Celebrating 10 Years! 1992 2002

ISCT TELEGRAFT

International Society for Cellular Therapy

formerly ISHAGE

Volume 9 • No. 3 A Quarterly Newsletter September 2002

Contents

# ISCT Sterility
## Testing Survey

The Legal and Regulatory Committee would like to thank all the members who completed the sterility testing survey. A total of 89 facilities responded to the survey. This survey was prepared to gather data about current sterility testing methods and was prompted by several recent interactions with the FDA by ISCT members, where IND questions similar to this were asked: "Please provide a detailed description of your sterility assay. The sterility testing performed should be as outlined in 21 CFR 610.12 or demonstrated to be of equal sensitivity and specificity as the recommended assay".

Shown below are the results of the ISCT Sterility Survey. Briefly, the majority of the responding sites were hospital-based and located in North America. As the complexity of the process increased, fewer sites performed the procedure. Ninety-three percent of the responders prepared minimally-manipulated products, 70% performed cellular manipulations that were completed within 12 hours and 42% prepared culture-expanded cells. The shift in the sterility method from blood culture bottles to either CFR or USP methods occurred with culture expansion. Most sites send sterility samples to the hospital microbiology laboratory, while 12% of the cell processing laboratories perform their own sterility testing and 8% send the samples to contract laboratories.

| 1. LOCATION OF THE RESPONDERS | |
|---|---|
| North America: | 74% |
| Europe: | 17% |
| Australia: | 4% |
| Japan/Korea: | 3% |
| South America: | 1% |

| 3. METHOD USED FOR MINIMALLY MANIPULATED PRODUCTS: | |
|---|---|
| 7% of the responders do not prepare this type of product. Of the remaining groups (93%) that do prepare minimally manipulated products, the methods used are as follows: | |
| Blood Culture: | 83% |
| 21CFR 610: | 8% |
| USP 25 <71>: | 6% |
| Blood Agar Plate: | 1% |
| Clinical Lab: | 1% |

| 5. METHOD USED FOR CULTURE-EXPANDED PRODUCT: | |
|---|---|
| 58% of the responders do not prepare these products or did not respond to the question. Of the remaining groups (42%) that do prepare culture-expanded products, the methods used are as follows: | |
| Blood Culture: | 56% |
| 21CFR 610: | 30% |
| USP 25 <71>: | 14% |

| 2. PROCESSING WAS BASED IN: | |
|---|---|
| Hospital: | 76% |
| Contract Lab: | 11% |
| Biotech Company: | 10% |
| Blood Center: | 2% |

| 4. METHOD USED FOR MANIPULATED PRODUCTS IN WHICH THE PROCEDURE IS COMPLETE WITHIN 12 HOURS: | |
|---|---|
| 30% of the responders do not prepare these products or did not respond to the question. Of the remaining groups (70%) that do prepare extensively manipulated, un-cultured products, the methods used are as follows: | |
| Blood Culture: | 84% |
| 21CFR 610: | 10% |
| USP 25 <71>: | 6% |

| 6. WHERE IS STERILITY TESTING PERFOMED: | |
|---|---|
| Hospital Lab: | 76% |
| Cell Processing Lab: | 12% |
| Contract Lab with Clean room: | 3% |
| Contract Lab with Isolator: | 5% |
| Public Health Lab: | 1% |
| No response: | 2% |

| 7: BOTTLE BRAND: | |
|---|---|
| BD: Bactec: | 42% |
| Organon Teknika:Bac T/Alert: | 48% |
| Other: | 10% |

## 2002 Corporate Members

ISCT wishes to thank its 2002 Corporate Members for their support. They are:

→ Baxter logo/Amgen logo will be placed later

BD Biosciences
Biosafe SA
Celmed Biosciences
Chimeric Therapies
Cordlife Pte Ltd
Custom Biogenic Systems
Edwards Life Sciences Research Medical
Gambro BCT
Genentech Biooncology/ IDEC Pharmaceuticals
Incara Pharmaceuticals
Kirin Brewery Cell Therapy Group
Kirin Brewery Pharmaceutical Division
Merix Biosciences
Miltenyi Biotec
MVE-Chart Industries
Oncosis
SEBRA
Sigma-Aldrich
StemCell Technologies
StemSoft Software
Therakos, a Johnson & Johnson Company
Titan Pharmaceuticals
Xcyte Therapies

ISCT 2003 Corporate Memberships are now available. For further information on the benefits of membership, please see the ISCT website (www.celltherapy.org) or contact the ISCT Head Office by phone at 604-874-4366 or e-mail at headoffice@celltherapy.org.

Diane Kadidlo and Kathy Loper wrote a summary of the issues and methods associated with sterility testing in the May 2002 edition of the Telegraft. Also included in that issue was a summary of the Cell and Gene Therapy Products USP Chapter 1046. This document acknowledged the unique features of cellular therapy products and how these affect sterility testing.

This survey showed that the majority of laboratories use a blood culture system to detect contamination of cellular products. However, validation of a blood culture system for cell therapy products to the USP or CFR methods has not been published. Four respondents indicated that they have sterility method validation data and are willing to share this data. The goal is to publish the data in Cytotherapy. Additionally, Dr. Elizabeth Read from the NIH is writing a validation protocol to demonstrate that the blood culture methods are equivalent or superior to the USP and CFR methods. Dr. Eda Bloom from the Cell & Gene Therapy Division of CBER/FDA has been contacted and will review the protocol. The Legal & Regulatory Committee will keep everyone updated.

*Janice Davis-Sproul*

Related Society Report

# CellularGraft Engineering Society

### A. History

The Cellular Graft Engineering Society was conceived after the meeting convened by U.S. Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration in April, 2001.

This meeting was arranged to allow the public to discuss in an open forum, the safety issues associated with sorting cells for re-implantation into humans. Laboratories preparing grafts by cell sorting, and groups considering such activities were represented. As participants shared information from their individual projects, it became clear that a forum was needed for focused discussion of technical, safety, and policy relating to sorting material for transplantation into humans. Several of the participants and attendees of the

FDA meeting started communicating by email and decided to organize their interactions into the CGES.

The first meeting of the CGES was held in Research Triangle Park, North Carolina on June 1, 2001. Approximately 30 people interested in clinical cell sorting were in attendance. Representatives from industry, academia, and the US Government, as well as some European organizations held fruitful discussion of the relevant topics. Presenters included people involved in current clinical trials, including Jim Houston from St. Jude's and Lillia Holmes from Greenville Hospital Systems.

The morning session was concluded with an overview of some of the relevant issues and topics involved in the process of clinical cell sorting, presented by Alan Fisher of StemCo Biomedical, Inc. The afternoon session was devoted to having general discussions centered around the processes and procedures involved in getting a clinical cell sorting protocol approved. We discussed topics ranging from facility design to protocol specificity, all in an attempt to bring together the various aspects of such an undertaking.

After the first meeting it was unanimously decided that the group should have future conferences. In order to reach more people, and to make the next meeting even more informative, we decided to expand the focus to the various aspects surrounding the actual cell sorting. More details concerning the agenda for the next meeting are presented below. All along, it has been our intention to become affiliated with a more established group such as ISCT. The publishing of this article is the first step in what we all believe will become a highly productive and mutually beneficial relationship.

