Tissue Adverse Event Reporting at FDA

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Tissue Transplant Safety Network

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Outline

1) FDA Reporting Rule

2) FDA Programs
   a) MedWatch
   b) Tissue Safety Team
   c) MedSun

3) Summary of Reports
FDA’s Current Good Tissue Practice Reporting Requirement
21 CFR 1271.350
Effective 5/25/05

Adverse reaction means a noxious and unintended response to any HCT/P* for which there is a reasonable possibility that the HCT/P caused the response.

* Human cells, tissues, and cellular or tissue-based products
FDA’s Current Good Tissue Practice Reporting Requirement
21 CFR 1271.350

Manufacturers must **investigate**:  
- *Any* adverse reaction **involving a communicable disease** related to an HCT/P that they made available for distribution.

Manufacturers must **report to FDA**:  
- An adverse reaction **involving a communicable disease** if it:  
  - Is fatal  
  - Is life-threatening  
  - Results in permanent impairment of function or permanent damage to body structure; or  
  - Necessitates medical or surgical intervention, including hospitalization.
JCAHO Tissue Standards

PC.17.10, PC.17.20 and PC.17.30

For organizations that store or issue tissue (hospitals, labs, ambulatory surgery centers)
Effective 7/1/05

PC.17.30 Investigate and Report Adverse Events
– Prompt reporting of adverse events from human cell and tissue transplants to the tissue establishment.
– Via phone, fax, mail or otherwise
– Not limited to communicable disease adverse events

• Submitting FDA MedWatch 3500 to HCT/P establishment can assist with fulfilling JCAHO requirements.
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MedWatch

FDA’s Safety Information and Adverse Event Reporting System

Voluntary: 3500 form
Manufacturer: 3500A form

- Mail
- Phone
- Fax
- On-line fillable pdf
FDA’s Tissue Safety Team

Center for Biologics Evaluation and Research (CBER)

OBE
Office of Biostatistics and Epidemiology

OCTMA
Office of Communication, Training, and Manufacturer Assistance

OCTGT
Office of Cellular, Tissue and Gene Therapies

OD
Office of the Director

OCBQ
Office of Compliance and Biologics Quality
Tissue Tracking at FDA

• AERS- Adverse Event Reporting System
  – Final repository for CBER and CDER MedWatch reports

• TST Real-Time Tracking Database
  – Contains reports under TST evaluation
  – Allows interoffice communication
  – Contains collected info on reports- patient and manufacturer records
MedSun is:
• A device surveillance program at ~300 hospitals (CDRH sponsored)

MedSun’s Tissue Pilot Project (31 hospitals)
• Electronic tissue reporting for hospitals
• Provides reports to manufacturers and FDA
• Assists hospitals with JCAHO requirement
• Assists manufacturers with FDA reporting
  – Utilizes MedWatch 3500A form
  – Provides supplemental info
HIPAA and HCT/P Reporting

- Permits covered entities to disclose protected health information (PHI), without authorization:
  - To non-public health authorities, if they are subject to FDA jurisdiction
  - For quality, safety or effectiveness of product regulated by the FDA
  - Examples of activities include:
    • Collecting or reporting adverse events
    • Tracking FDA-regulated products
    • Enabling product recalls or lookback (locating or notifying individuals who received recalled products)
    • Conducting post-marketing surveillance
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3) Summary of Reports
## Effect of Reporting Rules

Total Number of HCT/P MedWatch Reports to FDA

<table>
<thead>
<tr>
<th>Year(s)</th>
<th># Cell and Tissue Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2004</td>
<td>114 (average 29 reports/ year)</td>
</tr>
<tr>
<td>2005</td>
<td>143</td>
</tr>
</tbody>
</table>
Trend in Number of HCT/P MedWatch Reports
December 2004 - April 2006

# Reports Received

Month

Dec-04 Jan-05 Feb-05 Mar-05 Apr-05 May-05 Jun-05 Jul-05 Aug-05 Sep-05 Oct-05 Nov-05 Dec-05 Jan-06 Feb-06 Mar-06 Apr-06

Cell

Tissue

CGTP Rule
Case Definition

• Clinical or culture-confirmed infection
• In a recipient of allograft tissue
• Occurring within 1 year of implantation
• Reported to Medwatch
• Period: January 1, 2001– December 31, 2004
Results

- 83 reports met case definition
- Sex: 63% Male, 37% Female
- Age: 1 month to 87 years (Median: 40 years)
Tissue Types (N=83)

- Heart Valve: 42%
- Tendons/Ligaments: 34%
- Blood Vessel: 7%
- Bone: 8%
- Eye: 5%
- Skin: 4%
## Interventions and Outcomes (N= 80)*

