

The Convergence of Biologics and Medical Devices: CBER Perspective

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Outline

- FDA Organization
- CBER/Office of Cellular, Tissues, and Gene Therapies Overview
- Biologics/device combinations
- FDA Cross-Center Tissue Engineering Teams
- Regulations, guidance documents, voluntary standards
- Outreach

FDA Organization

- Office of the Commissioner
 - Office of Combination Products
- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy, screening tests for blood safety
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CDER (Center for Drug Evaluation and Research): drugs, monoclonal antibodies, therapeutic proteins)
- CVM
- CFSAN
- NCTR

CBER Organization

- Immediate Office of Director
- Office of Blood Research and Review
- **Office of Cellular, Tissue and Gene Therapies**
- Office of Vaccines Research and Review
- Office of Compliance and Biological Quality
- Office of Biostatistics and Epidemiology
- Office of Management

Office of Cellular, Tissue, and Gene Therapies

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Ruth Solomon, M.D., Director

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OCTGT Products

- Cellular therapies
- Tumor vaccines and immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues

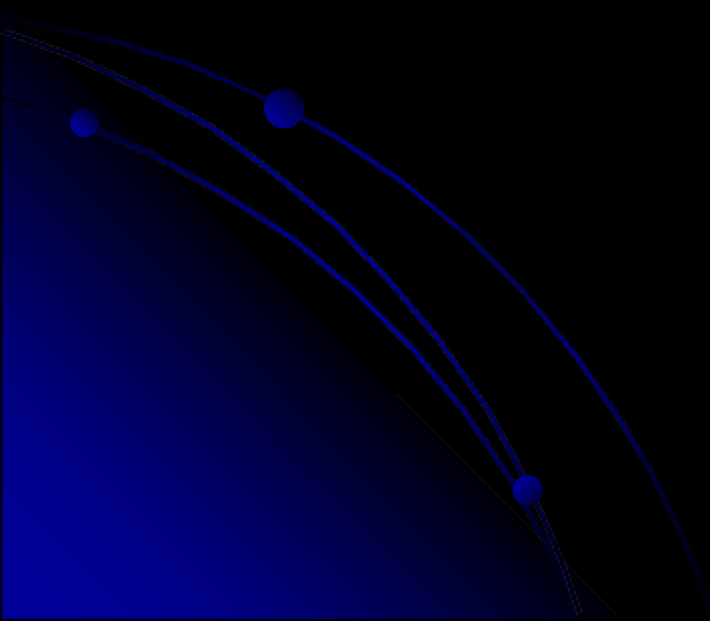
Device Biologics Convergence

- Physically combined products (coated devices, preassembled cell-scaffold combinations)
- Devices used to produce biologics at the point of care (autologous cell sorters, autologous tissue recovered, combined with a scaffold, and administered in one procedure, automated cell processing systems)
- Delivery devices/novel therapeutics
- Drug-diagnostic co-development

Regulation

- Regulation of human tissue (21 CFR Part 1271)
- Biologics (IND, BLA)
- Devices (IDE, 510k, PMA)
- Drugs (IND, NDA)

Human Tissue Regulation



What is Included?

Human Cells, Tissues and Cellular and Tissue-based Products (HCT/Ps)

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/device and other combination therapies

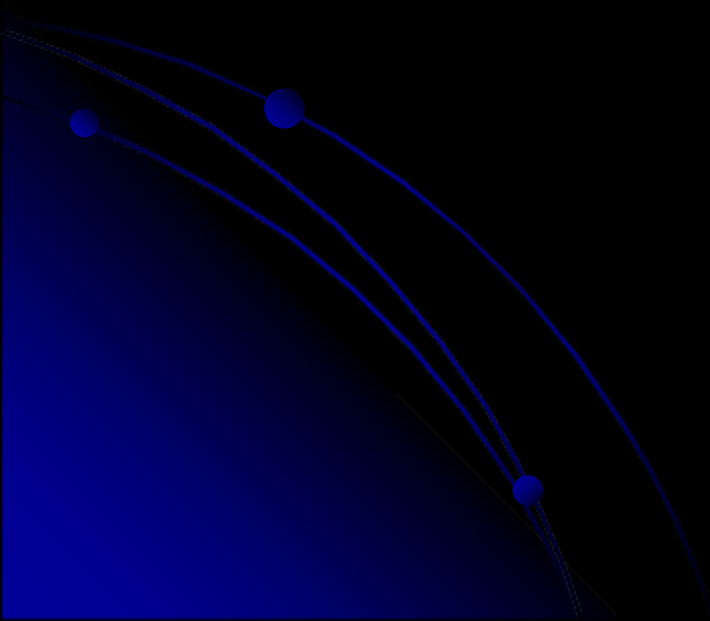
Tissue Rules

- Establishment Registration
- Donor Eligibility
- Good Tissue Practices
- Not a premarket review program