## B. Second Meeting

September 27, 2002 | Sands Beach Resort | Myrtle Beach, SC

With the second meeting of the CGES in Myrtle Beach, South Carolina, we hope to further expand the network of practitioners of cellular graft engineering. The overall structure will closely follow the course of the first meeting. In the morning, time will be allotted for companies to give presentations about their various products and services related to the field. Bio-ergonomics will begin by providing an overview of solutions to the pre-purification of samples for cell sorting in the talk entitled, "Novel Non-density Based Methodology for High Yield Recovery of Enriched Cell Subsets". Cytomation will follow with a presentation of the company's hardware for cell sorting.

After lunch, the meeting will continue with David Matsuyama from Becton-Dickinson, who will speak about, "Aseptic Sorting Tools From BD Biosciences". Paul Fallon, will follow with a presentation on the study being done at from Moffitt cancer center involving graft engineering. We will continue with an update from the FDA's Michele Keene-Moore, from CBER, on it's efforts to draft guidelines for clinical cell sorting. There will then be general discussions held concerning the recent ISCT and ISAC meetings and the final topic of the day will be CGES business and news. CGES extends an invitation to everyone to attend this second meeting and see what is transpiring in the area of cellular graft engineering. Finally, CGES would like to thank Becton Dickinson Immunocytometry Systems for sponsorship of the meeting.

*Alan Fisher*
*StemCo Biomedical Inc.*

### 10-Year Member correction:

We apologize for missing _____ on our list of 10-year members of ISCT in our last issue.

# Current Good Tissue Practice Workshop

ISCT is planning a cGTP workshop to precede the ISCT 2003 Annual Meeting in Phoenix (May, 30th – June, 1st). Currently, the FDA is addressing the public comments to the proposed rule "Current Good Tissue Practice for Manufacturers of Human Cellular & Tissue-Based Products: Inspection and Enforcement" and plan to publish a final rule during 2003. These proposed regulations include methods used in, and the facilities and controls used for, the manufacturer of human cellular and tissue-based products, recordkeeping, labeling, reporting, inspections and the establishment of a quality program. In anticipation of this event, a workshop has begun to be planned.

Organizing committee members are: Ruth Solomon, MD (CBER/FDA), Liana Harvath, PhD (NHLBI, NIH), Donna Przepiorka, MD, PhD (Baylor College of Medicine), John McMannis, PhD (MD Anderson Cancer Center), Cindy Elliott, MT, HP(ASCP) (American Association of Blood Banks) and Janice Davis-Sproul, MAS, MT(ASCP) SBB (Johns Hopkins University).

The objectives of this workshop are (1) to differentiate between cGTP and cGMP requirements for somatic cells, (2) to understand the requirements for cGTP compliance and (3) to apply cGTPs to laboratories based in academic centers, collection facilities, hospitals and contract facilities. The format will include lectures as well as panel discussions.

It is anticipated that the workshop will begin on the evening of Wednesday May 28th and continue on May 29th from 8 am to 5 pm. Additional information will be announced in the Telegraft and on the ISCT website **(www.celltherapy.org)**.

*Janice Davis-Sproul*

*Johns Hopkins University*

Cytotherapy
Official Journal of ISCT
(formerly ISHAGE)

International Society for Cellular Therapy
formerly ISHAGE

# Best Paper Award

Volume 4 - 2002

The Cytotherapy Best Paper Award is for the best overall original paper published in a given volume of Cytotherapy, the official journal of the International Society for Cellular Therapy (formerly ISHAGE).

The 2002 Cytotherapy Best Paper Award of $2500 is supported by an educational grant from Miltenyi Biotec and will be awarded at the 9th Annual ISCT Meeting in Phoenix, Arizona, May 29-June 1, 2003.

Any paper published in Cytotherapy, volume 4, will be considered for the 2002 Award. The Award will be given to the author or co-authors of the paper. The ISCT Publications Committee will constitute the jury for the Award.

Judging criterion will include consideration of the paper's quality, the significance of the contribution to the field, originality, and the applicability of the science presented to improvements in processing or engineering cells for potential therapeutic purposes.

Cytotherapy Co-Editors: Nancy Collins, MD & John Barrett, MD, FRCP

2002 Cytotherapy Best Paper Award Sponsored by

Miltenyi Biotec

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# Report of the Cytotherapy Editorial Board Barcelona 2002

The Editorial Board of Cytotherapy met in Barcelona on the occasion of the International Society of Cell Therapy meeting. The meeting was well attended by members of ISCT . Dr Nancy Collins as outgoing Editor introduced the meeting and passed the chair over to Dr John Barrett who thanked Dr Collins for her dedicated service to Cytotherapy through difficult times. Cate Lund reported on behalf of the publishers Martin Dunitz that after some earlier difficulties the journal was being printed and issued on time. The most significant advance was her announcement that the Journal was now on line in the National Library of Medicine's "PubMed". Jean Winter (Editorial Assistant) reported on the number of articles submitted and accepted which were growing satisfactorily.

Dr Barrett then announced the appointment of two new co-editors Dr. Graham Sharp and Dr Gunnar Kvalheim whose backgrounds would widen the areas of expertise in the editorship. Plans for 2002 included the production of several more "In Focus" issues covering allogeneic stem cell transplantation, adoptive T cell therapy, and mesenchymal stem cells. It was planned to introduce regular review articles with Dr Kvalheim as review editor. It is also planned to update the information for authors and to encourage email submissions to the Journal. Dr Barrett sought the opinion of the meeting on the desired future direction of the journal.

ISCT members voiced strong support for the continued focus on regulatory affairs and practical technical aspects of cell therapy. Dr. Sharp has agreed to make this his special area of activity. There was strong support for the journal capturing the growing area of research into stem cell plasticity, in addition to continuing to be a resource for technical clinical and scientific papers in the classical areas of cell therapy. Currently the journal will continue to be issued bi-monthly, but if original contributions continue to increase it may be possible to contemplate a monthly issue by 2004. The meeting closed with an exhortation by Dr. Barrett for ISCT members to submit their original work, letters and reviews to the journal of their society. The health of a journal can be judged by the thickness of each issue. In this regard Cytotherapy is looking increasingly robust.

# From the President's Desk

It is with great pleasure and excitement that I assume the Presidency of ISCT. Having been around for the birth of ISHAGE, it is quite rewarding to become the first President under the new ISCT banner. We always talk about the growth of our Society in terms of members and geography, but the internal growth in terms of depth and expansion into the new somatic cell therapy arena is as vital to us as increasing our membership. The ISCT President officially takes over during the annual meeting. Being "forced" to go to Barcelona at the end of May to assume the Presidency did not exactly fit into the hardship category for me. However, what I didn't expect was that 1 week prior to the annual meeting, we would be contacted by the FDA to offer comment on their proposed new office of Cells, Tissues and Gene Therapy. Apparently, this had been on the CBER agenda for a while, but was now coming to fruition. We were told that the framework for this new office was being determined now (May) and that it would be fully enacted by October 1st, 2002. FDA wanted ISCT's opinion and suggestions for such an office and how it should be structured. The downside – they needed them by May 31st!