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>60</td>
<td>75 %</td>
</tr>
<tr>
<td>Additional Procedure</td>
<td>47</td>
<td>59 %</td>
</tr>
<tr>
<td>Explantation</td>
<td>35</td>
<td>44 %</td>
</tr>
<tr>
<td>Retransplantation</td>
<td>11</td>
<td>13 %</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>38</td>
<td>48 %</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>14 %</td>
</tr>
</tbody>
</table>

* Events not exclusive of each other
64 reports with suspect organism

- **Fungus**: 25
- **Bacteria**: 42
  - **Aerobic**: 38
    - **Gram Positive**: 24
      - Staphylococcus: 13
    - **Gram Negative**: 14
      - Enterococcus: 6
  - **Anaerobic**: 10
- **CJD**: 1
Time Until Infection
Bacteria and Fungi (n=59)

- **Bacteria Median (1 mo)**
- **Fungus Median (3 mo)**

![Graph showing the time until infection for bacteria and fungi with median times and P-value](image)

- **P-value:** <0.0008

**Legend:**
- Bacteria
- Fungus
### Who’s reporting? (n=83)

<table>
<thead>
<tr>
<th>Reporter</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Processor Reporter</td>
<td>22</td>
<td>26.5%</td>
</tr>
<tr>
<td>Other Reporter</td>
<td>61</td>
<td>73.5%</td>
</tr>
<tr>
<td>Risk, Quality or Infection Control</td>
<td>27</td>
<td>44.3%</td>
</tr>
<tr>
<td>Physician</td>
<td>10</td>
<td>16.4%</td>
</tr>
<tr>
<td>Consumer</td>
<td>9</td>
<td>14.8%</td>
</tr>
<tr>
<td>Nurse</td>
<td>8</td>
<td>13.1%</td>
</tr>
<tr>
<td>OR or Surgery Staff</td>
<td>7</td>
<td>11.4%</td>
</tr>
</tbody>
</table>
Limitations

• Passive surveillance

• Incomplete information
  – Unable to evaluate causality

• Bias
  – Surveillance bias: related to 2002 recall
  – Serious infections more likely reported
Recommendations

• Improve detection and communication of infection events
  – MedSun Program
  – Tissue transplant safety network

• Improve evaluation of infection events
  – FDA’s Tissue Safety Team
  – Classification system of infections (AATB)

• Gather denominator data
Acknowledgments

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The findings and conclusions in this report are those of those author(s) and do not necessarily represent the views of the Food and Drug Administration (FDA) or the Centers of Disease Control and Prevention (CDC)
How do I report to MedWatch?

On-line reporting:  
www.fda.gov/medwatch

Download forms:  
www.fda.gov/medwatch/getforms.htm

Fax a report:  1-800-FDA-0178

Call-in a report:  1-800-FDA-1088

Mail a report to:  
MedWatch, HF-2,  
5600 Fishers Lane  
Rockville, MD 20852-9787
64 reports with suspect organism

Fungus
- 25
  - 9 Aspergillus
  - 9 Candida

Bacteria
- 42
  - Aerobic
    - 38
    - Gram Positive
      - 24
      - Staphylococcus
        - 13
      - Enterococcus
        - 6
    - Gram Negative
      - 14
      - 5 Enterobacter
      - 3 Pseudomonas
      - 1 Klebsiella
      - 2 E.coli
      - 1 Serratia
      - 1 Citrobacter
  - Anaerobic
    - 10
    - 3 Peptostreptococcus
    - 2 Clostridium
    - 2 Bacteroides

CJD
- 1
Allograft Processing

Recovery
- Consent
- Screening
- Recovery of tissue
- Blood Draw

Testing
- Donor blood testing for:
  - HIV-1, HIV-2
  - HBV
  - HCV
  - Syphilis

Processing
- Clean/Cut
- Micro Testing
- Disinfection
- Packaging

Transplantation
- Prepare as directed
- Recipient

Distribution
Send to distributor or
Health care facility

Photos provided by RTI, and Dupont™ Medical Packaging
Nationwide Recall of Allografts

Plundered body parts implanted in thousands
Macabre scandal may involve more tainted transplants than earlier feared

Man Accused of Illegally Harvesting Dead Bodies
Tissue From a New Jersey-Based Company May Have Been Transplanted in Patients Across the Country

Body Parts Thefts Spur Medical Fears

Stolen body parts victim launches $210M lawsuit
Biomedical Tissue Services (BTS) Allograft Recall

FDA press release
- Initial findings
- Recommendations
Epi-X posting

Voluntary recalls posted for all BTS recovered tissues

Tissue processor discovers record inaccuracies

FDA issues order for BTS to cease manufacturing

BTS owner indicted

FDA update:
- Strongly recommend recipient testing
Epi-X posting

9/29
9/30
10/14
10/26
1/31
2/23
3/2

2005
2006