HST.535

FEDERAL REGULATORY ISSUES:
US Food and Drug Administration
Medical Device Amendments

M. Spector, Ph.D.

TECHNOLOGY TOOL BOX
TISSUE ENGR./REGENERATIVE MED.

• SCAFFOLD (MATRIX)
  – Porous, absorbable biomaterial; can serve to regulate
cell function prior to its absorption
• CELLS
• REGULATORS
  – Cytokines (growth factors)
  – Genes for growth factors
  – Antagonists of inhibitors
  – Fluid flow
  – Mechanical loading
  – Hydrostatic pressure
  – Shock wave and ultrasound
  – Electromagnetic radiation and magnetic fields

FEDERAL AGENCIES THAT REGULATE MEDICAL DEVICES AND TISSUE ENGINEERED PRODUCTS

US Food and Drug Administration
China Chinese FDA
Europe Various agencies; “CE mark”
India None yet

US FDA ORGANIZATION

Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
National Center for Toxicological Research (NCTR)
Office of the Commissioner (OC)
Office of Regulatory Affairs (ORA)

Which center to review your application?
FDA

Center for Devices and Radiological Health
http://www.fda.gov/cdrh/index.html

FDA APPROVAL PROCESS

I. General Controls
No approval of FDA prior to selling the product.

II. Special Controls
Equivalent to Marketed Device?; Premarket Notification

III. Premarket Approval (PMA)
Human Trial
Investigational Device Exemption

510 (k)
Analysis of composition and properties, and in vitro and in vivo studies

PMA
Good Lab Pract. (GLP)

TISSUE ENGINEERED PRODUCTS

Unique Challenges for Tissue-Engineered Products

• Define the product.
  – Reproducibility
  – Track clinical problems encountered in use to ingredients/processing

• Claims for performance.

Premarket Review of Biological Products & Medical Devices

• Biological Products
• Medical Devices
• Combination Products
**Definition of a Medical Device**

- "...apparatus..., implant, *in vitro* reagent, including any component...or accessory..."
- intended for the diagnosis, mitigation, treatment, or prevention of disease...
- or intended to affect the structure or function of the body...
- and does not achieve its primary intended purposes through chemical action within or on the body...and which is not dependent upon being metabolized..."

**Examples of Medical Devices & Combination Products**

- **Medical Devices - collagen, hyaluronic acid and synthetic implants**
  - FocalSeal-L - aqueous PEG solutions modified to photo-polymerize *in situ*
  - Emdogain - porcine enamel matrix proteins
- **Combination Products -**
  - Apligraf - cells on bovine collagen

**CDRH Standards Program**

- [www.fda.gov/cdrh/stdsprog.html](http://www.fda.gov/cdrh/stdsprog.html)
- **Standards Participation**
  - ASTM F04
    - Division IV - Tissue Engineered Medical Products (TEMPS)
  - ISO TC 150
    - Working Group 11 - Tissue Engineered Implants (Reviewing Other Standards Development Activities)

**Premarket Approval Review**

- **Case-by-case approach**
- **Both safety and effectiveness evaluations**
- **Basic elements**
  - Product Manufacture
  - *In vitro* and *in vivo* testing
  - Clinical Performance
  - Product Labeling
- **Product Manufacture**
  - Cell, tissue & biomaterial sourcing
  - Product Processing
  - In-process and final product tests
  - Adventitious agents & co-purifying impurities
  - Lot-to-lot consistency
  - Quality control procedures
Premarket Approval Review

- *In vitro* and *in vivo* testing
  - Toxicity / Genotoxicity
  - Biomaterials biocompatibility
  - Immunogenicity / inflammatory responses
  - Models of product effectiveness
  - Product resorption/decomposition
- Investigating product safety and clinical benefit:
  - Patient population
  - Investigational and control treatments
  - Study endpoints
  - Study conduct
  - Data analysis
  - Labeling claims

The purpose of the workshop is to discuss issues that should be considered when evaluating cell/scaffold products and to determine which test methods are currently available and which new analytical procedures should be further researched in the evaluation of such products.

Organized by the:
- Food and Drug Administration (FDA)
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)
- National Institute of Standards and Technology (NIST)

http://www.fda.gov/cber/meetings/invitro120607.htm

FDA Public Workshop

Workshop on In Vitro Analyses of Cell/Scaffold Products

Agenda

Date and Time

December 6, 2007 from 8:30am-5:00pm
December 7, 2007 from 8:30am-4:00pm

Location

National Transportation and Safety Board (NTSB)
490 L’Enfant Plaza East, SW
Washington, DC 20594

Celia Witten  Ph.D., M.D.
Office Director
Office of Cellular, Tissue, and Gene Therapy
Center for Biologics Evaluation and Research
Food and Drug Administration

Validation of a Quality Assurance Program for Autologous Cultured Chondrocyte Implantation


Genzyme Tissue Repair, Cambridge, Massachusetts (2013)

Tissue Engineering
Volume 4, Number 3, 1998

FIG. 1. QA organization. Organizational chart for QA activities designed to comply with the requirements of GMPs and the MLA.
Analysis of Cell Quality Parameters

Sterility. Sterility tests are conducted at critical points during the processing of each patient lot.