Fortuitously, all the right people were present during the Executive Committee Meeting in Barcelona and a response was drafted. The initial portion of the letter reviewed ISCT's mission statement. For those that have not committed it to memory: "ISCT serves as a global forum and voice for clinicians, scientists and laboratory personnel engaged in basic research and development, translational studies and the clinical application of all cellular research, processing and therapies". This was rather important, since our society, as ISHAGE was typecast by many regulatory agencies and corporations as only concerned with the field of marrow and stem cell processing. It was important to clarify that we now represent the individuals listed above for the entire cellular therapy field. While ISCT applauded the new Federal office in our response, it also advised that FDA should find a way of gleaning the knowledge and expertise of our members in the cellular therapy field - be it through a consultancy arrangement or by a more formal advisory board similar in structure to the FDA sponsored Oncology Drugs Advisory Committee (ODEC). We essentially asked to be an integral part of the new office's organizational structure. More will surface on this with the opening of this new office.

Just as we were catching our breadth, FDA asked if ISCT would attend a public hearing in Rockville MD concerning the

regulation of skin derived products in conjunction with bio-matrices. Our opinion was sought as to whether these "Combination Products Containing Live Cellular Components"should be regulated under CDRH (which had been the practice) or CBER, since the latter FDA division felt that the cellular components with all their complexity and variability took precedence and needed tighter regulation (especially with the nearing inception of the Cells and Tissues regulations). While this hearing was intended to deal solely with products for wound healing, it was evident that decisions or opinions made here would most likely apply in some fashion to other cellular/matrix products. After discussions with the Executive Committee, Scott Burger and myself attended the meeting on June 14th and voiced our support of CBER, believing that regulation should be directed toward the most critical element(s) – that being the cellular and non-matrix components. However, ISCT cautioned that the "device-seasoned" CDRH division must have an advisory role, as should ISCT scientists. Certainly, consideration should be given for both a CBER and CDRH reviewer to be coupled to each application to review their respective areas of expertise. These remarks were entered into public record. We await the final FDA decision on this topic as well. In the meantime, CBER has released an SOPP entitled "Manual of Standard Operating Procedures and Policies Regulatory – Review Intercenter Consultative/ Collaborative Review Process: SOPP 8001.5 Version #1 Date: August 30, 2002". The stated purpose of the document is to provide the procedures for CBER staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs and biologics.

So that it does not appear that the FDA is the only one increasing their supervisory vigilance of this field, one more recent event has loomed in the summer sun. Senator Collins introduced a Bill in May 2002 essentially mandating FDA's authority to regulate cell therapies and materials. While these powers were already granted to FDA, Senator Collins relates that FDA has not been able to accomplish regulation and enforcement on their own. This bill would force the issue. Among other things, it would be mandated that all cellular products that test positive for contamination be reported to FDA. This is, of course, some of the fall out from a recent death in a patient receiving a contaminated orthopedic tissue graft. Some of our closely aligned organizations, such as FACT and ASBMT, have expressed concern that this further extends FDA's control over cellular therapies. ISCT has been asked to join these 2 entities for the purpose of evaluating the impact of this proposed Bill on the cellular therapy field. There is concern that a general lack of expertise in this arena will stifle much needed research in an area already damaged by the human embryonic tissue ban. After discussions with the FDA, ISCT has been given assurances that their office is working closely with the Senator's staff to modify the Bill in ways that would address many of these concerns. We are to be kept informed of the progress. Therefore, ISCT has decided to maintain our present collaborative stature with FDA entrusting they will consult us as necessary on the Bill. As a result we will not, at this time, enter joint discussions on this topic with FACT or ASBMT though we recognize the importance of their evaluation and response to the Bill as considered necessary to represent their independent interests. While this may appear trivial, very similar decisions were made early in ISHAGE's history when it was decided that FAHCT (now FACT) needed to be an independent entity with its own mission statement and goals. ASBMT came to the same conclusion during their initial meeting in Chicago. As ISCT now goes about restructuring and grappling to meet the needs of a rapidly developing cellular therapy field, it is felt we have more to gain by aligning with FDA and other governmental regulatory agencies who are also trying to determine their role in this arena.

Outside North America much of the "battle" appears to be more on the political front than the regulatory as different jurisdictions work to define their policies on embryonic stem cell research and cloning. Indeed, Paul Simmons, ISCT Regional Vice-President for Australasia, reported to the Executive Committee recently that he has been working tirelessly on this front in Australia.

Given my proximity to the regulatory power base in the United States, it is easier for me to keep up with the regulatory initiatives in this country than it is with those around the world. This underlies the urgent need we have as a Society to ensure we have committed representatives in other regions to keep the Society membership informed of regulatory affairs around the world. I urge you to recommend references, resources, and people who might assist in this regard to either myself, Linda Kelley (ISCT LRA Chair), or Lee Buckler at the Head Office.

If the reader feels that regulation has dominated this column, then you are primed for the next 2 years of my Presidency. During this time, the global cellular therapy community will be exposed, controlled and funded through various regulatory agencies, laws and societal opinions. It is within this fabric that we must nurture and develop ISCT to be a meaningful instrument for our members.

*Steve Noga*

# Just the FACTs

## NETCORD-FACT Global Interest

The first NETCORD-FACT inspections of cord blood banks have been scheduled for August 2002. To date, nearly 30 cord blood banks located throughout the United States as well as internationally have applied for accreditation. The NETCORD-FACT accreditation process will assess all aspects of cord blood banking activities including collection, processing and transplantation.

## Under Construction

The FACT website is currently undergoing renovation. The new design will allow ease in navigating through the website to obtain up-to-date information regarding the application process, accredited facilities, frequently asked questions related to the FACT Standards, and links for on-line access to the FACT Staff. Additionally, many of the most commonly used accreditation forms including facility application forms, publication order forms, document checklists and inspection evaluation forms will be downloadable from the new site. This site will also include an inspector forum, currently under development, to provide FACT inspectors with tips and tools for conducting the most efficient inspections as well as a mechanism to discuss issues with the FACT Technical Staff.

## Save on Accreditation Renewal

FACT accredited facilities are required to renew their accreditation every three years. Facilities now have the option to pay $6,000 annually for three years or a lump sum of $20,000 due the final year of their accreditation. The prepayment plan would allow facilities to budget for this expense annually as well as receive a $2,000 discount. For more details, contact the FACT Office.

## Accredited Facilities

Five additional BMT centers have gained FACT accreditation since the last issue of the Telegraft.

FACT has now accredited 108 centers. There are 93 other centers in various stages of application, inspection or accreditation process.

