U.S. Food and Drug Administration

Department of Health and Human Services

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Regulation of Combination Products in Regenerative Medicine

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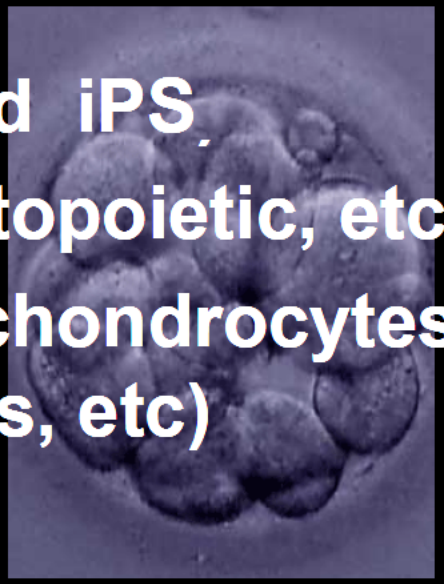
Regenerative Medicine Products

- Pluri_ otent Stem Cells _hESC and iPS_
- Stem cells (mesenchymal, hematopoietic, etc)
- Functional an_ structural cells (chondrocytes, pancreatic islets, cardiomyocytes, etc)
- Modified human/animal tissues
- Cells delivered by devices
- Tissue engineered and combination products (engineered tissue and organs)



Outline

- Brief FDA Overview
- Regulatory Framework for Combination Products used in Regenerative Medicine
- Review considerations for Cell-Scaffold Products
- FDA Interactions and Resources: Regulations, guidance documents, voluntary standards, publications, FDA website

