a regular schedule.

C11.6.9.4 System assignment of unique identifiers.

C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILTY

C11.7.1 The collection staff shall furnish to the facility of final disposition a copy of all records relating to the collection procedures performed in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

C11.7.2 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

PROCESSING FACILITY STANDARDS

PART D

PART D: PROCESSING FACILITY STANDARDS

D1: GENERAL

D1.1 These Standards apply to all processing, storage, and distribution activities performed in the Processing Facility on cellular therapy products obtained from living donors.

D1.2 The Processing Facility shall abide by all applicable laws and regulations.

D1.2.1 The Processing Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

D1.3 The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and at least one designated staff member actively performing cellular therapy product processing. This team shall have been in place for at least twelve (12) months preceding initial accreditation.

D2: PROCESSING FACILITY

D2.1 The Processing Facility shall be of adequate space, design, and location for the intended procedures.

D2.1.1 The Processing Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.

D2.1.2 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.1.3 The Processing Facility shall be secure to prevent the entrance of unauthorized personnel.

D2.1.4 The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

D2.1.5 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

D2.2 Processing Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of personnel.

D2.3 Critical facility parameters that may affect processing, storage, or distribution, including temperature and humidity at a minimum, shall be assessed for risk to the cellular therapy product.

D2.3.1 Critical Facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

D2.4 When using procedures that may result in contamination or cross-contamination of cellular therapy products or when performing more than minimal manipulation, critical

environmental conditions shall be controlled, monitored, and recorded where appropriate for air quality and surface contaminates.

D2.4.1 The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.

D2.5 The Processing Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

D2.6 There shall be adequate equipment and materials for the procedures performed.

D2.7 The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

D2.8 The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological hazards.

D2.9 All waste generated by the Processing Facility activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.

D2.10 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

D3: PERSONNEL

D3.1 PROCESSING FACILITY DIRECTOR

D3.1.1 There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree in a relevant science, qualified by a minimum of two (2) years training and experience for the scope of activities carried out in the Processing Facility.

D3.1.2 The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program of the Processing Facility, including compliance with these Standards and other applicable laws and regulations.

D3.1.3 The Processing Facility Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed or certified physician with a minimum of two (2) years postgraduate training and practical and relevant experience in the preparation and clinical use of cellular therapy products.

D3.2.2 The Processing Facility Medical Director or designee shall be directly responsible for all medical aspects related to the Processing Facility.

D3.2.3 The Processing Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

D3.3 QUALITY MANAGER

D3.3.1 There shall be a Processing Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Processing Facility.

D3.3.2 The Processing Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy processing and/or quality management annually at a minimum.

D3.4 STAFF

D3.4.1 The number of trained processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage.

D4: QUALITY MANAGEMENT

D4.1 The Processing Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

D4.1.1 The Processing Facility Director or designee shall annually review the effectiveness of the Quality Management Program. Documentation of the review findings shall be provided to the Clinical Program Director, as applicable.

D4.2 The Processing Facility shall establish and maintain a written Quality Management Plan.

D4.2.1 The Processing Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Processing Facility.

D4.2.2 The Processing Facility Director or designee shall review and report to staff quality management activities, at a minimum, quarterly.

D4.2.3 The Processing Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Processing Facility.

D4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions and functions within the Processing Facility.

D4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

D4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for each key position in the Processing Facility. Personnel requirements shall include at a minimum:

D4.4.1 A current job description for all staff.

D4.4.2 A system to document the following for all staff:

D4.4.2.1 Initial qualifications.

D4.4.2.2 New employee orientation.

D4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

D4.4.2.4 Competency for each critical function performed.

D4.4.2.5 Continued competency at least annually.

D4.4.2.6 Continuing education.

D4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

D4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.

D4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

D4.5.2.1 Policies and Standard Operating Procedures.

D4.5.2.2 Worksheets.

D4.5.2.3 Forms.

D4.5.2.4 Labels.

D4.5.3 The document control policy shall include:

D4.5.3.1 A standardized format for policies, procedures, worksheets, forms, and labels.

D4.5.3.2 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.

D4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

D4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

D4.5.3.5 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), effective date, and archival date.

D4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years

from archival or according to governmental or institutional policy, whichever is longer.

D4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.

D4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.