Endotoxin. Endotoxin assays were performed as a lot release criteria.

Cell viability. Chondrocyte viability ranged from 82% to 99% at the time of release.

Population doubling time.

Nonconformances related to biopsy receipt. After trimming extraneous tissue, optimal biopsy wet weight should be 300–300 mg. Surgeons are trained in proper biopsy collection techniques. Nevertheless, surgeons had difficulty in achieving a consistent biopsy size. Mean biopsy weight was 33.3 mg (range, 16–2,800 mg). Nonconformances were caused for the most part during biopsy collection and shipment procedures. Of 1,377 cartilage biopsies processed, 86 nonconformances were identified relating to biopsy quality.

Nonconformances related to cell processing. Approximately 9% of cell processing activities generated nonconformances. The majority fell into the less critical levels 1 and 2 categories and did not impact patient safety. As GMPs matured, the overall rate declined from a mid-year peak of 6.5% to ~3.5%. The three types of nonconformances most prevalent were related to process, documentation, and raw materials.
Tissue Engineering: The End of the Beginning

MICHAEL J. LYSAGHT, Ph.D., and ANNE E. HAZLEHURST, S.R.
Center for Biomedical Engineering, Brown University, Providence, Rhode Island.

This study was undertaken to assess the impact of current economic conditions and recent disappointing product launches on the field of tissue engineering.

Tissue engineering is clearly having difficulty transitioning from a development stage industry to one with a successful product portfolio. This is often the case for breakthrough medical technologies.

Table 3. FDA-Approved Tissue-Engineered Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Year</th>
<th>Description</th>
<th>2002 annual sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apligraf (Organogenesis)</td>
<td>1998</td>
<td>Living skin equivalent for diabetic and venous ulcers</td>
<td>$2 million</td>
</tr>
<tr>
<td>Corticel (Genzyme Biosurgery)</td>
<td>1999</td>
<td>Autologous chondrocytes for cartilage repair</td>
<td>$25 million</td>
</tr>
<tr>
<td>Dermagraft (ATS)</td>
<td>2001</td>
<td>Living skin equivalent for diabetic and venous ulcers</td>
<td>$1.5 million</td>
</tr>
<tr>
<td>OrCet (Osteo)</td>
<td>2001</td>
<td>Living skin equivalent for burn patients</td>
<td>&lt;$100,000</td>
</tr>
</tbody>
</table>

*Note: Both Organogenesis and Advanced Tissue Sciences have discontinued operations. Smith & Nephew has taken over production, marketing, and sales of Dermagraft. The future of Apligraf is unclear.

Table 4. Projects Engaged, Failed, or Abandoned in Clinical Trials as of December 31, 2002

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Trans (Excella)</td>
<td>E-collar cell production kit for specific disease</td>
</tr>
<tr>
<td>BioArtificial liver</td>
<td>Treatment of diabetic foot ulcers</td>
</tr>
<tr>
<td>Artificial heart</td>
<td>Treatment of spinal cord injury</td>
</tr>
<tr>
<td>Sphincter (TissuePharmaceutical)</td>
<td>Encapsulated cell therapy for Parkinson’s disease</td>
</tr>
<tr>
<td>ILAD (VitaGen)</td>
<td>BioArtificial liver</td>
</tr>
<tr>
<td>Renal assist device</td>
<td>Treatment of acute renal failure</td>
</tr>
<tr>
<td>LIVERX 2000 (Algenus)</td>
<td>BioArtificial liver</td>
</tr>
<tr>
<td>MyoCell (Biostore)</td>
<td>Myocardiogenesis</td>
</tr>
<tr>
<td>Myocardial stem cells</td>
<td>Myocardiogenesis</td>
</tr>
<tr>
<td>Failed or abandoned</td>
<td></td>
</tr>
<tr>
<td>HepaAssist (Crye)</td>
<td>Bioartificial liver</td>
</tr>
<tr>
<td>Cerecloth (CytoTherapeutics)</td>
<td>Encapsulated cells for chronic pain</td>
</tr>
<tr>
<td>Articell (AMY)</td>
<td>Keratinocyte bunion dressing</td>
</tr>
<tr>
<td>Neuralcel (Innovia)</td>
<td>Intracerebral needle jets</td>
</tr>
<tr>
<td>ChondroGen (Cores)</td>
<td>For bladder reflux and adult incontinence</td>
</tr>
<tr>
<td>Vascugel (Cordis)</td>
<td>To improve potency in coronary grafts</td>
</tr>
</tbody>
</table>

*Indicates product engaged in phase III, all others are in phase II.
*Indicates products that failed to meet efficacy during phase III.
*Indicates products abandoned during phase II.