The latest facilities to gain voluntary accreditation, along with their Program Directors are listed in the categories below:

Autologous bone marrow and peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- *Cedars-Sinai Medical Center, Los Angeles, CA*
  *Program Director: Michael Lill, MD*

Allogeneic & autologous bone marrow and peripheral blood progenitor cell transplantation, including collection and laboratory processing:

- *Arlin Cancer Institute at Westchester Medical Center, Hawthorne, NY*
  *Program Director: Tauseef Ahmed, MD*
- *Bone Marrow and Stem Cell Transplant Program, University of Pennsylvania Medical Center, Philadelphia, PA*
  *Program Director: Edward Stadtmauer, MD*
- *Rocky Mountain Blood and Marrow Transplant Program, Denver, CO*
  *Program Director: Robert Rifkin, MD*
- *The University of Kansas Medical Center Hematopoietic Cell Transplant Program, Kansas City, KS*
  *Program Director: Barry Skikne, MD*

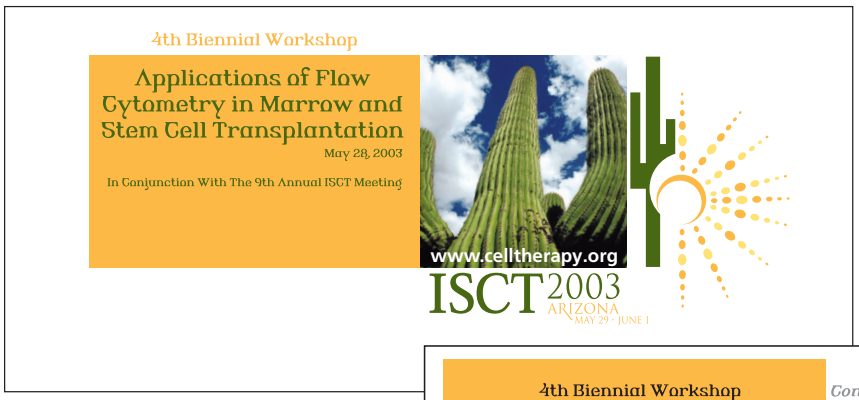
## Renewal Accreditation

The accreditation renewal cycle continues for facilities that previously achieved FACT accreditation. Hackensack University Medical Center in Hackensack, New Jersey under the direction of Scott Rowley, MD recently completed the FACT renewal process. Hackensack has obtained reaccreditation for allogeneic and autologous bone marrow and peripheral blood progenitor cell transplantation, including collection and laboratory processing.

For a complete list of accredited facilities, please visit the FACT website.

FACT Accreditation Office: (402) 561-7555
www.factwebsite.org

| | |
|---|---|
| Facilities Registered | 201 |
| Facilities Inspected | 144 |
| Accredited | 108 |
| Inspected/Pending Accreditation | 36 |
| Inspections in Process | 14 |
| Facilities Completing Checklists | 43 |
| Inspectors Trained | 348 |





## MESENCHYMAL AND NONHEMATOPOIETIC STEM CELLS - FOCUS ON ADULT STEM CELLS

**Date:** September 26-28, 2002
**Location:** New Orleans, Louisiana, USA
**Abstract Deadline:** July 15, 2002
**Topics:** Biology of Adult Stem Cells, Stem Cell Therapy of Skeletal and Cardiac Muscle, Mesenchymal Cell Therapy to Support Hematopoietic Stem Cell Engraftment and Regulatory Issues Surrounding Clinical Trials of Adult Stem Cells.
**Program Chairs:** Drs. Edwin Horwitz, Darwin Prockop, Armand Keating, Brian Butcher and Malcolm Brenner

For further information, registration, hotel and abstract forms may be downloaded from the ISHAGE website at www.celltherapy.org For further information contact Edwin Horwitz, MD, PhD, St. Jude Children's Research Hospital, 332 North Lauderdale, Memphis, Tennessee, USA, 38105. Tel: 901-495-2746; Fax: 901-495- 2176; Email: edwin.horwitz@sjude.org

### CONFIRMED SPEAKERS

**KEYNOTE SPEAKER:** Ronald D.G. McKay

>Tim Brazelton
>Diane Krause
>Giuliana Ferrari
>Andra Miller
>Alan Fine
>Lars Olson
>Francesco Frassoni
>Donald Phinney
>Stanton Gerson
>Mark Pittinger
>Margaret Goodell
>Darwin Prockop
>Marc Hedrick
>David Shine
>Karen Hirschi
>Paul Simmons
>Edwin Horwitz
>Evan Snyder
>Jeffery Kocsis
>Catherine Verfaillie

*Sponsored by the International Society for Cellular Therapy, ISCT (formerly ISHAGE), St. Jude Children's Research Hospital and Center for Gene Therapy of the Tulane University Health Sciences Center*

# Good (X) Practices

## cGMP

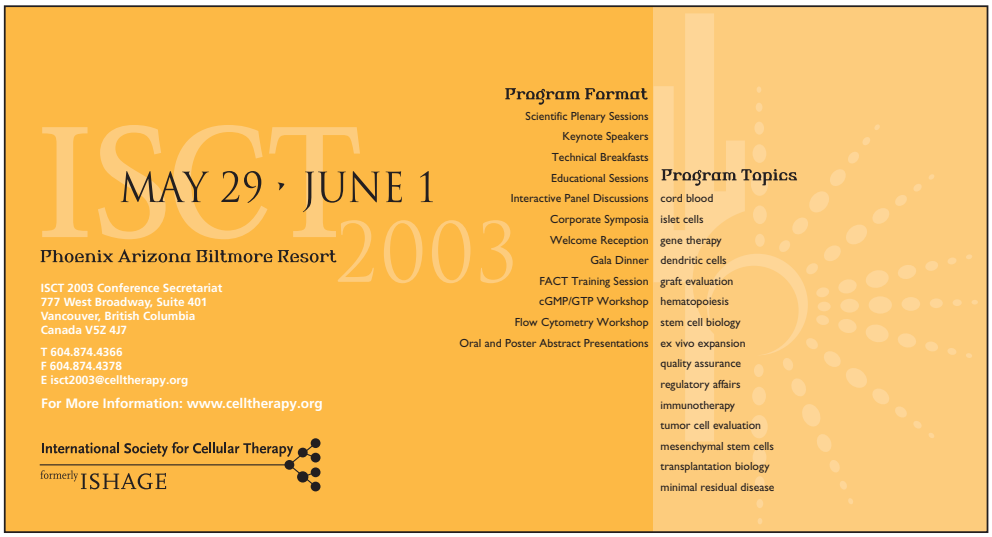
Recently the FDA announced plans to increase cGMP inspections in fiscal 2003 to over 1400 from the 949 inspections in the current year. Foreign cGMP inspections are also expected to double. The number of Warning Letters for non-compliance with cGMP rules is expected to increase correspondingly. "Failure to Validate" remains one of the primary reasons for Form 483 citations. Full compliance with 21 CFR11 compliance is still considered to be a goal rather then a reality for most companies and laboratories.

Consider ISCT your cell-processing cGMP resource. Order cGMP materials from recent workshops (CD-ROM, binder materials, or audio-cassettes). Talk to ISCT about holding a cGMP workshop near you or tailored for your facility.