D4.6.1 Agreements shall include the responsibility of the facility performing any step in processing, testing, or storage to comply with applicable laws and regulations and these Standards.

D4.6.2 Agreements shall be dated and reviewed on a regular basis.

D4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

D4.7.1 Criteria for cellular therapy product safety, product efficacy, and/or the clinical outcome, shall be determined and shall be reviewed at regular time intervals.

D4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product shall be evaluated.

D4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

D4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

D4.8.3 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements shall be audited annually.

D4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

D4.9.1 Documentation and product labeling.

D4.9.2 Product quarantine.

D4.9.3 Criteria for product release.

D4.9.4 Identification of individuals authorized to approve release, including the Processing Facility Director at minimum.

D4.9.5 Investigation of cause.

D4.9.6 Notification of the recipient's physician, collection staff, and/or any other facility in receipt of the cellular therapy product.

D4.9.7 Reporting to regulatory agencies if appropriate.

D4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, serious adverse events, and complaints, including the following activities at a minimum:

D4.10.1 Detection.

D4.10.2 Investigation.

D4.10.2.1 A thorough investigation shall be conducted by the Processing Facility in collaboration with the collection staff and Clinical Program, as appropriate.

D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.

D4.10.3 Documentation.

D4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.

D4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Processing Facility Director, Medical Director, or designee and the Quality Manager.

D4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.

D4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products.

D4.10.4 Reporting.

D4.10.4.1 When it is determined that a cellular therapy product was responsible for a serious adverse reaction, the reaction report and results of the investigation shall be made available to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws.

D4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

D4.10.5 Corrective and preventive action.

D4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

D4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

D4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Processing Facility's operations are interrupted.

D4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical supplies, manufacturers, vendors, reagents, equipment, and facilities.

D4.13.1 Qualification plans shall be reviewed and approved by the Processing Facility Director or designee.

D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.

D4.14.1 Critical procedures to be validated or verified shall include at least the following: processing techniques, cryopreservation procedures, labeling, storage, and distribution.

D4.14.2 Each validation shall include:

D4.14.2.1 An approved validation plan, including conditions to be validated.

D4.14.2.2 Acceptance criteria.

D4.14.2.3 Data collection.

D4.14.2.4 Evaluation of data.

D4.14.2.5 Summary of results.

D4.14.2.6 Review and approval of the validation plan, results, and conclusion by the Processing Facility Director or designee and the Quality Manager or designee.

D4.14.3 Changes to a process shall include evaluation of risk to confirm that they do not create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.

D5: POLICIES AND PROCEDURES

D5.1 The Processing Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in D4. These documents shall include all elements required by these Standards and shall address at a minimum:

D5.1.1 Donor and recipient confidentiality.

D5.1.2 Cellular therapy product receipt.

D5.1.3 Processing and process control.

D5.1.4 Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.

D5.1.5 Prevention of mix-ups and cross-contamination.

D5.1.6 Labeling (including associated forms and samples).

D5.1.7 Cryopreservation and thawing.

D5.1.8 Cellular therapy product expiration dates.

D5.1.9 Cellular therapy product storage to include alternative storage if the primary storage device fails.

D5.1.10 Release and exceptional release.

D5.1.11 Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.

D5.1.12 Cellular therapy product recall, to include a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.

D5.1.13 Cellular therapy product disposal.

D5.1.14 Critical reagent and supply management.

D5.1.15 Equipment operation, maintenance, and monitoring, including corrective actions in the event of failure.

D5.1.16 Recalls of equipment, supplies, and reagents.

D5.1.17 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.

D5.1.18 Environmental control to include a description of environmental monitoring plan.

D5.1.19 Hygiene and use of personal protective equipment.

D5.1.20 Disposal of medical and biohazard waste.

D5.1.21 Emergency and disaster plan, including the Processing Facility response.

D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.

D5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

D5.3.1 A clearly written description of the objectives.

D5.3.2 A description of equipment and supplies used.

D5.3.3 Acceptable end-points and the range of expected results.

D5.3.4 A stepwise description of the procedure.

D5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

D5.3.6 A reference section listing appropriate literature.

D5.3.7 Documented approval of each procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.

D5.3.8 Documented approval of each procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.

D5.3.9 Reference to a current version of orders, worksheets, reports, labels, and forms.

