Regulation of Combination Products in Regenerative Medicine

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Outline

- Regulatory Framework for Combination Products used in Regenerative Medicine
- Review considerations for Cell-Scaffold Products
- Use of Standards in Review
- Resources: Regulations, guidance documents, voluntary standards, publications, FDA website
Regenerative Medicine Products

- Pluripotent Stem Cells (hESC and iPS)
- Stem cells (mesenchymal, hematopoietic, etc)
- Functional and structural cells (chondrocytes, pancreatic islets, cardiomyocytes, etc)
- Modified human/animal tissues
- Cells delivered by devices
- Tissue engineered and combination products (engineered tissue and organs)
Cell-Device Combination Products Regulated by OCTGT/CBER

- Tissue-engineered and regenerative medicine products (TEMPs): Cell-scaffold constructs
  - for tissue repair and replacement:
    - Orthopedic, cardiovascular, wound healing, musculoskeletal, ophthalmologic, osteogenic …. indications
  - for bioartificial metabolic support system:
    - Hepatic, urinary, renal …… indications
- Cells (and other biologics) + delivery device (catheters, injection/spray devices, etc):
  - for cardiovascular, orthopedic, musculoskeletal, wound healing……. indications
Regenerative Medicine Products

- Tissue
- Biologic
- Device
Applicable Regulations for Cell-Device Combination Products

- **Tissue Rules**
  - 21 CFR 1271
    - Donor Eligibility (21 CFR 1271 Subpart C)
    - Current Good Tissue Practice (cGTP; 21 CFR 1271 Subpart D)

- **Biological Product Regulations**
  - 21 CFR Parts 600-680

- **Medical Device Regulations**
  - 21 CFR Parts 800-898

- **Current Good Manufacturing Practices (cGMP) / Quality System Regulations (QSR)**
Combination Products

- Combinations of different categories of regulated articles:
  - Drug-device
  - Device-biologic
  - Drug-biologic
  - Drug-device-biologic

- Can be:
  - Physically or chemically combined
  - Co-packaged in a kit
  - Separate, cross-labeled products
Combination Products
Common Themes

• Specifically intended for use together.
• Both components required to mediate the intended therapeutic effect.
• Components used alone would be regulated under different regulatory authorities.

Guidance (2006): Early Development Considerations for Innovative Combination Products
http://www.fda.gov/oc/combination/innovative.html
Where does my product go?

Jurisdictional Inquiries

- Center Jurisdictional Officers
- Tissue Reference Group (TRG): whether or not product eligible for regulation solely as a tissue
- Office of Combination Products (OCP)
  - Request for Designation (RFD): lead review center designated based on primary mode of action determination, inter-center agreements, precedence

Publically Available Resources

- TRG Recommendations
- OCP Jurisdictional Updates
How does FDA assign jurisdiction for Combination Products?

- Jurisdiction is assigned based on **Primary Mode of Action (PMOA)**, the regulatory criterion FDA must use (21 CFR Part 3.4). PMOA is the primary reason for assignment.

- PMOA is defined as the single mode of action of a combination product that provides the most important intended therapeutic action of the combination product.


**Example:** Two completely different MOA, neither of which is subordinate to the other:

**PMOA?**
Lead Center Designation vs. Regulatory Pathway

Center Assignment ≠ Regulatory Authority

- Regulatory pathway decision typically determined by the lead Center.
- Potential regulatory pathways at CBER:
  - Combination product may be regulated under a single application or may need two.
  - Consult/collaborative review of a component may be performed by another Center/Office.
Cell-Device Combination Products

**CELLS**
- Cell Source
- Cell Processing/Manufacturing
- Characterization and Testing

**SCAFFOLD**
- Starting Materials
- Design and Properties
- Manufacturing and Testing

Cell and Device Combined
Final Product
Cell Component

- Source (auto, allo, xeno)
- Sterility (bacterial, fungal, mycoplasma)
- Purity (cellular impurities profile, endotoxin)
- Viability
- Identity
  - Morphologic evaluation
  - Unique biochemical markers
  - Phenotype-specific cell surface antigens
  - Gene and protein expression analysis
- Cell number
- Potency/Biologic activity
- Stability
Material selection, design and fabrication contribute to defining the functional properties of the final product.

Biocompatibility, physical properties, and resorption kinetics of the scaffold are crucial attributes for safety and effectiveness of TEMPs.

Resorption profile may include degradation products, decomposition mechanism, and kinetics of cell in-growth.

Sterility assurance

- for synthetic scaffolds – achieved through validation of sterilization, process control, and monitoring.
- for biological scaffolds – through validation of the source material and control and testing of aseptic processing conditions.
Cell-Scaffold Constructs - Challenges

- Development of appropriate *in vitro* and *in vivo* testing and characterization methods due to:
  - Complexity in structure (3D)
  - Heterogeneity in composition
  - Small lot sizes (“lot of one”)
  - Remodeling of product post-implantation
- “Final” product specification from *in vitro* testing may not be predictive about clinical safety and efficacy
  - Product is not designed to be “stable”
- Defining potency/performance requirements
  - Multiple modes of action
  - Specific to both product type and intended use (cartilage, vascular graft, etc.)
A demonstration of product potency may be necessary depending upon the regulatory pathway. For cell-scaffold products, potency may be regarded as a component of “product performance”.