## cGTP

Currently, the FDA is addressing the public comments to the proposed rule "Current Good Tissue Practice for Manufacturers of Human Cellular & Tissue-Based Products: Inspection and Enforcement" and plan to publish a final rule during 2003. These proposed regulations include methods used in, and the facilities and controls used for, the manufacturer of human cellular and tissue-based products, recordkeeping, labeling, reporting, inspections and the establishment of a quality program. In anticipation of this event, a workshop has begun to be planned.

Plan to attend the ISCT cGTP Workshop designed with and attended by FDA/CBER representatives in anticipation of the Final Rule on GTPs. May 28-29, 2003. Phoenix, AZ. Watch www.celltherapy.org for further details.


## cGLP

Discuss with ISCT opportunities for tailoring a cell-processing cGLP workshop specifically for your company or institution.

# Second Somatic Cell Therapy Meeting

## BRINGS TOGETHER A CROSS SECTION OF STAKEHOLDERS

Clinicians, technicians, regulators and researchers all found a receptive forum for discussing the challenges of delivering gene and cellular therapies at the second annual Somatic Cell Therapy Symposium in early May at Sanibel Island, Florida. Documentation, compliance, product safety and patient rights highlighted the concerns that practitioners share about how to safely deliver highly manipulated cells to patients with a variety of diseases. An atmosphere of collegiality pervaded the open discussions that followed short presentations by panels of experts from a wide variety of disciplines.

The degree to which regulatory requirements have impacted day to day operations of a cell processing facility were exemplified by John McMannis' description of MD Anderson's discussions with FDA concerning product release criteria and conduct of clinical trials. Designed to guarantee that products are fully characterized and safe when released for clinical use, the release criteria have added a great deal of testing and documentation to graft preparation time. The necessity of filing an IND for studies in which grafts are used is something of a departure from how studies have typically been done at academic cancer research centers. In the discussion that followed, several centers shared the challenges and frustrations of trying to introduce into their hospital environments the type of procedures that pharmaceutical companies routinely follow.

The increased expectations placed on Institutional Review Boards was discussed by Steve Noga's panel, with an emphasis placed on the need for sharing the responsibilities of human research subject protection. An accreditable IRB program must include multiple

checks and balances, a high degree of communication and information sharing, and a great deal of diligence throughout the product development process.
Since cell and gene therapies are relatively new, there is great potential for unexpected adverse reactions and unanticipated risks. The federal government has initiated a more integrated approach through the Office of Human Research Protections, whose initiatives include the "SUEE" Task Force, which is driven by "simplification; uniformity; efficiency; and effectiveness."

New gene therapies extend the manipulation of cells to the subcellular level. Dale Ando and his colleagues emphasized the need for thorough characterization of cell lines and vectors. Negative attention to those few cases of "gene therapy gone wrong" with disastrous consequences has cost the research community the public trust. More precise understanding of the effects of transduction on cell function, longer follow-up times, and greater attention to GCPs, GMPs and GLPs are critical. Much still needs to be learned about the use of viruses as transduction agents, and how the processes affect their virulence. Joyce Frey of FDA described two government initiatives, the Gene Therapy Patient Tracking System and the Genetic Modification Clinical Research Information System, which will help to integrate the growing body of knowledge about gene therapies, and improve regulatory oversight.

Liana Harvath, who recently joined NHLBI, stated the purpose of the Good Tissue Practices as being to prevent circumstances that could result in the introduction, transmission and spread of communicable diseases. Her panel reviewed public comments on proposed legislation and emphasized the importance of comprehensive validation procedures for processing human tissues intended for transplant.

A challenging conundrum put forth by Andrew Pecora in his discussion of the Good Clinical Practice Guidelines posed the question of whether the needs of the many or the needs of the few were paramount in the conduct of clinical trials. Is it justifiable to risk the safety of a single individual in our quest for medical knowledge that may help large populations? The role of IRBs is to safeguard the rights, safety and well being of all trial subjects. The principles of the ICH-GCP guidelines insure that risks are outweighed by potential benefits in a clinical trial, and that all participants have the opportunity to freely give truly informed consent.

The importance of product safety and potency testing for cellular therapies prior to their release for clinical use was again emphasized by Madhusudan Peshwa and his panel. They extended the general safety criteria, which include integrity, identity, purity, potency and viability to include sterility, detection of mycoplasma, pyrogenicity, and freedom from adventitious agents. The various steps in the production of cellular therapies at which testing should be done were described, and the fundaments for facility licensure were reviewed.

In the closing session of the meeting, Ed Horwitz defined somatic cell therapies as "the administration to humans of autologous, allogeneic or xenogeneic living cells that have been manipulated or processed ex vivo." His summary of the scientific and institutional challenges of preparing and providing cell therapies for research and clinical purposes were relevant to the entire spectrum of professionals represented in the audience. The need for external regulatory oversight recognized by clinicians, commercial developers, and the legal community marked an important evolution in the relationship of these various interest groups. Historically polar, and frequently adversarial, these groups were brought together during this meeting in wide agreement about the importance of rigorous science, precise product development, and the protection of patients.

This meeting, which all hope will continue to be held annually, represents a unique forum in the course of the year's usual events. Unlike most meetings in which this audience participates, it is geared toward cross-functional problem solving, frank discussion, and fruitful sharing of ideas, approaches, and uncertainties. Thanks to Steve Noga, Janice Davis-Sproul, and ISCT for their hospitality and hard work in creating such a worthwhile event.

*Lisa Beth Ferstenberg*

*StemCo Biomedical Inc.*

# Taipei International Stem Cell Forum 2002

The "Taipei International Stem Cell Forum 2002" is one of the many biotechnology conferences held annually in Taiwan to promote and foster mutual understanding and to create opportunities for international collaboration in technology and business. The forum was held August 10 to 11 at the Taipei International Convention Center (TICC), Taipei, Taiwan.

The purpose of this forum is to improve stem cell research & development in Taiwan and to provide a channel for information sharing and experience exchange between Taiwan and the foreign stem cell researchers and companies. Speakers attended from all over the world to cover topics of the Developmental Biology in Stem cells; Therapeutic Applications; Blood banking and Ethical issues.

The forum was in conjunction with the "Bio Taiwan 2002: The Third Taiwan International Biotech Fair 2002" held August 9 through August 12, 2002. This four-day biotech fair serves as a public awareness educational tool locally and to promote biotechnology business opportunities worldwide.