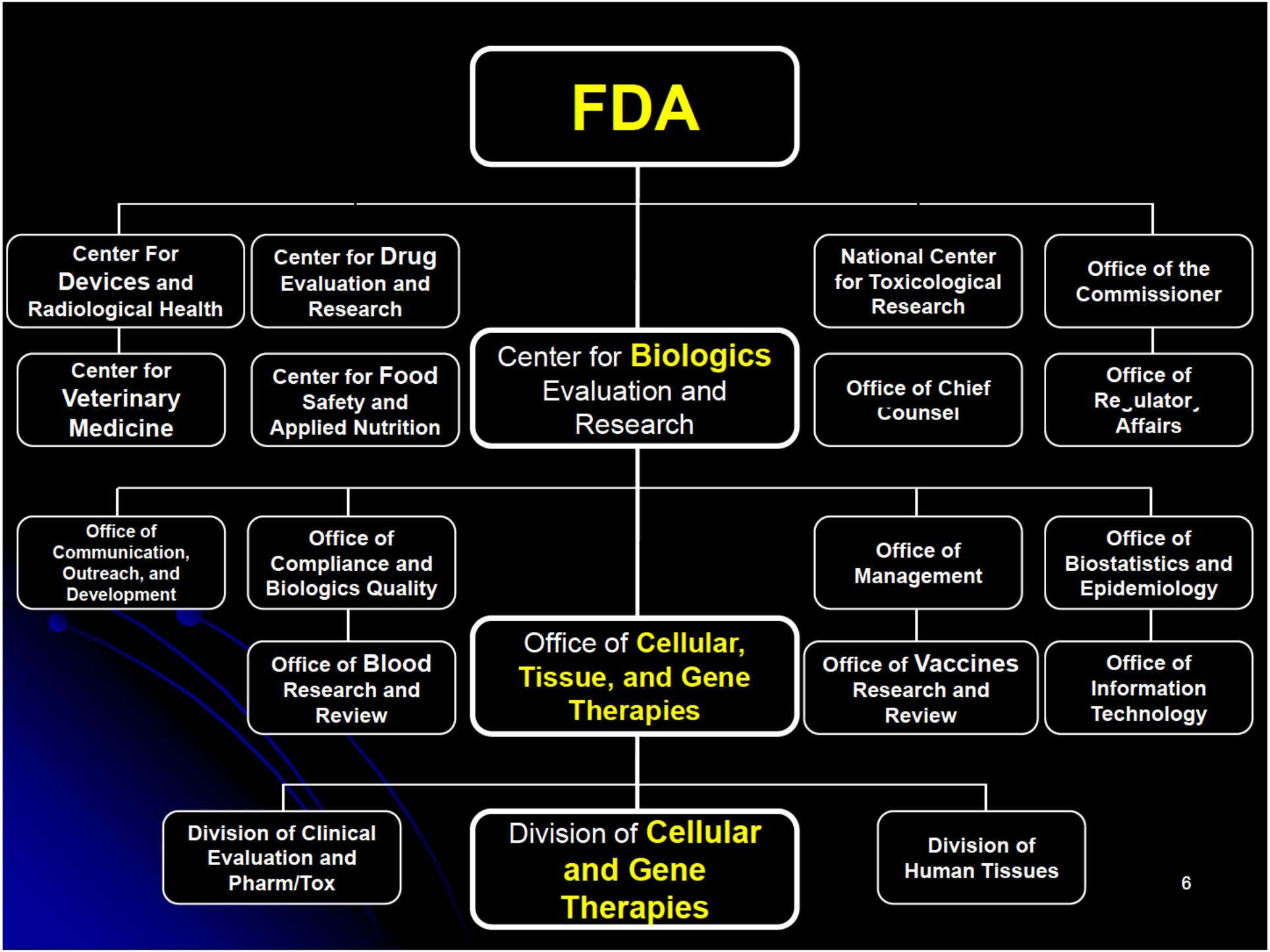
FDA Mission Statement

The FDA is responsible for **protecting the public health** by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

The FDA is also responsible for **advancing the public health** by helping to *speed innovations* that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Basis for FDA Regulation

- Statutes: THE LAW --- passed by Congress and signed by the President
  - 42 USC 262 (United States Code)
- Regulations: details of the law --- written by the Agency and approved by the Executive Branch
  - 21 CFR 312 (Code of Federal Regulations)
- Guidance: the Agency's interpretation of the Regulations --- written and approved within the Agency
  - 68 FR 49488 (Federal Register)


FDA
Center For Devices and Radiological Health
Center for Drug Evaluation and Research
National Center for Toxicological Research
Office of the Commissioner
Center for Veterinary Medicine
Center for Food Safety and Applied Nutrition
Center for Biologics Evaluation and Research
Office of Chief Counsel
Office of Regulatory Affairs
Office of Communication, Outreach, and Development
Office of Compliance and Biologics Quality
Office of Management
Office of Biostatistics and Epidemiology
Office of Blood Research and Review
Office of Cellular, Tissue, and Gene Therapies
Office of Vaccines Research and Review
Office of Information Technology
Division of Clinical Evaluation and Pharm/Tox
Division of Cellular and Gene Therapies
Division of Human Tissues

Human Medical Products

- CDER: drugs, monoclonal antibodies, therapeutic proteins*
- CBER: vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy
- CDRH: devices f_r treatment, implants, diagnostic devices

* This does not include proteins used in therapeutic vaccines, which are regulated by OCTGT (CBER)

CBER Office of Cellular, Tissue and Gene Therapies

- Cellular Therapies (Including Stem Cells)
- Cancer Vaccines and Immunotherapy
- Gene Therapies
- Xenotransplantation Products
- Tissues and Tissue-Based Products
- Devices Used for Cells and Tissues
- Combination Products

