Office of Cellular, Tissue, and Gene Therapy: Update

Celia Witten, Ph.D. MD

Office Director, Office of Cellular Tissues and Gene Therapy, Center for Biologics Evaluation and Research, FDA

7th Annual Somatic Cell Therapy Symposium

September 26, 2007

Bethesda, Maryland

Outline

- Organizational Structure
- Guidance Update
- Tissue Program Update
- Tissue Engineering and Science
- Current Activities

Office of Cellular, Tissue, and Gene Therapies
Celia M.Witten, Ph.D, M.D.
Stephanie Simek, Ph.D., Office Deputy Director
Richard McFarland, Ph.D, M.D. Associate Director for Policy
Suzanne Epstein, Ph.D., Associate Director for Research
Recruiting, Director RPM

Division of Cellular and Gene Therapies
Raj Puri, Ph.D., M.D., Director

Division of Human Tissues
Ruth Solomon, M.D., Director

Division of Clinical Evaluation and Pharmacology/Toxicology
Ashok Batra, M.D.

Guidance Update

- Final Guidance
- Draft Guidance
- Guidance Agenda

Guidance

- Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)-Small Entity Compliance Guide 8/24/2007
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products 8/8/2007

Guidance

- Guidance for Industry: Class II special Controls Guidance Document: Cord Blood Processing System and Storage Container 1/13/2007
- Guidance for Industry: Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donors Who Were Tested For Communicable Diseases Using Pooled Specimens or Diagnostic Tests 1/23/2007

Guidance

- Guidance for Industry: Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events 11/28/06
- Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors

Draft Guidance

- Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs) 7/23/07
- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage 7/6/07

Draft Guidance

- Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies 1/16/07

Annual Guidance Document Agenda: OCTGT

- Licensure of Minimally Manipulated, Unrelated, Allogeneic Placenta/Umbilical Cord Blood Intended For Hematopoietic Reconstitution in Patients With Hematological Malignancies
- Preparation of Investigational Device Exemptions and Investigational New Drugs for Products Intended to Repair or Replace knee Articular Cartilage
- Initiation and Conduct of Clinical Trials Using Cellular Therapies for Cardiac Disease
- Potency Measurements for Cell and Gene Therapy Products
- Considerations for Allogeneic Pancreatic Islet Cell Products
- Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue Based Product Establishments
- Certain Distributed and Inventoried Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donors Who Were Improperly Tested
- Continue…..

Annual Guidance Document Agenda: OCTGT

- Clinical Study Design for Early Phase Studies of Cellular and Gene Therapies
- Devices Involved in Manufacture, Storage and Administration of Cellular Products and Tissues
- Validation of Rapid Microbiological Methods for Assessing Sterility of Cellular and Gene Therapy Products
- Submission of Information for the National Xenotransplantation Database
- Registration and Listing for Human Cell, Tissue, and Cellular and Tissue-Based Products Establishments
- Preparation of Investigational Device Exemptions and Investigational New Drugs for Tissue Engineered and Regenerative Medicine Products
- Facilities and Controls for Cellular and Gene Therapy Products Manufacturing Operations Guidance
- Link for Docket number: 2004N-0234 http://www.accessdata.fda.gov/scripts/oc/ohrms/frbydocket.cfm

Tissue Program Update

- HTTF (Human Tissue Task Force)
- Inspectional Summary FY06

HTTF

- Formed in August 2006, as part of the Agency's efforts to evaluate and, where needed, strengthen its risk-based system for regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- The primary goal of the HTTF was to assess challenges that had occurred in implementation of the new system and to identify any additional steps needed to further protect the public health by preventing the transmission of communicable disease while assuring the availability of safe products.

HTTF: Members

- Office of Regulatory Affairs (ORA)
- Center for Biologics Evaluation and Research (CBER)
- Office of the Commissioner

Areas Considered

- Inspection and Compliance Activities
- Partnering, Leveraging, Education, and Outreach
- Adverse Reaction Reporting and Analysis
- Additional Regulations and Guidance Development
- The Science of Tissue Safety

Inspections and Compliance Activities

- 2023 registered establishments; 859 manufacture from non-living donors
- From October 1, 2006-March 31, 2007, 153 inspections of domestic musculoskeletal recovery establishments were conducted.
- Assignment designed by CBER and ORA to detect inaccuracies and deficiencies in records like those noted during the Biomedical Tissue Services and Donor Referral Services inspections and to collect information on industry practices affecting the risk of communicable disease transmission
- Though deviations from the regulations were noted during some of the inspections, there were no major inaccuracies or deficiencies observed in records
- No inspections resulted in regulatory action

HTTF Conclusions: Inspections

- Recommendations for inspectional goals and priorities made
- Resources needed include: training, time, planning, human and financial resources

Partnering, Leveraging, Education, and Outreach

- Federal Partners: CDC, HRSA, FTC
- States
- Eye Banking and Tissue Industry
- Academic and Professional Organizations

HTTF Conclusions: Partnering and Outreach

- Partnering, leveraging, education, and outreach activities, could expand, but such expansion would require additional resources.
- Such activities could enable: improvements to our communication network with state and federal regulatory partners, sharing of information, and greater knowledge of industry operations and clinical practices. Additional resources could also allow enhanced communication with academic and professional organizations.