D5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

D5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

D5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

D5.7 Variances shall be pre-approved by the appropriate Processing Facility Director and/or Medical Director, and reviewed by the Quality Manager.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

D6.1 Equipment, supplies, and reagents used to process cellular therapy products shall be used in a manner that maintains product function and integrity and prevents product mix-ups, contamination, and cross-contamination.

D6.2 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for the following, at a minimum:

D6.2.1 Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.

D6.2.2 Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

D6.2.3 Storage of materials under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.

D6.2.4 Use of supplies and reagents coming into contact with cellular therapy products during processing, storage, and/or administration that are sterile and of the appropriate grade for the intended use.

D6.2.5 Cleaning and sterilizing of non-disposable supplies or instruments using a procedure verified to remove infectious agents and other contaminants.

D6.2.6 Use of supplies and reagents in a manner consistent with manufacturer instructions.

D6.2.7 Process to prevent the use of expired reagents and supplies.

D6.3 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

D6.4 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

D6.5 The equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use.

D6.6 The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.6.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

D6.6.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.

D6.7 There shall be a procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.8 Equipment shall conform to applicable laws and regulations.

D6.9 Lot numbers, expiration dates, and manufacturers of critical reagents and supplies and identification of key equipment used in each procedure shall be documented.

D6.10 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include at a minimum:

D6.10.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D6.10.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.10.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

D7.1 LABELING OPERATIONS

D7.1.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

D7.1.1.1 Stocks of unused labels representing different cellular therapy products shall be stored in a controlled manner to prevent errors.

D7.1.1.2 Obsolete labels shall be restricted from use.

D7.1.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Processing Facility Director or designee to confirm accuracy regarding identity, content, and conformity.

D7.1.3 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director or designee.

D7.1.4 A system for label version control shall be employed.

D7.1.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

D7.1.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

D7.1.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

D7.1.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

D7.1.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

D7.1.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process to verify the information or two (2) qualified staff members prior to distribution of the cellular therapy product.

D7.1.8 Labeling elements required by applicable laws and regulations shall be present.

D7.1.9 All data fields on labels shall be completed.

D7.1.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

D7.1.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

D7.1.12 The label shall be validated as reliable for storage under the conditions in use.

D7.2 PRODUCT IDENTIFICATION

D7.2.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

D7.2.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

D7.2.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

D7.2.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

D7.2.1.4 Supplementary identifiers shall not obscure the original identifier.

D7.2.1.5 The facility associated with each identifier shall be noted on the label.

D7.2.1.6 If the original identifier is replaced, documentation shall link the new identifier to the original.

D7.2.2 Cellular therapy products shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

D7.3 LABEL CONTENT

D7.3.1 At the completion of processing and at distribution for administration, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

D7.3.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

D7.3.3 Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

D7.3.4 The name and address of the facility that determines that the cellular therapy product meets release criteria and the name and address of the facility that makes the product available for distribution shall either appear on the product label or accompany the product at distribution.

D7.3.5 Cellular therapy products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix III accompany the cellular therapy product when it leaves the Processing Facility.

D7.3.6 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.

D8: PROCESS CONTROLS

D8.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products so that products meet predetermined release specifications.

D8.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to assure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.

D8.1.2 There shall be a documented system for the identification and handling of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient.

D8.1.2.1 There shall be a mechanism to identify the individual obtaining the sample, the sample source, the date, and the time, if appropriate.

D8.1.2.2 Samples obtained for testing shall be representative of the cellular therapy product to be evaluated.

D8.1.3 There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.

D8.1.3.1 For all cellular therapy products, enumeration and viability assays shall be performed for clinically relevant cell populations.

D8.1.3.2 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.

D8.1.4 For tests required by these Standards performed within the Processing Facility:

D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.

D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.

D8.1.4.5 For tests performed within the Processing Facility, there shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director or designee and outcomes reviewed with the staff.

D8.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.

D8.1.6 Infectious disease testing required by these Standards shall be performed using screening tests approved or cleared by the governmental authority for cellular therapy product donors.

D8.1.7 Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director or other designated physician.

D8.1.8 Notification of the recipient's physician of nonconforming cellular therapy products and approval for their release shall be documented.

D8.2 Before a cellular therapy product is processed, shipped, or otherwise prepared for administration, there shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing.

