CBER SAFETY INITIATIVES: TISSUE SAFETY TEAM

51st Annual FDLI and FDA Conference
Washington, DC
March 27, 2008

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Definitions

- **Human cell, tissue or cellular or tissue-based product (HCT/P) [1271.3(d)]**
  - **An article containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient**
  - ***Examples*: bone, tendon, cornea, skin, heart valve, dura mater, vascular grafts, hematopoietic stem/progenitor cells from peripheral or cord blood, islet cells, autologous chondrocytes, epithelial cells on a synthetic matrix, semen, oocytes**
  - ***Does not include:* organs, blood or blood products, secreted or extracted human products (e.g., milk, collagen), minimally manipulated bone marrow, non-human cells, tissues or organs**
  -

HCT/P Regulatory Pathways

- **HCT/Ps can be regulated as:**
  - ***Tissues*—to prevent the introduction, transmission, or spread of communicable disease; *no pre-market review*, legal authority from section 361 of PHS Act ("361" Tissues)—therefore, can only regulate preventing communicable disease transmission**
  - ***Biological products*—to ensure safety and effectiveness, under IND or licensed**
  - ***Medical devices*—to ensure safety and effectiveness, under IDE or cleared or approved**

HCT/P Rules

- **Establishment registration and product listing**
- **Donor eligibility**
- **Current good tissue practice (includes requirements for adverse reaction reporting to FDA)**
- **All codified in 21 CFR Part 1271**
- **All effective on May 25, 2005 for HCT/Ps recovered on or after that date**

Definitions

- ***Adverse Reaction*** **to a "361" tissue [1271.3(y)]**
  - **A noxious and unintended response to an HCT/P for which there is a reasonable possibility that the HCT/P caused the response**
- ***Adverse Experience*** **to a biological product [600.80(a)]**
  - **Any adverse event associated with the use of a biological product in humans, whether or not considered product related….**

Reporting Requirements for "361" Tissues [1271.350(a)]

- **Tissue establishments must *investigate:***
  - **Any adverse reaction involving a communicable disease related to an HCT/P that they made available for distribution**
- **Tissue establishments must *report to FDA:***
  - **An adverse reaction involving a communicable disease if it:**
    - **Is fatal**
    - **Is life-threatening**
    - **Results in permanent impairment of body function or permanent damage to body structure; or**
    - **Necessitates medical or surgical intervention, including hospitalization**

Requirements, cont.

- **To report adverse reactions, tissue establishments must submit a MedWatch report using Form FDA 3500A to FDA within 15 days of receipt of information**
- **And submit follow-up reports within 15 days of receipt of new information from the investigation**
- **Voluntary reporters (physician, patient) use Form FDA 3500 and in addition, promptly report to the HCT/P establishment**

Tissue Safety Team (TST)

- **First CBER Safety Team**
- **First meeting in May 2004**
- **Purpose:**
  - **Provide a coordinated, efficient approach to the receipt, routing, investigation, evaluation, documentation and trending of reported adverse reactions involving HCT/Ps across 5 Offices in CBER and beyond the Center**