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

Combination Products

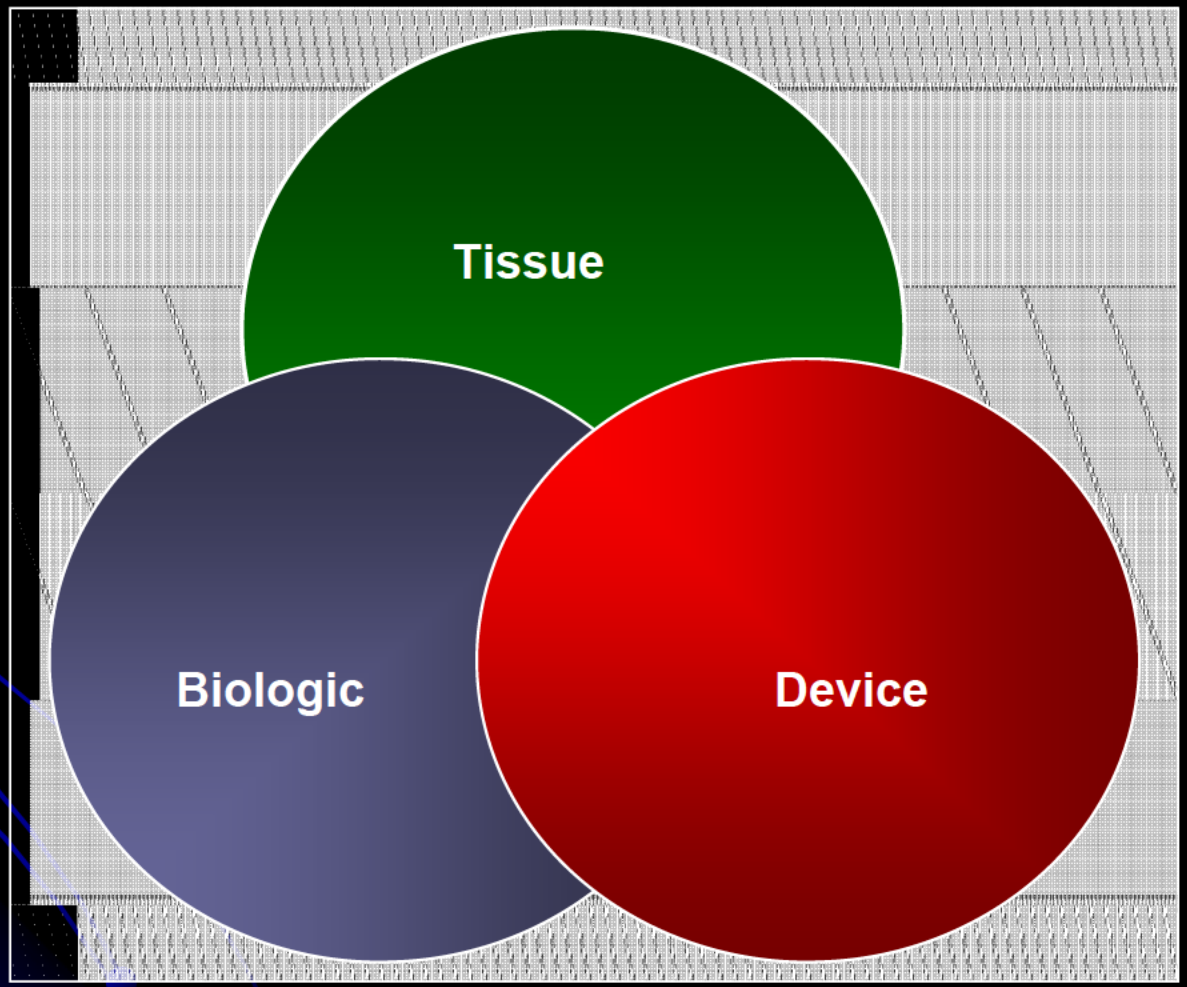
- Combinations of different categories of regulated articles:
  - Drug-device
  - Device-biologic
  - Drug-biologic
  - Drug-device-biologic
- Can be:
  - Physically or chemically combined
  - Co-, acka ed in a kit
  - Separate, cross-labeled products

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/cdrh/combination/innovative.html