D8.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:

D8.3.1 A statement of donor eligibility.

D8.3.2 For ineligible donors, the reason for their ineligibility.

D8.3.3 For ineligible donors or donors for whom eligibility determination is incomplete, documentation of urgent medical need and physician approval for use.

D8.4 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D8.4.1 Published validated processes shall be verified within the Processing Facility prior to implementation.

D8.4.2 The Processing Facility shall use validated methods for preparation of cellular therapy products for administration.

D8.4.3 If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.

D8.4.3.1 The Processing Facility should verify the processing procedures utilizing practice units similar to the cellular therapy product intended for administration when feasible.

D8.5 Critical control points and associated assays shall be identified and performed on each cellular therapy product as defined in Standard Operating Procedures.

D8.6 Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D8.6.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D8.6.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

D8.7 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing as specified in Standard Operating Procedures.

D8.7.1 The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.

D8.7.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.

D8.8 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and administration or disposal/disposition/distribution of each cellular therapy product in such a way that all steps may be accurately traced.

D8.8.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

D8.8.2 Records shall show the test results and the interpretation of each result, where appropriate.

D8.9 The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release or distribution.

D8.10 There shall be documented notification to the recipient's physician and the Processing Facility Medical Director of clinically relevant processing end-points not met and remedial actions taken.

D8.11 Processing using more-than-minimal manipulation shall only be performed with Institutional Review Board or Ethics Committee approval, with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product, and in compliance with applicable laws and regulations.

D8.11.1 The Processing Facility shall adhere to good manufacturing practices (GMP) appropriate for the degree of cellular therapy product manipulation.

D8.12 For allogeneic cellular therapy products containing red blood cells at the time of administration sufficient to cause a transfusion reaction:

D8.12.1 Results for ABO group and Rh type testing shall be available from two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D8.12.2 When relevant, results for a red cell antibody screen on the recipient shall be available.

D8.13 One or more samples representing the cryopreserved cellular therapy product shall be stored.

D8.13.1 Sample(s) from cryopreserved cellular therapy products shall be stored under conditions that achieve a valid representation of the clinical product.

D8.13.2 Cryopreserved samples shall be retained according to institutional Standard Operating Procedures.

D9: CELLULAR THERAPY PRODUCT STORAGE

D9.1 Processing Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.

D9.2 STORAGE DURATION

D9.2.1 Processing Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.

D9.2.2 There shall be a written stability program that evaluates the viability and potency of cryopreserved cellular therapy products, minimally annually.

D9.3 TEMPERATURE

D9.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

D9.3.2 Noncryopreserved cellular therapy products shall be maintained within a specific temperature range to maintain viability and function, to inhibit infectious agents, and for a period of time not to exceed that specified in Standard Operating Procedures.

D9.3.3 Cryopreserved cellular therapy products shall be stored within a temperature range as defined in Standard Operating Procedures that is appropriate for the product and cryoprotectant solution used.

D9.3.4 Prior to receipt of a cellular therapy product from an external facility, there shall be confirmation that the product can be appropriately stored.

D9.4 PRODUCT SAFETY

D9.4.1 Materials that may adversely affect cellular therapy products shall not be stored in the same refrigerators or freezers as the cellular therapy products.

D9.4.2 For cellular therapy products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.

D9.4.3 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.

D9.4.3.1 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

D9.4.3.2 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents and/or positive microbial cultures shall be quarantined.

D9.4.3.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.

D9.5 STORAGE MONITORING

D9.5.1 Refrigerators and freezers used for storage where cellular therapy products are not fully immersed in liquid nitrogen shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

D9.5.2 There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.

D9.6 ALARM SYSTEMS

D9.6.1 Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.

D9.6.2 Alarm systems shall have audible and visible signals or other effective notification methods.

D9.6.3 Alarm systems shall be checked periodically for function.

D9.6.4 If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.

D9.6.5 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.

D9.6.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.

D9.6.6.1 Instructions shall include a procedure for notifying processing personnel.

D9.6.7 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

D9.7 The storage device shall be located in a secure area and accessible only to authorized personnel.

D9.8 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated samples. The inventory control system records shall include:

D9.8.1 Cellular therapy product unique identifier.

D9.8.2 Recipient name or unique identifier.

D9.8.3 Storage device identifier.

