FDA’s Perspectives on Cellular and Gene Therapy Regulation

International Regulatory Forum of Human Cell Therapy and Gene Therapy Products
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Outline

- FDA overview & U.S. regulatory framework
- U.S. regulatory approaches to cellular, tissue, and gene therapy products
- U.S. regulatory approaches to combination products
- Expedited Programs for Serious Conditions
FDA Regulated Human Medical Products

- **Drugs**
  - Definition: 21 USC 201(g)

- **Biologics §**
  - Definition: 42 USC 351(i)

- **Medical Devices**
  - Definition: 21 USC 201(h)

- **Combination Products**
  - Definition: 21 CFR 3.2(e)(1)

§ Include **HCT/Ps** (human cells, tissues, and cellular and tissue-based products); 21 CFR 1271.3(d): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient
U.S. Regulatory Framework: 3-Tiered System

- **Statutes (Laws):**
  Passed by Congress and signed by the President
  - Food, Drug & Cosmetic Act (FD&C Act)
  - Public Health Service Act (PHS Act)

- **Regulations (Details of the law):**
  Written by FDA and approved by the Executive Branch
  - 21 CFR (Code of Federal Regulations)

- **Guidance (FDA’s interpretation of the regulations):**
  Written and approved within FDA
  - Advice non-binding on FDA or sponsor
U.S. Paradigm for Medical Product Regulation

- **Centralized authority for oversight**
  - FDA oversees the **entire lifecycle** of a medical product from investigational product development to post-marketing surveillance/study

- **Applicable laws with enforcement provisions**
  - Medical products subject to laws and regulations regarding **clinical investigations** and **marketing authorization**

- **Documented policies and guidelines available to public**
  - Federal Register (FR)
  - FDA Guidance Documents

- **Transparency / forum for public discussion**
  - FDA advisory committees; FDA-sponsored public workshops
  - NIH Recombinant DNA Advisory Committee (RAC)
FDA Organization

- **Office of the Commissioner**
  - OCP (Office of Combination Products)
  - CBER (Center for Biologics Evaluation and Research)
    - OCTGT (Office of Cellular, Tissue, and Gene Therapies)
  - CDRH (Center for Devices and Radiological Health)
  - CDER (Center for Drug Evaluation and Research)
  - CVM (Center for Veterinary Medicine)
  - CFSAN (Center for Food Safety and Applied Nutrition)
  - CTP (Center for Tobacco Products)
  - NCTR (National Center for Toxicological Research)
  - ORA (Office of Regulatory Affairs)
OCTGT Regulated Products

- **Somatic cell therapies**
  - Stem cells (hematopoietic, embryonic), mesenchymal stromal cells, chondrocytes, myoblasts, keratinocytes, pancreatic islets, hepatocytes

- **Gene therapies**
  - Gene-modified cells (in vivo or ex vivo); plasmids, bacterial/viral vectors

- **Cancer/therapeutic vaccines and immunotherapies**
  - Cells (including gene-modified), tumor tissue-derived products, peptides, protein-based products

- **Tissues, tissue-based & tissue-engineered products**

- **Combination products** (device-biologic; drug-biologic)

- **Devices**
  - Point-of-care devices producing therapeutic biologic as device output; cell/gene delivery devices

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

- **Definition:** Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient (21 CFR 1271.3 d).

- **Examples of HCT/Ps**
  - Musculoskeletal tissue, skin, ocular tissue, human heart valves; vascular graft, dura mater, reproductive tissue/cells,
  - Stem/progenitor cells; other cellular therapy products
  - Cells transduced with gene therapy vectors
  - Combination products (e.g., cells or tissue + device)

- **Not HCT/Ps**
  - Blood and blood products; xenografts – separate regulatory pathways
  - Minimally manipulated unrelated donor bone marrow – overseen by Health Resources and Services Administration (HRSA)
  - Vascularized human organs – overseen by HRSA
  - Secreted or extracted products (e.g., human milk, collagen, cell factors)
HCT/Ps – Regulatory Goals

- Prevent unwitting use of tissues from infected donors with potential for transmitting infectious disease
- Prevent improper handling or processing that might contaminate tissues/cells
- Ensure that clinical safety and efficacy are demonstrated for cells and tissues that are highly processed, used for purposes other than direct re-placement, that are combined with non-tissue components, or that have systemic effects dependent on metabolic activity
HCT/Ps – Two Regulatory Tiers

Risk determines the level of regulation:

- **Tissue** (“361 HCT/P”) – *lower risk*
  - Section 361 of PHS Act
  - Premarket review and approval not required; Product regulated *solely under Tissue Regulations* to control communicable disease (21 CRF 1271)
  - Establishment registration and product listing required (21 CRF 1271 -Subpart B)

- **Therapeutic** (“351 HCT/P”) – *higher risk*
  - Sections 351 & 361 of PHS Act, FD&C Act
  - Product regulated under Tissue Regulations and premarket review requirements (21 CFR Parts 1271, 600’s, 200’s, 312, 800’s, 812)
  - Regulatory pathway: can be **BIOLOGIC** or **DEVICE**
361 HCT/P or 351 HCT/P?

- Minimally manipulated? Yes/No
- Homologous use? (normal function) Yes/No
- Combined with drug or device? Yes/No
- Systemic effect or dependent on metabolic activity of the cells? Yes/No

If Yes to Minimally manipulated?