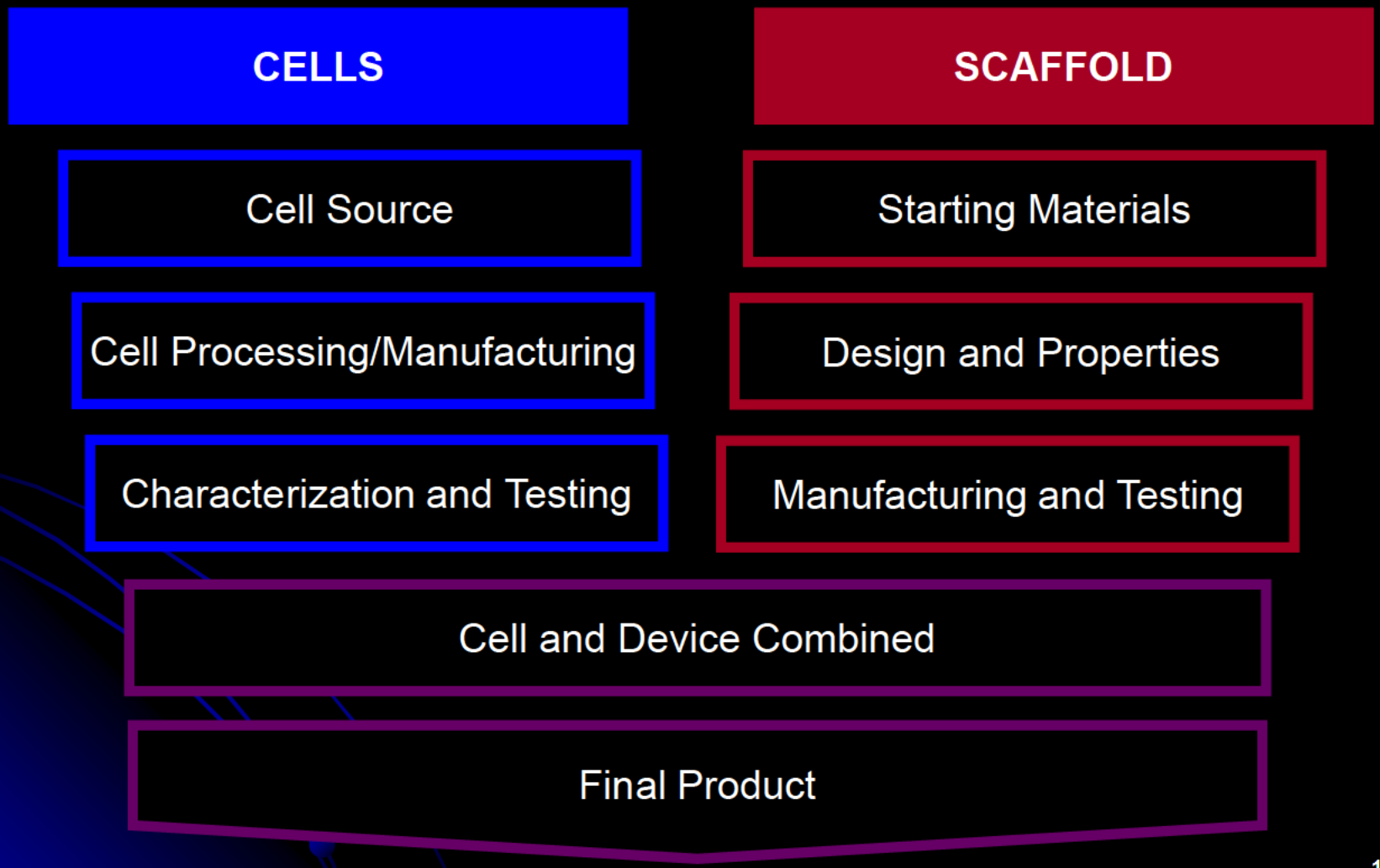
Regenerative Medicine Products



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)

Cell-Scaffold Combination Products



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

Scaffold Characterization

Chemistry Issues

- Material Source
  - Monomers, impurities, adventitious agents, immunogens, pyrogens
  - Crystalline / non-crystalline phases, cation / anion ratio
  - Impact of material on cells
- Materials Testing
  - Leachable chemicals / Extracts for biocom¸ atibilit¸ studies
  - In-situ polymerizing / assembling materials
    - Set-time, Rx temperature, Rx with normal tissue
  - Decomposition products
- Sterilization Conditions
  - Impact on product
  - Residue's impact on cells