D9.8.4 Location within the storage device.

D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

D10.1 Procedures for transportation and shipping of cellular therapy products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

D10.2 The primary product container for non-frozen cellular therapy products shall be placed in a secondary container and sealed to prevent leakage.

D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.

D10.4 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

D10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

D10.5.1 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

D10.5.2 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.

D10.5.2.1 The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.

D10.5.2.2 The shipping facility shall maintain a record of the temperature over the period of travel.

D10.5.3 The outer container shall be secured.

D10.5.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.

D10.5.5 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.

D10.5.6 The outer container shall be labeled in accordance with applicable laws and regulations regarding the cryogenic material used and the transport or shipment of biological materials.

D10.6 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.

D10.7 There shall be plans for alternative means of transport or shipping in an emergency.

D10.8 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

D11: DISTRIBUTION AND RECEIPT

D11.1 DISTRIBUTION CRITERIA

D11.1.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director or designee for compliance with Standard Operating Procedures and applicable laws and regulations prior to product release or distribution.

D11.1.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

D11.1.2 Each cellular therapy product shall meet pre-determined release criteria prior to distribution from the Processing Facility. The release criteria shall include donor eligibility determination for allogeneic products.

D11.1.2.1 The Processing Facility Director or designee shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

D11.1.2.2 The Processing Facility Medical Director or designee shall give specific authorization for release when the cellular therapy product does not meet clinically relevant release criteria.

D11.1.2.3 Documentation of agreement of the Processing Facility Medical Director or designee and the recipient's physician consent to use any non-conforming product shall be retained in the processing record if such release is allowed by policies, procedures, or package inserts of licensed products.

D11.1.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and appropriate labeling.

D11.1.3.1 A cellular therapy product shall not be released when the container is compromised and/or recipient or donor information is not verified unless the Processing Facility Director or designee gives specific authorization for the product's release.

D11.1.4 For each type of cellular therapy product, the Processing Facility shall maintain and distribute or make a document available to clinical staff containing the following:

D11.1.4.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

D11.1.4.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.

D11.1.4.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.

D11.2 The cellular therapy product processing records shall contain a written record of product distribution including, at a minimum:

D11.2.1 The distribution date and time.

D11.2.2 Unique identifier of the intended recipient.

D11.2.3 The proper product name and identifier.

D11.2.4 Documentation of donor eligibility determination.

D11.2.5 Identification of the facilities that requested and distributed the product.

D11.3 Records shall permit tracing of the cellular therapy product from one facility to another, and shall include:

D11.3.1 Date and time cellular therapy product was distributed.

D11.3.2 Date and time cellular therapy product was received.

D11.3.3 Identity of the transporting or shipping facility.

D11.3.4 Identity of the receiving facility.

D11.3.5 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D11.3.6 Identity of the courier.

D11.3.7 Documentation of any delay or problems incurred during transportation or shipping.

D11.4 RECEIPT OF CELLULAR THERAPY PRODUCTS

D11.4.1 Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.

D11.4.2 The receipt of each cellular therapy product shall include inspection to verify:

D11.4.2.1 The integrity of the cellular therapy product container.

D11.4.2.2 The appearance of the cellular therapy product for evidence of mishandling or microbial contamination.

D11.4.2.3 Appropriate labeling.

D11.4.3 If the primary container or temperature of the cellular therapy product has been compromised, the Processing Facility Director or designee shall give specific authorization to return the product to inventory.

D11.4.4 There shall be procedures to verify that the cellular therapy product was appropriately transported or shipped.

D11.4.4.1 The receiving facility shall document the temperature of the outer container upon arrival.

D11.4.4.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the outer container temperature during shipping.

D11.4.5 The receiving facility shall review and verify product specifications provided by the manufacturer, if applicable.

D11.4.6 There shall be procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.

D11.4.7 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.

D11.4.7.1 For cellular therapy products received from an external facility, there shall be documented evidence of donor eligibility screening and testing in accordance with applicable laws and regulations.

D11.4.8 When cellular therapy products are returned to the Processing Facility after distribution for administration, there shall be documentation in the Processing Facility records of the events requiring return, the temporary storage temperature when at the clinical facility, the results of inspection upon return, and subsequent action taken to protect product safety and viability.