If No to Homologous use?

If No to Combined with drug or device?

If No to Systemic effect or dependent on metabolic activity of the cells?

- Is it a sterilizing, preserving, or storage agent with no new clinical safety concerns? Yes/No
- Autologous use? OR Allogeneic use in first or second degree relative? OR Reproductive use? Yes/No

Tissue

EXCEPTION: HCT/Ps are not regulated if they are removed from and returned to the patient in the same surgical procedure – 21 CFR 1271.15(b)
# Single Entity HCT/Ps

<table>
<thead>
<tr>
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<th>361 HCT/P</th>
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<td><strong>Tissue</strong></td>
<td>361 PHS Act</td>
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<td><strong>Therapeutic Biologic</strong></td>
<td>FD&amp;C Act</td>
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<td><strong>Device</strong></td>
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**Applicable Laws**
- 361 PHS Act
- 351 PHS Act
- FD&C Act

**Applicable Regulations**
- 21 CFR 1271
- 21 CFR 600’s
- 21 CFR 200’s
- 21 CFR 312
- 21 CFR 800’s

**Marketing Pathway**
- Premarket review not required
- BLA
- PMA, HDE 510(k)

*Note: Not all applicable Laws and Regulations are shown.*
Combination Products

- A product composed of different categories of regulated articles:
  - Device-biologic, biologic-drug, drug-device, biologic-drug-device \(\text{(not biologic-biologic, etc)}\)

- Constituents are:
  - intended for use together
  - \text{required to mediate the intended therapeutic effect}

- Can be:
  - Physically or chemically \text{combined}
  - \text{Co-packaged}; or packaged separately but \text{cross-labeled}
Cell-Device Combination Product Examples

- **Cell-scaffold constructs: Tissue-engineered medical products and regenerative medicine products**
  - For tissue regeneration, repair and replacement:
    Orthopedic, cardiovascular, wound healing, musculoskeletal, ophthalmologic, osteogenic …… indications

- **Bioartificial metabolic support system:**
  - Hepatic, urinary, renal …… indications

- **Cells + delivery device (catheters, injection/spray devices):**
  - Cardiovascular, orthopedic, musculoskeletal, wound healing….. indications
Determining Lead Review Center for Combination Products

- **Publicly Available Resources**
  - [http://www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm)

- **Informal Jurisdictional Inquiries**
  - Center Jurisdictional Officers

- **Office of Combination Products (OCP)**
  - OCP Jurisdictional Updates
  - **Request for Designation (RFD):** lead review center designated based on primary mode of action determination, inter-center agreements, most relevant expertise, precedents
Combination product (CP) may be regulated under a single application or may need two.

Review of a constituent part of a CP may be performed by another Center or Office within the same Center (consult/collaborative review).
Expedited Programs for Serious Conditions

- Guidance for Industry: Expedited Program for Serious Conditions – Drugs and Biologics (May 2014)
- Speed availability of new therapy to patients with serious conditions especially where there are no satisfactory alternatives
- While preserving appropriate standards of safety and efficacy
- Four Expedited Programs for Drugs and Biologics:
  - Fast track designation
  - Breakthrough therapy designation
  - Accelerated approval
  - Priority review designation
Comparison of Expedited Programs for Serious Conditions

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
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<td>-Serious condition AND</td>
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<td>-Nonclinical or clinical data demonstrate the <em>potential</em> to address unmet medical need</td>
<td>-Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints</td>
<td>- Meaningful advantage over available therapies</td>
<td>-Demonstrates potential to be a significant improvement in safety or effectiveness</td>
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<td>Note: Information to demonstrate <em>potential</em> depends upon stage of development at which FT is requested</td>
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<td>- Demonstrates an effect on either: a surrogate endpoint or an intermediate clinical endpoint</td>
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Comparison of Expedited Programs (cont’d)

<table>
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<tr>
<th>Features</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
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<tr>
<td></td>
<td>-Actions to expedite development and review</td>
<td>-All fast track designation features</td>
<td>-Approval based on an effect on a surrogate of intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit</td>
<td>-Shorter review clock for marketing application: 6 months (compared to 10 months)</td>
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<td>-Rolling review</td>
<td>-Intensive guidance on efficient drug development during IND as early as phase 1</td>
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<td>-Organizational commitment involving senior management</td>
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## Comparison of Expedited Programs (cont’d)

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<tr>
<th>When to submit</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
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<tr>
<td></td>
<td>-With IND or after Pre-IND or Pre-NDA</td>
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<td>-The sponsor should discuss the possibility of accelerated approval with review division during development, supporting the use of a planned endpoint as a basis for approval and discussing confirmatory trials</td>
<td>-With original BLA, NDA or efficacy supplement</td>
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OCTGT Regulatory Resources

- General information for OCTGT and related regulatory references:

- Guidance documents for cell and gene therapies:

- Regulatory questions:
  Regulatory Management Staff at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or call (240) 402-8361
Public Access to CBER

- **CBER website:**
  
  http://www.fda.gov/BiologicsBloodVaccines/default.htm
  Phone: 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch (CAB)**
  
  Email: ocod@fda.hhs.gov
  Phone: 240-402-8010

- **Manufacturers Assistance and Technical Training Branch (MATTB)**
  
  Email: industry.biologics@fda.gov

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