Scaffold Characterization

Design and Physical Issues

- Device mass, volume, density, pH, porosity, particle size
- Compare properties of construct with other approved/cleared products and normal tissue
- Resorption Kinetics
  - Kinetics of cell in-growth
  - Mechanism and pathway of decomposition
- Mechanical Properties:
  Compress… strength, Tensile/F.e… strength, Elastic modulus, Fatigue/Abrasion resistance, Fixation strength

Test sufficient number of samples! (Intra- and Inter-lot)

Cell-Scaffold Constructs - Challenges

- "Final" product specification from *in vitro* testing may not be predictive about clinical safety and efficacy
  - Product is not designed to be "stable"
- 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
- Defining potency/performance requirements
  - Multiple modes of action
  - Specific to both product type and intended use (cartilage, vascular graft, etc.)

Functional Characterization of Cell-Scaffold Products

- 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 ma_ be used as a measure of _otenc_.
- 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

SCAFFOLD

Cell Source
Donor eli_ibilit_, MCB testin_

Starting Materials
Safety, Quality, Biocom_atibilit_

Cell Processing/Manufacturing
GMP, In-process testing

Design and Properties
Mechanical/Physical Characteristics

Characterization and Testing
Safety, Identity, Purity, Potency

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

Starting point for FDA interaction

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

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/AAMIISO 7198 Cardiovascular Implants: Vascular Graft Prostheses*

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 Da.. (SEED)

- Advisory committee/panel meetings, transcripts

  - Cellular and gene therapy products for treatment of retinal disorders (June 2011)
  - Clinical issues related to FDA draft guidance “Preparation of IDEs and INDs for ¸ roducts intended to re¸ air or re¸ lace knee cartila¸e” ¸Ma¸ 2009)
  - Animal models for porcine xenotransplantation products intended to treat type I diabetes or acute liver failure (May 2009)
  - Cellular thera¸ ies derived from human embr¸ onic stem cells – considerations for pre-clinical safety testing and patient monitoring (April 2008)
  - Potency measures for cell, tissue and gene therapies (Feb 2006)
  - Somatic cell thera¸ ies for ¸oint surfaces ¸Mar 2005¸
  - Somatic cell cardiac therapies (Mar 2004)
  - Allogeneic islet cell therapy for diabetes (Oct 2003)

Selected FDA Guidances

- **Guidance for Industry: Somatic Cell Therapy for Cardiac Disease (October 2010)**

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm

- **Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage**

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073390.htm

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

  htt ://www.fda. ov/MedicalDevices/DeviceRe ulationandGuidance/GuidanceDocuments/ucm073790.htm

- **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)**

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm

- **Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (Jan 2011)**

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072571.htm

General FDA Information

- **Code of Federal Regulations**
  http://ecfr.gpoaccess.gov/
- **Tissue & Tissue Products**
  http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm
- **CBER Biologics Guidances**
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- **CDRH Databases & G_idances**
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
- **Device Advice**
  http://www.fda.gov/cdrh/devadvice/ide/index.shtml
- **OCTGT Learn Webinars**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Recent FDA References in Regenerative Medicine

- KJ Whittlesey, MH Lee, JM Dang, M Colehour, J Arcidiacono, E Lazarus, D Kaplan, D Fink, CN Durfor, A Batra, SL Hilbert, D Lavoie Grayeski, R Mcfarland, C Witten. "Overview of FDA Regulatory Process," in Principles of Regenerative Medicine, 2nd Edition, A Atala, R Lanza, J Thomson and R Nerem (eds.), Amsterdam, Academic Press, Elsevier, 2010.

- MH Lee, JA Arcidiacono, AM Bilek, JJ Wille, CA Hamill, KM Wonnacott, MA Wells, SS Oh. "Considerations for Tissue Engineered and Regenerative Medicine Product Development," Tissue Engineering, Part B: Reviews 16:1 (2010)

- JA Arcidiacono, E Evdokimov, MH Lee, J Jones, L Rudenko, B Schneider, PJ Snoy, C-H Wei, AK Wensky, K Wonnacott. "Regulation of Xenogeneic Porcine Pancreatic Islets," Xenotransplantation 17:1 (2010)

- DW Fink Jr., "FDA Regulation of Stem Cell-Based Products," Science 324: 1662 (2009)

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