D11.4.8.1 The Processing Facility Director or designee shall consult with the recipient's physician regarding reissue or disposal of the returned product.

D12: DISPOSAL

D12.1 Disposal of cellular therapy products shall include the following requirements:

D12.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal of cellular therapy products.

D12.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.

D12.1.4 Approval by the Processing Facility Medical Director or the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.

D12.1.5 A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.

D12.1.6 Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.

D12.1.6.1 Recipients, donors, and associated Clinical Programs should be informed about policies for directed cellular therapy products as part of the informed consent process and before the cellular therapy product collection.

D12.1.7 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the intended recipient is lost to follow-up, the storage facility shall make a documented effort to notify the donor, cellular therapy product manufacturer, or designated recipient's physician and facility about product disposition, including disposal or transfer.

D12.2 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

D13: RECORDS

D13.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

D13.1.1 The records management system shall facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.

D13.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D13.1.3 For cellular therapy products that are to be distributed for use at another institution, the Processing Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing at or before the time of product distribution.

D13.1.4 Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.

D13.1.5 Records shall be accurate, legible, and indelible.

D13.1.6 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and their recipients and donors, shall be established and followed in compliance with applicable laws and regulations.

D13.2 ELECTRONIC RECORDS

D13.2.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Processing Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

D13.2.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

D13.2.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.

D13.2.2.2 The critical electronic record system shall maintain unique identifiers.

D13.2.2.3 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

D13.2.3 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation of the Processing Facility in the event that critical electronic record systems are not available. The alternative system shall be validated and Processing Facility staff shall be trained in its use.

D13.2.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

D13.2.4.1 A method shall be established or the system shall provide for review of data before final acceptance.

D13.2.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

D13.2.5 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

D13.2.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:

D13.2.6.1 Systems development.

D13.2.6.2 Numerical designation of system versions, if applicable.

D13.2.6.3 Prospective validation of systems, including hardware, software, and databases.

D13.2.6.4 Installation of the system.

D13.2.6.5 Training and continued competency of personnel in systems use.

D13.2.6.6 Monitoring of data integrity.

D13.2.6.7 Back-up of the electronic records system on a regular schedule.

D13.2.6.8 System maintenance and operations.

D13.2.6.9 System assignment of unique identifiers.

D13.2.7 All system modifications shall be authorized, documented, and validated prior to implementation.

D13.3 RECORDS TO BE MAINTAINED

D13.3.1 Processing Facility records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years by the Processing Facility, or longer in accordance with applicable laws or regulations, or with a defined program or institution policy.

D13.3.1.1 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years or longer in accordance with applicable laws or regulations, or with defined program or institution policy. All other facility maintenance records shall be retained as in D13.3.1.

D13.3.1.2 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, and donor and recipient information as found on the original container.

D13.3.1.3 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to applicable laws and regulations or institutional policy, whichever requires the longest maintenance period.

D13.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D13.4.1 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

D13.4.2 The Processing Facility shall furnish to the facility of final disposition a copy of all records relating to the collection, processing, and storage procedures performed in so far as the records concern the safety, purity, or potency of the cellular therapy product involved.

D13.4.3 If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show plainly the extent of its responsibility.

APPENDIX I

CELLULAR THERAPY PRODUCT LABELING

Each label shall include at least the elements detailed in the following table[1]:

Element[2]	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution for administration[3]
Unique numeric or alphanumeric identifier[4]	AF	AF	AF	AF
Proper name of product [5]	AF	AF	AF	AF
Product attributes [5]			AC	AC
Recipient name and/or identifier		AT	AT	AT
Identity and address of collection facility or donor registry		AT	AC	AC
Date, time collection ends, and (if applicable) time zone		AT	AC	AC
Approximate volume		AT	AT	AT
Name and quantity of anticoagulant and other additives		AC	AC	AC
Donor identifier and (if applicable) name		AT	AT	AT
Recommended storage temperature range		AT	AT	AT
Biohazard and/or Warning Labels (as applicable, see C7.3.2, D7.3.2).		AT	AT	AT
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" Statement "WARNING: Advise Patient of Communicable Disease Risks" Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"		AT AT AT	AT AT AT	AT AT AT
Identity and address of processing and distribution facility(ies)			AC	AC
Statement "Do Not Irradiate"			AT	AT
Expiration Date (if applicable)			AC	AC
Expiration Time (if applicable)			AC	AT
ABO and Rh of donor (if applicable)			AC	AC
RBC compatibility determination (if applicable)				AC
Statement indicating that leukoreduction filters shall not be used.				AT
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AT
Date of distribution				AC

AF=Affix, AT=Attach or Affix, AC=Accompany, Attach or Affix

[1]Container and full package labeling requirements for licensed products or products under Investigational New Drug (IND) application shall follow applicable laws and regulations. In the U.S., see 21 CFR 312.6(a).

