FDA's Perspectives on Cellular and Gene Therapy Regulation

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

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)

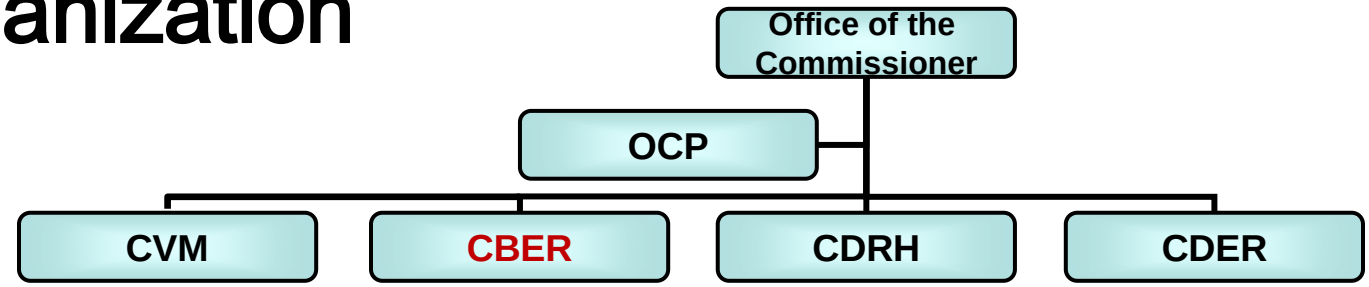
- **Guidance (FDA's interpretation of the regulations):**

  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

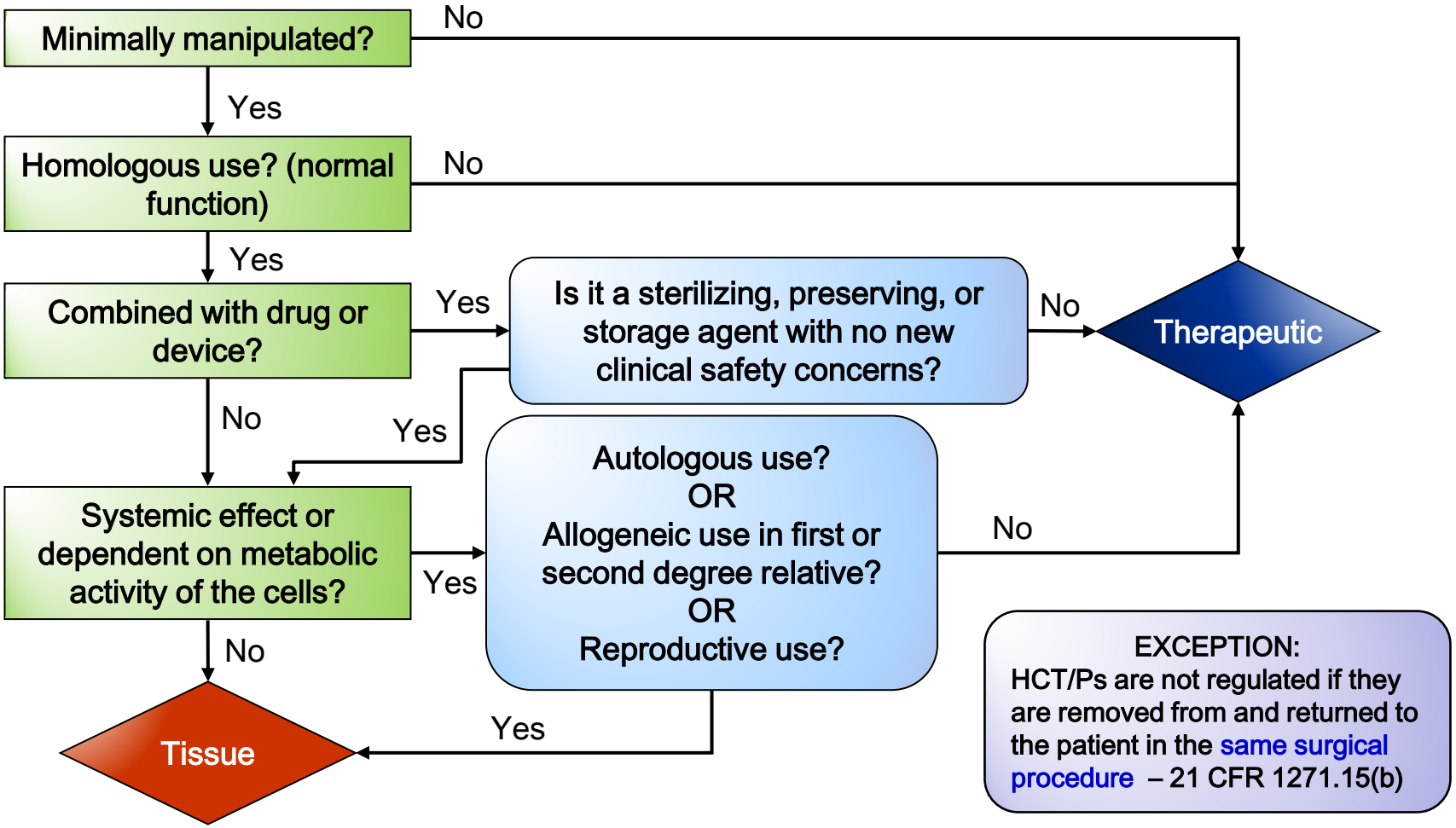
- Prevent unwitting use of tissues from infected donors with potential for **transmitting infectious disease**
- Prevent improper handling or processing that might **contaminate tissues/cells**
- Ensure that **clinical safety and efficacy are demonstrated** for cells and tissues that are highly processed, 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 ?