**Speakers included:**

- Chao-Ying Kuo, Ph.D., BMEC/ITRI
- Vanderson Rocha, M.D. Clinical Coordinator of Eurocord Hospital Saint Louis, Paris, France
- Kim Tan, Ph.D. FRSM Founder of GeneMedix, UK
- Chris Tsai, Ph.D., CEO. Bionet Corp., Taiwan
- John Yu, M.D., Ph.D. Professor, The Scripps Clinic Research Center, U.S.
- Makoto Asashima, Ph.D., Professor, Department of Life Science, The University of Tokyo, Japan
- Linsong Li, Ph.D., Professor & Director of Peking University Stem Cell Center, China
- Tatsutoshi Nakahata, M.D., Sci. Prof.& Chairman, Department of Pediatrics, Kyoto, University, Japan
- Yung-Hsiao Chiang, M.D., Ph.D., Tri-Service General Hospital, National Defense University, Taipei, Taiwan
- Herng-Der Chern, M.D., Ph.D., Deputy Executive Director, Center for Drug Evaluation, Taiwan
- Helen Shu, Ph.D. Consultant, BMEC/ITRI (Former VP of Regulatory Affairs, AP Cell Inc., Menlo Park, CA)
- James G. Kenimer, Ph.D. President, the Biologics Consulting Group
- Shiaw-Min Hwang, Senior Scientist Fellow & Vice-Head of Bioreasource Collection and Research Center, FIRDI, Hsinchu
- Jae-Hung Shieh, Ph.D., Senior Research Scientist, Memorial Sloan-Kettering Cancer Center, New York
- Zheng P. Zhuang, M.D., Ph.D. Chief, Molecular Pathogenesis Unit, NINDS, NIH.
- Jae-Hung Shieh, Ph.D. Senior Research Scientist, Developmental Hematology Laboratory, Memorial Sloan-Kettering Cancer Center, USA
- Lin Shiow-Fen Huang, Ph.D. Research Scientist, Institute of Grassland and Environmental Research (IGER), UK
- Kathyjo Ann Jackson, Ph.D. Center for Cell and Gene Therapy, Baylor Collage for Medicine, USA.
- Oscar Kuang-Sheng Lee, M.D., Ph.D. Department of Orthopaedics & Traumatology, Veterans General Hospital, Taiwan

# The New Trend

## in Quality and Correspondence

In the past several months there have been two letters sent by the FDA's Department of Health and Human Services **(scott: isn't this now called CMS?)** that seem to be sending a strong message to clinical trial investigators and cell therapy manufacturers that the FDA intends to tighten clinical and manufacturing requirements and quality standards as it strives to protect human subjects. In this issue we would like to briefly review the contents of these letters, discuss their relevance and postulate about where we see our future.

The first letter, dated April 17, 2002, was an open letter from Greg Koski, PhD, MD, Director of the Office for Human Research Protections (OHRP), Department of Health and Human Services. It is available on line at **http://ohrp.osophs.dhhs.gov** and was published in the May 2002 issue of Telegraft. The letter and the website publicize OHRP's new Quality Improvement (QI) Program intended to assist institutions in assessing, monitoring and enhancing their human research protection program. OHRP's collaborative and interactive approach is intended for institution IRB's (Institutional Review Board) and OHRP to work jointly "ensuring that research activities are conducted not only in a manner that complies with federal regulations for the protection of human subjects, but also meets ever evolving ethical standards related to advances in technology, science, and changing cultural values and societal issues". **(quote from website)**. Through consultation services OHRP will offer self-assessments, instruction, education, and sharing of best practices in order to improve the quality of an institution's human subjects protection program. **(not a quote but taken from website)** To go along with their "do it right, together" mantra OHRP is asking institutions to initiate participation voluntarily.

We encourage readers to refer to the website for a complete description. Recent events and patient safety issues have caused regulators to look more closely at entire systems from cell processing QA to IRB procedures and practices. While this "self-assessment" may be voluntary initially, one can't help but expect it will become the norm and that it may clarify expectations. It would seem prudent for academic institutions to begin this process sooner rather than later as we suspect the outcome will be inevitable.

On the heels of the OHRP's announcement, a letter was sent from FDA's Department of Health and Human Services, Office of Therapeutics Research and Review to primary investigators of IND's involving the transplantation of living somatic cells (but not involving gene therapy processes), requesting information regarding by their institution's quality control practices for product manufacturing, clinical oversight and clinical trial patient monitoring. Many of you involved in cell manufacturing may have been asked to assist in developing a response to the letter.

As stated in the letter, *"The information is being requested in order to determine whether product manufacturing quality control procedures and clinical oversight and monitoring practices are consistent with current standards for development of these products. In addition, we expect that this letter will provide an opportunity for you to establish appropriate programs to correct any deficiencies that may be identified."*

The holder of the IND is being asked to submit product information including descriptions of: product manufacturing quality control and quality assurance programs, how deficiencies are prevented, detected and corrected, qualification of supplies and equipment, audit schedules, organization structure, product tracking and labeling, sanitization and environmental monitoring programs, in-process testing, lot release testing, product characterization testing, stability studies and listing of cross-referenced files. Clinical information being requested includes: a listing of all studies under the IND and the status of each study, a description of the institution's clinical trial monitoring program and personnel responsible for monitoring and auditing the program, organizational structure that identifies individuals, their duties, and qualifications who are responsible for monitoring the study or clinical program, a description of monitoring/audit program, and a listing of changes to the clinical monitoring program. **REFERENCE LETTER not sure what you want here**. Both letters send a similar message in that they mark an end of the era in which academic investigator-sponsored INDs were not really held to the same standards as INDs sponsored by pharmaceutical/biotech companies.

The FDA has discovered what many of us working in academic cell therapy knew well - that investigators often did not grasp how seriously GMPs and GCPs must be taken, and that applying more relaxed standards to academic centers did not help matters. Many investigators still view an IND application as something akin to a grant proposal - one can promise to do many things, without really being prepared to do them. The investigations of numerous gene therapy programs, following the patient death at Penn, revealed some pretty appalling deficiencies in GCPs and GMPs. The most common GCP violations were failure to follow the stated protocol, and failure to provide appropriate medical care.

The death of Jesse Gelsinger almost certainly would have been prevented had the investigator taken his obligations seriously. Other issues have arisen at various centers and these were exacerbated by the death of a healthy research volunteer at Hopkins. Since then, numerous citations have been issued and research temporarily halted at several institutions, only to re-open with OHRP approval of corrective action. Some centers have completely revised their IRB and QA audit.

The FDA reaction has been to insist on much more rigorous evidence that GMPs, GTPs, and GCPs are followed. For labs that already were doing quite a good job, the requirements of the cell therapy letter do not entail changing fundamental practices or ways of thinking. You got the message long ago. The consequence is mainly more work and more documentation - quite tough enough. The clinician-investigators will have a harder time, however, as the arm reaches out to IRBs and institutions. The labs that were not making real efforts to incorporate GMPs will have the toughest time of all. FDA clearly is tightening up cell, gene, and tissue-based therapies, looking much more closely at GMPs, GTPs, and GCPs, and requiring a much higher level of control and documentation than in the past. For additional reading, we refer you to the regulatory committee link on the ISCT website.

*Scott Burger*
*Kathy Loper*
*Diane Kadidlo*

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# Mesenchymal and Nonhematopoietic Stem Cells:

*Edwin M. Horwitz, MD, PhD*

Once again, ISCT is assisting investigators by providing a forum for the exchange of ideas and dissemination of knowledge, by hosting, in conjunction with St. Jude Children's Research Hospital and Tulane University Health Sciences Center, the Second Annual Meeting on Nonhematopoietic and Mesenchymal Stem Cells: Focus on Adult Stem Cells," in New Orleans September 26-28, 2002.