[2]Facilities registered with ICCBBA who have fully implemented ISBT 128 labeling shall follow the ISBT 128 Standard for the location of information on the label and/or the accompanying documentation.

[3]Products thawed at the bedside do not require a new label.

[4]Overlay labels for supplementary identifiers shall not obscure the original identifier.

[5]Product proper names and attributes are listed in Chapter Three of the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.

APPENDIX II

CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

Each container for shipping and transport on public roads shall include a document on the inside of the container and a label on the exterior of the container with at least the elements detailed in the following table:

Element	Inner container document	Outer container label
Date of distribution, if appropriate	AC	AC
Time[1] of distribution, if appropriate	AC	AC
Statement "Do Not X-Ray" and /or "Do Not Irradiate", if applicable	AC	AF
Statements "Human Cells for Administration" or equivalent and "Handle with Care"	AC	AF
Shipper handling instructions	AC	AF
Shipping facility name, street address, contact person, and phone number	AC	AF
Receiving facility name, street address, contact person, and phone number	AC	AF
Biohazard and/or Warning Labels (as applicable, see C7.3.2, D7.3.2).	AC	
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" Statement "WARNING: Advise Patient of Communicable Disease Risks" Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AC AC AC	

AC= Accompany, AF=Affix

[1]Time shall include the time zone when shipping or transport of the cellular therapy product involves crossing time zones.

APPENDIX III

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the Collection or Processing Facility with at least the elements detailed in the following table[1]:

Documentation	Allogeneic Donors-Eligible	Allogeneic Donor-Ineligible[2]	Allogeneic Donor-Incomplete[2]
Statement that the donor has been determined to be either eligible or ineligible, based upon results of donor screening and testing	X	X	
Summary of records used to make the donor-eligibility determination[3]	X	X	
Name and address of the establishment that made the donor-eligibility determination	X	X	
Listing and interpretation of the results of all communicable disease testing performed	X	X	X
Statement that the communicable disease testing was performed by a laboratory meeting regulatory requirements[4]	X	If applicable	If applicable
Statement noting the reason(s) for the determination of ineligibility		X	
Statement that the donor-eligibility determination has not been completed			X
Statement that the product must not be transplanted or infused until completion of the donor-eligibility determination, except under condition of urgent medical need			X
Listing of any required screening or testing that has not yet been completed			X
Results of donor screening that has been performed			X
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening			X
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases[1]	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility[1,5]	X	X	X

[1]For autologous cellular therapy products, instructions for product use to prevent the introduction, transmission, or spread of communicable diseases and for reporting serious adverse reactions or events to the distributing facility are always required for autologous products. Furthermore, a donor eligibility determination is not required by FDA. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

[2]May only be distributed after release by the Processing Facility Medical Director due to urgent medical need. For ineligible cellular therapy products or incomplete donor eligibility determination, the product shall be shipped in quarantine. For products distributed prior to completion of donor eligibility, determination shall be completed and the physician shall be informed of the results.

[3]Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

[4]This includes laboratories certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 or those laboratories that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services, or those that have met equivalent non-U.S. requirements.

[5]Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same facility.

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Immune Effector Cell Task Force

Helen Heslop – Chair
Michael Lill – Vice Chair
Elizabeth Shpall – Vice Chair
Carlos Bachier
Kevin Curran
David Maloney
Marcela Maus
Philip McCarthy
Sarah Nikiforow
Jae Park
David Porter
Phyllis Warkentin

Staff
Andra Moehring
Kara Wacker

FACT Accreditation Office
University of Nebraska Medical Center
986065 Nebraska Medical Center
Omaha, NE 68198-6065

Phone: (402) 559-1950
Fax: (402) 559-1951
E-mail: fact@unmc.edu
Website: www.factwebsite.org