Single Entity HCT/Ps

	361 HCT/P	351 HCT/P	
	Tissue	Therapeutic Biologic	Device
Applicable Laws	361 PHS Act	361 PHS Act 351 PHS Act FD&C Act	FD&C Act
Applicable Regulations	21 CFR 1271	21 CFR 1271 21 CFR 600's 21 CFR 200's 21 CFR 312	21 CFR 800's
Marketing Pathway	Premarket review <u>not</u> 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 (not biologic-biologic, etc)**
- Constituents are:
  - intended for use together
  - **required to mediate the intended therapeutic effect**
- Can be:
  - Physically or chemically **combined**
  - **Co-packaged**; or packaged separately but **cross-labeled**

Cell-Device Combination Product Examples

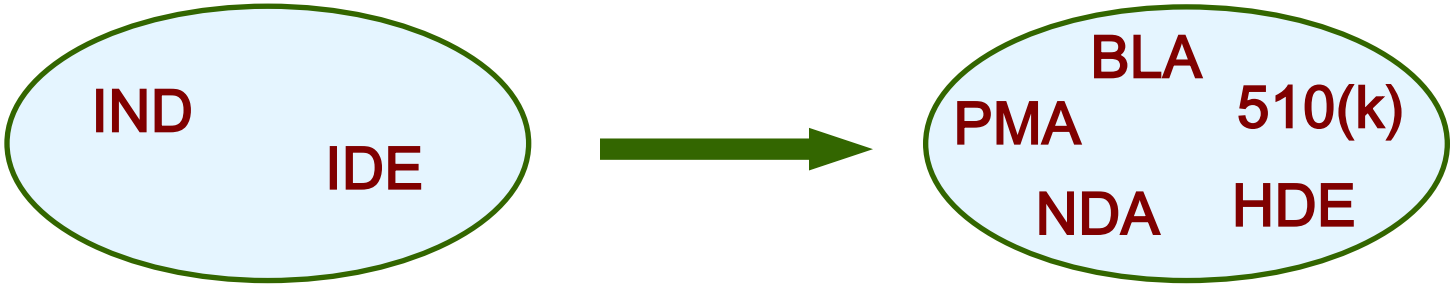
- **Cell-scaffold constructs: Tissue-engineered medical products and regenerative medicine products**
  - **For tissue regeneration, repair and replacement:**

    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
- **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

CBER Regulatory Pathways for Combination Products



- 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

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Criteria	-Serious condition AND -Nonclinical or clinical data demonstrate the *potential* to address unmet medical need Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-Serious condition AND -Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints	-Serious condition AND - Meaningful advantage over available therapies - Demonstrates an effect on either: a surrogate endpoint or an intermediate clinical endpoint	-Serious condition AND -Demonstrates potential to be a significant improvement in safety or effectiveness

Comparison of Expedited Programs (cont'd)

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

Comparison of Expedited Programs (cont'd)

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
When to submit	-With IND or after -No later than Pre-BLA or Pre-NDA	-With IND or after -Ideally no later than end-of-phase 2	-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	-With original BLA, NDA or efficacy supplement

OCTGT Regulatory Resources

- General information for OCTGT and related regulatory references:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Guidance documents for cell and gene therapies:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm
- 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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