Potency: interpreted to mean the specific ability or capacity of the product ....to effect a given result – 21 CFR 600.3(s).

Due to the complex nature of TEMP, a multiple assay approach (Assay Matrix) correlated to intended biological activity or function may be used as a measure of potency.

Post-implantation performance issues should be addressed in the potency assay matrix:

migration of cells out of the scaffold to the host tissue.
Performance/Potency Issues Specific to Product Type and Intended Use

- **TEMPs Indicated for vascular graft:**
  - Biomechanical testing to tolerate repeated accesses without leaking
  - Testing to withstand a pre-defined burst pressure

- **TEMPs Indicated for wound healing:**
  - Testing to address water permeability
  - Testing to address gas exchange function

- **TEMPs Indicated for repairing cartilage:**
  - Demonstrating the formation of cartilage tissue in vivo possibly using a panel of validated functional markers.
Cell-Device Combination Products

**CELLS**
- Cell Source
  - Donor eligibility, MCB testing
- Cell Processing/Manufacturing
  - GMP, In-process testing
- Characterization and Testing
  - Safety, Identity, Purity, Potency

**SCAFFOLD**
- Starting Materials
  - Safety, Quality, Biocompatibility
- Design and Properties
  - Mechanical/Physical Characteristics
- Manufacturing and Testing
  - QSR, Design control, Performance

**Cell and Device Combined**
- Dose Response, Cell Growth, Cell Functions, Cell-Scaffold Interactions

**Final Product**
- Safety, Potency, Durability, Cell Fate, Structural and Biomaterial Decomposition
Regulations vs. Standards

- **Regulations**
  - Define specific requirements for safety
  - Provide accurate information to health professionals and consumers

- **Standards**
  - Describe how manufacturers might meet regulatory requirements
Use of Standards in OCTGT

Use in Review of Applications

- Sponsor cites standard in meeting or application
  - Ex. ISO 10993.xx (Biocompatibility)
  - Ex. ATCC VR-1516 (Adenovirus Type 5 Reference Material)

Use as Information Resource

- Ex. ASTM 2451-05 – Standard Guide for in vivo assessment of implantable devices intended to repair or regenerate articular cartilage
- Ex. ANSI/AAMI/ISO 7198 Cardiovascular Implants: Vascular Graft Prostheses
FDA Standards Policy (SMG 9100.1)

- FDA adopts by reference, either in their entirety or in part, standards developed through NGO and intergovernmental international standards organizations in lieu of internally developed government unique standards and guidance when most appropriate and not in conflict with US law or regulation.

- FDA will preferentially use internationally harmonized standards developed by SDO when most appropriate and not in conflict with US law or regulation.
Use of Standards in OCTGT

- Leverage Industry Efforts
  - SDO can sometime produce documents or physical standards more quickly than FDA can produce Guidance Documents
  - Effort shared with non-FDA experts
  - SDO can cover areas that are difficult to put in FDA Guidances
    - Specific (proprietary) methods for tests or processes
    - Critical reviews of emerging fields
Starting point for FDA interaction

- **Product-specific guidances**
  - Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (draft)
  - Somatic Cell Therapy for Cardiac Disease (draft)

- **General guidances to support specific areas of tissue engineered medical products**
  - CMC guidances for cellular products
  - General preclinical guidances
  - Guidances for scaffolds and devices
  - General clinical guidances

- **Standards from SDOs** (ASTMi, ICH, ISO, USP...)

- **Pre-submission meeting with appropriate FDA Center/office**
Advice for Starting Clinical Studies

- Identify FDA organizational unit and regulatory pathway early
- Early interactions with FDA are critical
- Know your guidance documents
- Consider early in development the questions that will be asked at the clinical study phase
- Think about some of the early commercialization issues and opportunities
For more information...

- Publically available summary of licensed or approved products
  - Summary Basis of Approval (SBA)
  - Summary of Safety and Effectiveness Data (SEED)
- Advisory committee/panel meetings, transcripts
  - Orthopedics Panel for Carticel (Mar 1997)
  - Dermagraft, Graftskin (Apligraf) PMA review (Jan 1998)
  - Examination of risks posed by different types of Xenotransplantation products (Jan 2000)
  - Hematopoietic stem cells for hematopoietic reconstitution (Feb 2003)
  - Allogeneic islet cell therapy for diabetes (Oct 2003)
  - Somatic cell cardiac therapies (Mar 2004)
  - Somatic cell therapies for joint surfaces (Mar 2005)
  - Potency measures for cell, tissue and gene therapies (Feb 2006)
Recent FDA References in Regenerative Medicine


Selected FDA Guidances

- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (July 2007)
  

- Draft Guidance for Industry: Somatic Cell Therapy for Cardiac Disease (March 2009)
  

- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
  

- Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh
  

  
General FDA Information

- Code of Federal Regulations
  http://ecfr.gpoaccess.gov/

- Tissue & Tissue Products
  http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm

- CBER Guidances

- CDRH Databases & Guidances
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm

- Device Advice
  http://www.fda.gov/cdrh/devadvice/ide/index.shtml
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