Biologics Licensing Application

- Safety, Efficacy, Purity and Potency
- Regulation of both product and process
- Quality control of product and intermediates
- Reproducibility of lots

Cell Therapy Characterization and Safety



Cells: Examples of Indications/Sources

- Pancreatic islets for diabetes
- Stem and skeletal muscle progenitor cells for ischemic cardiac
- Hematopoietic reconstitution in treatment of malignancies
- Stem cells for metabolic storage diseases
- Stem cells for CNS indications (Parkinson's disease)
- Expanded autologous cartilage for joint repair

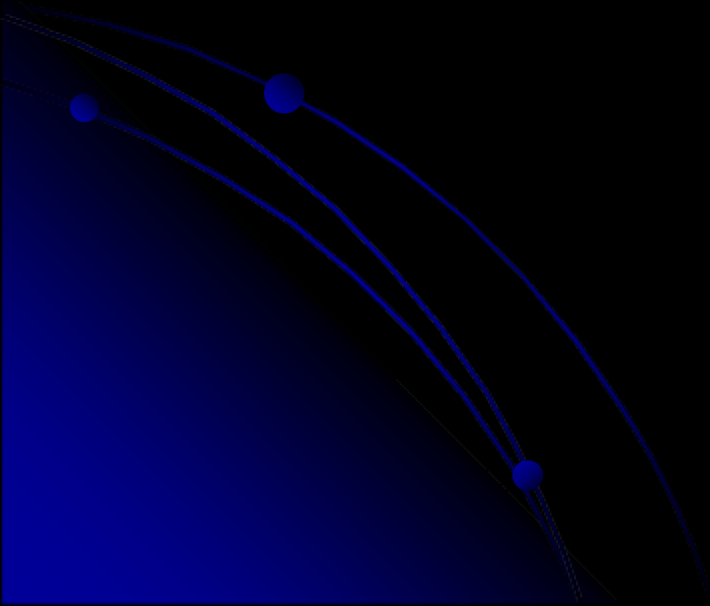
Cell Therapy Characterization

- **Cell source**
- **Morphologic and phenotypic evaluation**
- **Unique biochemical markers**
- **Unique gene and protein expression profile**
- **Cellular impurities profile**
- **Biologic activity /Potency**
- **Identity: HLA, other unique marker**

Cell Therapy Safety

- Migratory potential
- Cellular differentiation
- Cell phenotype expression
- Post transplant survival
- Anatomic/functional integration into host physiology
- Tumorigenicity of activated/transformed cells
- And...

Gene Therapy Characterization and Safety



Gene Therapies

- Transferred directly to the subject or ex vivo modified cells administered to subjects
- Gene Therapy Vectors
 - Plasmid
 - Adenovirus
 - Adeno-associated virus
 - Retrovirus & Lentivirus
 - Poxvirus
 - Herpesvirus
 - Bacteria

Gene Therapy Characterization

- Full sequence for vectors <40KB
- Removal of genes not needed for therapy or manufacturing
- Adventitious Viruses
- Wild type Virus & Replication Competent Recombinants
- Biologic activity /Potency

Gene Therapy Safety

- Biodistribution of vector
- Kinetics of gene expression
- Insertional mutagenesis
- Germline alteration
- Tumorigenic effect of transgene
- Uncontrolled or ectopic transgene expression
- Immunogenicity of transgene products, potential for self reactivity
- Potential to spread viral vectors to the environment
- And...

Cell Scaffold Products: Characterization and Safety

CELLS

Cell Donor
(Safety Testing)

MCB/WCB
(Safety/Identity/Purity/Consistency)

Production Level Cells
(In process testing: safety, purity, biomarker
for function)

SCAFFOLD

Scaffold Material Selection
(Safety Testing)

Scaffold Design
(Resorbable/Permanent
2D/3D Structure)

Scaffold Fabrication

Cell seeding
Dose response, cell growth, cell functions, cell-scaffold interactions

Final Cell/Scaffold Product
In Vitro or *In vivo* testing
Safety, potency, durability, cell fate, structure and biomaterial decomposition products,
Product performance

Clinical Studies

Regulation of Regenerative Medicine Products

- Guidances for Cellular, Gene Therapies, and Devices
- Leveraging existing guidances to support specific areas of tissue engineered medical products
 - CMC guidances for cellular products
 - General (CT and GT) preclinical guidances
 - Guidances for devices may be applicable to scaffolds
 - Many clinical guidances cross-cut product areas

CBER/CDRH Tissue Engineering Cross-Center Teams

- Facilitate intercenter co-operation and solutions of TE issues
- Provide a core resource of TE review expertise to CBER, CDRH, OCP
- Participate in development of regulatory policy and pathways
- Facilitate FDA participation in Standards Organizations
- Provide a strong, consistent FDA voice in outreach activities with academia, industry, other governmental programs
- Provide an educational resource for reviewers within CBER and CDRH

CBER/CDRH Tissue Engineering Cross-Center Teams-Composition

CBER

- Office of Cellular, Tissue and Gene Therapies
- Office of Compliance and Biologics Quality