This meeting follows the successful gathering in March 2001 where attendees distilled the state of the art knowledge and advanced ideas for the future of our field. The upcoming meeting promises to be even more exciting as we have organized speakers from the most basic biology to preclinical applications and the current clinical trials. We will discuss controversies such as cellular engraftment versus cellular therapy and hear about the most recent and innovative clinical trials of adult stem cells.

ISCT is providing an outstanding opportunity for established investigators and scientists to share their most current data and for young investigators and scientists to interact with leaders in our field. I encourage all interested "cell therapists" to join us for this exciting and surely productive meeting.

For this 2nd annual meeting, we are pleased to announce an excellent roster of speakers, a significant growth in the number of accepted abstracts, and outstanding growth in the number of registered delegates attending from around the world.

The meeting abstracts and presentation summaries will be published in an upcoming issue of Cytotherapy.

# Upcoming Meetings

- Commercialisation of Stem Cells Technologies For Biotechnology and Pharmaceuticals
  24-25 September 2002

  Location: Millennium Gloucester Hotel, London, UK
  http://www.marcusevans.com/events/CFEventinfo.asp?EventID=6490#event

- 2nd Annual Mesenchymal & Nonhematopoietic Stem Cells Meeting
  September 26-28, 2002
  New Orleans, LA

  Chair: Dr. Edwin Horwitz, St. Jude Children's Research Hospital

  For more information, contact the
  ISCT Head office: 604.874.4366 (tel), 604.874.4378 (fax), isct@celltherapy.org.
  www.celltherapy.org

- Stem Cells Regenerative Medicine: Commercial Implications for the Pharmaceutical and Biotech Industries

  October 8-9, 2002 Wyndam Emerald Plaza
  San Diego, CA
  http://www.srinstitute.com/part_iter_site_page.cfm?iteration_id=324

- Cell Culture & Separations for Cell & Gene Therapies
  15th Annual ASME Bioprocess Technology Seminars

  Oct. 28 - Nov. 1, 2002
  Paradise Point Resort San Diego, CA
  http://www.asme.org/education/techsem/bio.htm

  Registration fee discount for ISCT/ISCT members
  For further information please contact
  Brandy Smith - Phone: 212/591-7413
  Email: smithb@asme.org

- 4th Biennial Workshop: Applications of Flow Cytometry in Marrow and StemCell Transplantation
  May 28, 2003
  Phoenix, Arizona, USA
  May 29-June 1

  For more information, contact the
  ISCT Head Office: 604.874.4366p, 604.874.4378f
  isct@celltherapy.org ISCT2003@celltherapy.org

- cGTP Workshop
  May 28-9, 2003
  Phoenix, AZ
  Phoenix, Arizona, USA
  May 29-June 1

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Volume 9 No. 3 A Quarterly Newsletter September 2002

# Pharmaceutical cGMPnitiative Questions and Answers

August 21, 2002

### 1. What did the FDA announce today?

Today the Agency announced that it would be undertaking a significant new initiative concerning regulation of pharmaceutical manufacturing and product quality. The initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach will cover veterinary drugs and human drugs, including human biological drug products.

As we approach the 25th anniversary of the last major revisions to the drug cGMP regulations, FDA concluded that it was time to step back and evaluate the currency of both the cGMP program and the pre-market review of chemistry and manufacturing issues. The initiative announced today is intended to build on the many successes of the pre-market approval and pharmaceutical cGMP programs. The initiative will help these programs continue to be successful in the future by keeping pace with advances in pharmaceutical science and manufacturing technology.

### 2. Why is FDA launching this initiative on cGMPs now?

Advances in quality assurance techniques and manufacturing technologies provide an opportunity to evaluate how these advances can be applied to pharmaceutical manufacturing. This initiative will integrate the most current quality systems and risk management approaches and will encourage the adoption of modern and innovative manufacturing technology. In addition, it will better integrate the inspection programs with the review of drug quality that is performed as a part of the pre-approval process. The initiative will also use existing and emerging science and analysis to ensure that limited resources are best targeted to address important manufacturing quality issues, especially those associated with predicted or identifiable health risks.

### 3. Why is it being called a risk-based approach? Is FDA's current regulation of pharmaceutical products not based on risk?

The initiative is intended to build on the many successes of the cGMP and pre-approval programs and help them continue to be successful in the future by keeping pace with the most up-to-date quality systems and risk management approaches. It will also allow FDA to enhance the scientific underpinnings of cGMPs and to facilitate the latest innovations in pharmaceutical engineering.

In addition, the risk-based approach will enhance FDA's ability to focus on identifying and controlling critical factors that effect process and product quality. This enhancement is expected to facilitate targeting of cGMP and application requirements that better reflect improved scientific understanding of product quality.

### 4. How will the process work?

FDA is forming internal working groups composed of representatives from across the Agency, to begin various projects that are discussed in the concept paper, and there will be ample opportunity for public and stakeholder comment as the process moves forward.

### 5. How long will it take?

There are a variety of projects that fall within the scope of this initiative, and some will take longer than others. Among the first projects that FDA will take on include:

- Holding scientific workshops with stakeholders;
- Including product specialists, as needed, as part of inspection teams;
- Having FDA's product Centers provide a scientific and technical review of all drug cGMP warning letters; and
- Developing a technical dispute resolution process that integrates technical experts from the Centers and addresses perceived inconsistencies between Centers

### 6. What sorts of things are you likely to do?

The plan calls for various projects to be carried out by FDA's product Centers, the Office of Regulatory Affairs, and other components of the agency. They include such innovations as:

- internal and external reviews and analyses of the agency's internal
- quality-assurance programs, practices, and approaches;
- regulatory process changes to encourage manufacturing innovations, emphasize a risk-based approach to quality control, and enhance key aspects of FDA inspections; and
- augmented scientific training and communications, both internally and with the regulated industry.

### 7. How will FDA assess the success of the risk-based cGMP program?

Each project under the initiative will be judged on its own merits, and success will be measured by appropriate outcomes identified during project development. The overall success of the program will depend on its ability to help the agency achieve its mission of public health promotion and protection by ensuring that safe and effective pharmaceutical products are available to the American public. We believe that the success of the initiative will depend on incorporating the following principles:

- Risk-based orientation;
- Science-based policies and standards;
- Integrated quality systems orientation; and
- Strong public health focus.

### 8. FDA's announcement talks about better integrating the pre-approval review and cGMP inspection programs. What does this mean?

FDA ensures product quality by inspecting and evaluating firms' compliance with cGMP requirements and also, as part of the pre-approval review program, by evaluating the chemistry and manufacturing controls associated with drug production. We intend to perform an external review of the two programs, including evaluation of potential

inconsistencies and redundancies. Our goal is to ensure that the two programs operate in a fully coordinated and synergistic manner.

**9. How will consumers and patients benefit from this work?**

More than 40 years ago, Congress required that all drugs must be produced in accordance with current Good Manufacturing Practice (cGMP). This requirement was intended to address substantial concerns about substandard drug manufacturing practices by applying quality assurance and control principles to drug manufacturing. The last comprehensive revisions to the regulations implementing cGMP requirements occurred almost 25 years ago. In addition, for many years, pre-market approval requirements, pertaining to chemistry and manufacturing controls, have also been in place to ensure quality manufacturing of approved drugs.