Adverse Reaction Reporting and Analysis

- Reviewed FDA's current procedures for adverse reaction receipt, analysis and follow-up utilized by the Tissue Safety Team (TST).
- Enlisted the consultative services of a nongovernmental academic infectious disease specialist with extensive clinical experience to identify opportunities to improve procedures for investigation, classification, and analysis of adverse reaction reports related to tissue transplants.

HTTF Conclusions: Adverse Reaction Reporting and Analysis

- Refine the activities of the TST
- Continuing interactions with outside experts
- Coordinating with CDC regarding the proposed Transplantation Transmission Sentinel Network (TTSN) project to assure that the TTSN complements FDA's existing surveillance system, and

HTTF Conclusions: Adverse Reactions and Analysis (cont.)

- Sponsoring a workshop with CDC and FDA's Center for Devices and Radiological Health on tissue processing, October 10-11, 2007
  - http://www.fda.gov/cber/meetings/allog101107ag.htm
- Health care providers, scientists and industry have been invited to share knowledge and experiences regarding technologies and methods to enhance tissue safety.

The Science of Tissue Safety

- Tissue microbiology program
- Critical path activities and partnerships to evaluate and identify manufacturing practices that reduce infectious disease risks

HTTF: Future Role

- Issues that require cross-agency, multidisciplinary perspective
- Track implementation of recommendations
- Discuss emerging issues and opportunities

FY06 HCT/P Inspections

FY06 HCT/P Inspections Accomplished

Type of HCT/P establishment	# Inspections Accomplished	Hours/ Inspection
Reproductive tissues	87	45.7
Cord blood stem cells Peripheral blood stem cells	36	42.8
All other HCT/Ps (e.g. musculoskeletal, ocular, recovery, distributors)	234	44.1
Total	**354***	

*Sum of individual inspections do not equal total (354) due to two inspections that were conducted for products in multiple categories

FY06 Inspectional Observations: Hematopoietic Stem Cells

- Procedures [1271.180 and 47]
  - Procedures not established
    - Processing
    - Labeling control
    - Storage/Distribution
    - Handling of positive test results
  - Procedures not followed
    - Donor screening

FY 2006 Inspectional Observations Hematopoietic Stem Cells

- Quality Program [1271.160]
  - No quality program established
  - Quality program does not ensure:
    - Documentation of corrective actions
    - Investigation and trending of HCT/P deviations

FY 2006 Inspectional Observations Hematopoietic Stem Cells

- Equipment [1271.200]
  - Procedures for equipment cleaning, sanitization, and maintenance not established
  - Equipment not cleaned, sanitized, and maintained according to schedule
- Supplies and Reagents [1271.210]
  - Supplies and reagents not verified
  - No records of receipt of supplies and reagents

FY 2006 Inspectional Observations Hematopoietic Stem Cells

- Records [1271.270]
  - Records do not identify person performing work
- Donor Testing [1271.80]
  - FDA licensed/approved/cleared tests not used
  - Manufacturer’s instructions not followed

Regulation of Regenerative Medicine Products

- Guidances for Cellular, Gene Therapies, and Devices
- Leveraging existing guidances to support specific areas of tissue engineered medical products
  - CMC guidances for cellular products
  - General (CT and GT) preclinical guidances
  - Guidances for devices may be applicable to scaffolds
  - Many clinical guidances cross-cut product areas

CBER/CDRH Tissue Engineering Cross-Center Teams

- Facilitate intercenter co-operation and solutions of TE issues
- Provide a core resource of TE review expertise to CBER, CDRH, OCP
- Participate in development of regulatory policy and pathways
- Facilitate FDA participation in Standards Organizations
- Provide a strong, consistent FDA voice in outreach activities with academia, industry, other governmental programs
- Provide an educational resource for reviewers within CBER and CDRH

Collaboration and Outreach

- MATES/Strategic Plan
  - http://tissueengineering.gov/welcome-s.htm
- FDA/NIST Workshop: "In Vitro Analyses of Cell-Scaffold Products" December 6-7
- Liaison meeting with Tissue Engineering Regenerative Medicine Centers
- ASTM TEMPS

Current Activities

- International efforts (Eustite, DGSanco, WHO)
- Liaison Meetings (Cell Therapy Liaison)
- PHS Advisory Committee on Blood Safety and Availability
  - Expansion of Charter, includes tissues and organs
  - Biovigilance focus
- Guidance Documents
- Human Tissue Task Force (HTTF)
  - recent release of report with recommendations
- MedSun Tissue and Cell Pilot Project
  - surveillance for tissue & cell transplant adverse events
  - >50 hospitals, >100 hospital personnel trained
- Transplantation Transmission Sentinel Network (TTSN)
  - Tissue and organ common donor ID, adverse event reporting
- Collaboration with HRSA
  - Advisory Committee on Organ Transplantation, policy issues

Contact Information

Celia Witten, PH.D., M.D.
Office Director, OCTGT
CBER/FDA
1401 Rockville Pike (HFM 700)
Rockville, MD 20852-1448
Celia.witten@fda.hhs.gov
301-827-5102