CDRH

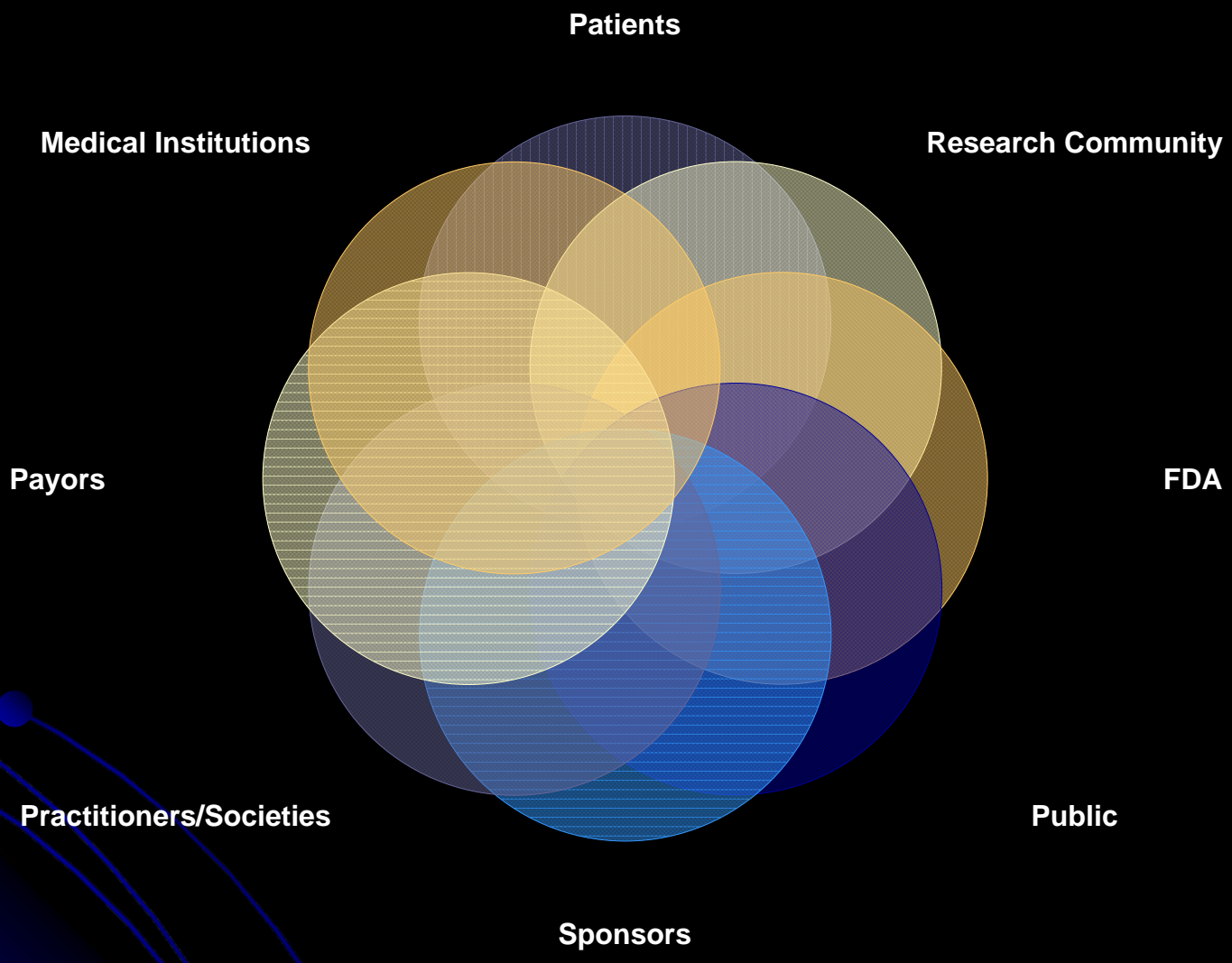
- Office of Device Evaluation
- Office of Science and Engineering Laboratories
- Office of Compliance

FDA Collaboration/Outreach

- Product specific confidential enquires during pre-IND (IDE), IND (IDE) process
- Standards activities
- Guidance documents
 - References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT)
<http://www.fda.gov/cber/genadmin/octgtprocess.htm>
 - (<http://www.fda.gov/cdrh/guidance.html>)
- Advisory Committee Discussions
 - (<http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm>)
- Site Visit Program (RSVP)
 - (FR Notice)
- Workshops
- Interagency and other collaborations (MATES)
- Critical Path Initiative

U.S. Regulatory Framework for Standards Development

- 21 CFR 10.95, Participation in outside standard-setting activities
- Policy regarding the development and use of standards with respect to International Harmonization of Regulatory Requirements and Guidelines” (60 FR53077, October 11, 1995).
http://www.access.gpo.gov/nara/cfr/waisidx_04/21cfr10_04.html



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