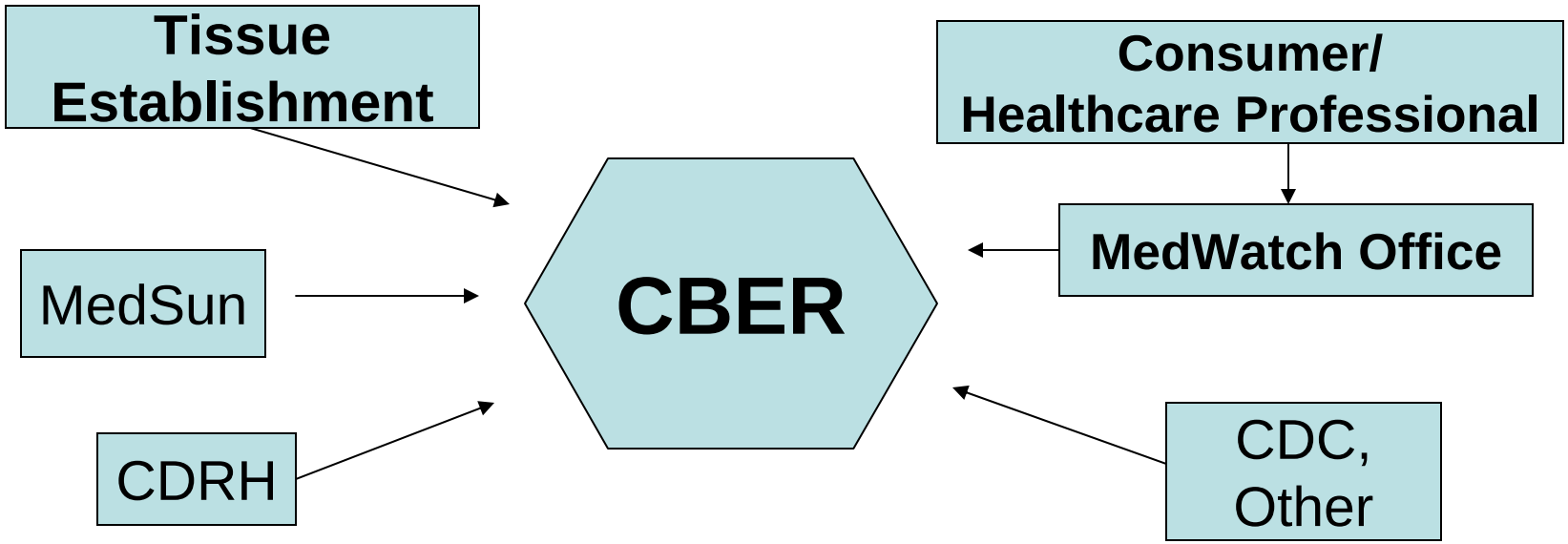
Composition of TST— Points of Contact from:

- **Five offices within CBER**
  - **Office of Biostatistics and Epidemiology (OBE)**
  - **Office of Cell, Tissue and Gene Therapies (OCTGT)**
  - **Office of Communication, Training and Manufacturers Assistance (OCTMA)**
  - **Office of Compliance and Biologics Quality (OCBQ)**
  - **Office of the Center Director**
- **Outside of CBER**
  - **Center for Devices and Radiological Health (CDRH)**
  - **Office of Regulatory Affairs (ORA)**
  - **Office of Criminal Investigations (OCI)**
- **Outside of FDA**
  - **CDC, HRSA, CMS**
  - **CDC Epidemic Intelligence Service (EIS) Officer at FDA**

SOPP 8508
Version #2

- **Procedures for handling adverse reaction reports**
- **Responsibilities of each office and TST**
- **Interactions with CDC and Foreign Government regulatory authorities**
- **Bi-weekly meetings of TST Working Group; monthly meeting of TST; quarterly meetings with Center Director**

Sources of Reports



- **Reports received from various sources**
  - **Tissue establishment submits MedWatch report**
  - **Consumer, healthcare professional submits direct report through MedWatch, MedSun, CDC**
  - **Periodic searches of AERS and MAUDE databases**

Tracking & Routing Reports

- **Reports received by OBE from Adverse Event Reporting System (AERS) contractor**
- **Determine if “361” HCT/P**
- **Enter into Adverse Event and Product Problems Database (AEPP)--shared database in CBER**
- **If an infectious adverse event, determine if High Priority (criteria pre-determined) and immediately notify TST Working Group**
- **Clinical f/u by OBE**
- **Manufacturer f/u by OCBQ**
- **Notification of entire TST and Center Director’s Office**

Clinical Follow-up

- **For reports that are not high priority, determine if additional clinical information needed (pre-determined criteria)**
  - **OBE contacts reporter**
  - **Questions:**
    - **Product name, lot #, manufacturer?***
    - **Time interval between implant and onset of symptoms?***
    - **Culture results (pre-implant, recipient infection)?***
    - **What treatment / interventions were required? Explant?**
    - **What is recipient's current condition?**
    - **Was an Infectious Disease consult obtained?**

Clinical Follow-up, cont.