The initiative is intended to ensure that FDA resources are used most effectively and efficiently to maximize the public health impact of the agency's actions. The initiative will strengthen the public health protection achieved by FDA's regulation of pharmaceutical manufacturing, and FDA remains committed to strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

**10. Many of FDA's major enforcement actions are based on violations of cGMP.**

Isn't this really just an effort to deregulate the drug making process?
No, this initiative will strengthen the public health protection achieved by FDA's regulation of pharmaceutical manufacturing. Enhancing and reinforcing the scientific underpinnings of our cGMP program will not interfere with our ability to enforce cGMP requirements. FDA remains committed to strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to the programs.

**11. You mention a "risk-based" approach to cGMPs. Does that suggest that the manufacturing process will not be regulated if industry can persuade FDA that there is minimal risk?**

No. FDA remains committed to strong law enforcement. FDA has always placed higher priority on legal violations that pose direct and significant safety risks to the public, but FDA also recognizes that enforcement against indirect health risks is important too. Although certain legal violations may not pose direct safety risks, they may, by context or association with other violations or conditions collectively, threaten product quality or the integrity of the regulatory system that serves important public health protection objectives.

The cGMP requirements ensure that the American public does not have to wait until there are injuries and deaths before the FDA can intervene to assure drug safety and effectiveness. The cGMP requirements are intended to prevent such harms by building quality into the design and production of pharmaceuticals and thereby reducing the risks that deficient drug products will be produced.

**12. Does FDA have evidence of patients actually being harmed because of cGMP violations? If not, why does the FDA take them so seriously? Are they needed at all?**

The cGMP requirements ensure that the American public does not have to wait until there are injuries and deaths before the FDA can intervene to assure drug safety and effectiveness. The cGMP requirements are intended to prevent such harms by building quality into the design and production of pharmaceuticals and thereby reducing the risks that deficient drug products will be produced. In addition, there are numerous examples of manufacturing problems--that could have been avoided with full cGMP compliance--that have resulted in the distribution of drug products that needed to be recalled because of compromised safety or effectiveness.

**13. Is this initiative reflective that FDA is being overly cautious with its review of drugs and now with its manufacturing standards?**

No. The initiative does not represent a ratcheting up of manufacturing standards. It reflects FDA's plan to implement the most up-to-date concepts of risk management and quality systems approaches and ensure that FDA's resources are used most effectively and efficiently to address the most significant health risks.

**14. Does this effort mean that current FDA enforcement of cGMPs is inconsistent?**

No, the initiative announced today is intended to build on the many successes of the pharmaceutical cGMP programs. This initiative will help this program continue to be successful in the future by keeping pace with advances in pharmaceutical science and manufacturing technology.

**15. Will this impose additional costs to industry and patients?**

We believe that enhancing the scientific underpinnings of our regulation of drug quality will be more efficient and effective for both FDA and industry because it will better target agency and industry resources to address problems that may adversely affect product quality.

**16. Will the cGMP standards be the same for generic and innovator drugs?**

Yes

**17. Doesn't this initiative suggest that FDA's cGMP regulations are obsolete?**

Why not simply stop enforcing them until the new ones are in place?
The cGMP program has been extremely successful, and pharmaceuticals produced for Americans are widely recognized for their safety and effectiveness. This initiative is intended to build on the successes of this program to ensure that the program continues, in the future, to achieve this level of success. FDA remains committed to strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

**18. Will FDA continue to enforce its existing GMP regulations?**

While FDA is examining and revising its approach to the pharmaceutical cGMP program, the agency will continue to enforce its cGMP regulations.

FDA believes that the regulations provide ample flexibility to incorporate the central principles underlying this initiative.

**19. The FDA announcement talks about major changes in science, technology, and manufacturing methods. Does this mean that the pharmaceutical industry is not keeping up?**

Pharmaceuticals produced for Americans are widely recognized for their safety and effectiveness. The initiative intends to build on these successes and facilitate the adoption of advances in pharmaceutical science, manufacturing technologies, and quality systems approaches.

**20. Is industry involved in this re-evaluation?**

As discussed in the announcement, there will be ample opportunities for industry to participate in this initiative.

**21. Are consumer and patient groups involved?**

As discussed in the announcement, there will be ample opportunities for consumer and patient groups to participate in this initiative.

**22. What is the bottom-line message for industry? For patients and consumers?**

This initiative will strengthen public health protection achieved by FDA's regulation of pharmaceutical manufacturing. It will also allow FDA to enhance the scientific underpinnings of the regulation of pharmaceutical quality and to facilitate the latest innovations in pharmaceutical engineering. FDA remains committed to strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

**23. Will this initiative have an impact on other on-going revisions to the drug cGMPs and guidances?**

The Agency will continue and expand efforts to provide cGMP guidance that is consistent with this initiative, and, if necessary, to reevaluate such guidance on a case-by-case basis.

**24. What kind of impact will this have on the blood GMPs?**

We have been evaluating our regulation of blood and are revising our regulations and policies as part of our Blood Action Plan. While the GMP regulations specific to blood are not the focus of the initiative to reexamine pharmaceutical GMPs, what we learn in our evaluation of pharmaceutical GMPs generally can be used in our efforts in other areas.

**25. What kind of impact will this have on the proposed tissue good tissue practice (GTP) regulations?**

The Agency has a comprehensive approach to the regulation of human tissues. One part of the approach is the proposed GTP regulations. The effort to reexamine pharmaceutical GMP regulations is not intended to cover the tissue regulations; however, what we learn in our evaluation of pharmaceutical GMPs generally can be used in our efforts in other areas

**26. As far as a risk-based approach, does it mean it is more likely that efforts will be concentrated on human pharmaceuticals rather than veterinary?**

This initiative is consistent with the agency's current approach that ensures that adequate resources are provided to address safety risks to humans associated with pharmaceuticals. However, FDA's statutory mission requires appropriate regulation of veterinary pharmaceuticals, including those intended for companion animals.

**27. The FDA initiative covers veterinary drugs. Does this mean that Type A medicated articles and medicated feeds are included in the initiative?**

While the cGMP regulations specific to medicated articles and medicated feeds are not the focus of the initiative to reexamine pharmaceutical cGMPs, what we learn in our evaluation of pharmaceutical cGMPs generally can be used in our efforts in other areas.

**28. What does this initiative means for foods and medical devices and the Centers that regulate these products?**

These products are the subjects of recent initiatives that incorporate many of the same principles, including an emphasis on quality systems regulation with strong scientific underpinnings.

**29. Are there any international implications associated with this initiative?**

This initiative is focused on FDA programs to assure the quality of drugs available to the American public. These include drugs produced domestically and in foreign countries for the U.S. market. Given the global nature of pharmaceutical production today, FDA fully intends to undertake this initiative in close concert and consultation with its regulatory counterparts internationally.