- **Do you suspect the tissue product?**
- **Have you seen infectious problems with this product previously; with allografts from this processor?**
- **Are there other problems with this organism at your institution? Did hospital infection control investigate?**
- **Relevant recipient past medical history (risk factors)?**
- **Anything unusual about the surgery (e.g., length of time)?**
- **Any devices implanted?**

Manufacturer Follow-up

- **For reports that are not high priority, determine if additional manufacturing information needed (pre-determined criteria)**
  - **OCBQ contacts tissue processor**
  - **Questions:**
    - **Was the manufacturer aware of the complaint/report?**
    - **Was an investigation conducted?**
    - **Donor eligibility determination review?**
    - **Processing method used for this tissue?**

Manufacturer Follow-up, cont.

- **Any deviations in processing? Environmental monitoring? Sterility failures?**
- **Were pre- and post- processing cultures performed? Results? What laboratory did the cultures?**
- **Did product meet release criteria?**
- **Other complaints related to same donor?**
- **What follow-up/corrective action was taken, if any? Notified consignees (voluntary recall)? District office informed?**

Evaluating Reports

- **Evaluation at TST Working Group meetings**
  - **OBE, OCBQ, OCTGT points of contact**
  - **Meet bi-weekly or more often as needed**
  - **Present & discuss *all* HCT/P reports (except if no adverse reaction occurred)**
  - **Review follow-up information**
  - **Did the HCT/P cause the infection? –usually can't prove**
- **If no further action indicated, close case—does not rule out possibility that HCT/P caused adverse reaction, only that TST investigation is complete and, based on available evidence, further action is not recommended**

Further Actions

- **If further actions indicated (e.g., recall):**
  - **Determine which tissues and organs (and how many) were recovered and by which recovery establishment**
  - **Determine which processors received tissue**
  - **For each processor—determine which tissues are still in inventory—quarantine; which tissues have been distributed and to whom; which tissues have been implanted**
- **Coordination with CDC**
  - **Traceforward/ Traceback activities if needed**
  - **Assistance with laboratory testing of retained samples**
  - **CDC EIS Officer assigned at FDA is instrumental in CDC Coordination**

2007 HCT/P MedWatch Reports

- **Total Reports: 139**
  - **Tissues 123**
  - **Cells 16**
- **Tissue Report Sources**
  - **Manufacturer 68%**
  - **Direct 11%**
  - **MedSun 10%**
  - **Combination/other 11%**

2007 Tissue MedWatch Reports

Tissue Type		
Soft tissue	45	37%
Skin	27	22%
Bone	26	21%
Eye	15	12%
Cardiac	5	4%
Tissues, NOS	4	3%
Blood vessel	1	1%
Total	123	

2007 Tissue MedWatch Reports

- **Tissue Adverse Reactions**
  - **Infectious adverse reactions: 91**
  - **Non-infectious adverse reactions: 10**
- **Product Problems (No adverse reaction) 22**

Accomplishments

- Routing of MedWatch reports
  - List of HCT/Ps and establishments to contractor
  - Access to CDRH database
- SOPP 8508
- Revised MedWatch Form
  - More user friendly
- Guidance for completing MedWatch Form
  - www.fda.gov/cber/gdlns/advhctp.htm
- Improvement of database
- Additional information entered into database for easy access
- Improved training and communication with FDA field
- F/U on all reports received

Challenges

- **Obtaining additional, accurate information from the health care professional—labor-intensive follow-up activities**
- **Clinical cultures not performed; results not available; no archived cultures or materials (fluids, tissue) from donor or recipient to perform additional testing (e.g., DNA matching)**
- **Drawing conclusions with limited information**

Challenges, cont.

- **Well-known limitations of passive safety surveillance (under-reporting, biases, etc.)**
- **Lack of denominator information**
- **Distinguishing graft-attributable infections vs. common post-operative wound infections**
- **Tissue establishment reporting to FDA for non-infectious adverse events is not mandatory**

Helpful Websites

- www.fda.gov/cber/tiss.htm
- www.fda.gov/cber/regsopp/8508.htm
- www.fda.gov/medwatch

Thank you!