Development of Regenerative Medicine Products: FDA Perspectives

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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 (the FDA's interpretation of the Regulations):
  Written and approved within FDA
  - Advice non-binding on FDA or sponsor

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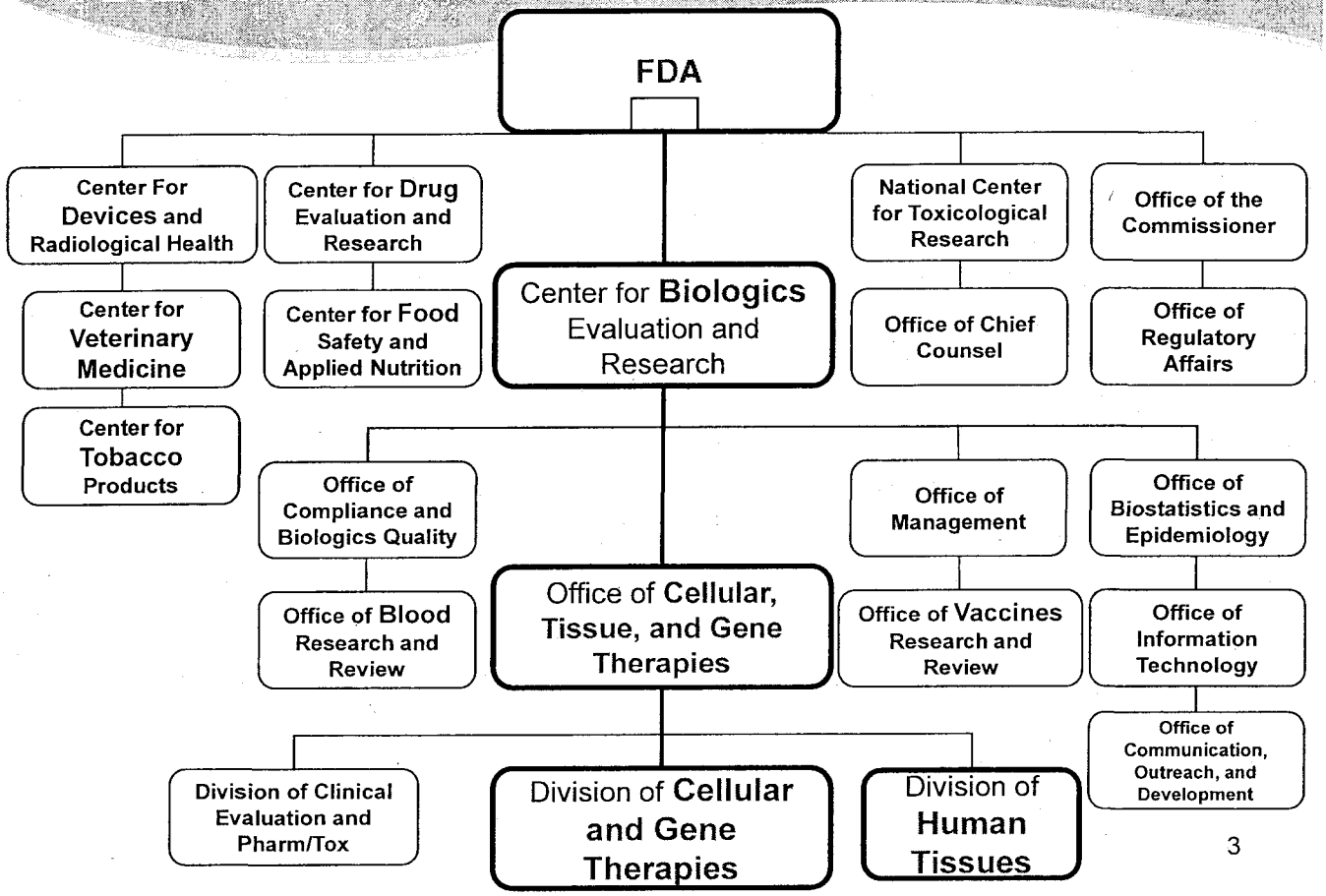

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What is and is not an HCT/P

Regulated as HCT/Ps

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves; vascular graft
- Dura mater
- Reproductive tissue/cells
- Hematopoietic stem/progenitor cells; other cellular therapies
- Combination products (e.g., cells or tissue + device)

Not regulated as HCT/P's

- Vascularized human organs
- Minimally manipulated unrelated donor bone marrow
- Xenografts-separate regulatory pathway
- Blood and blood products - separate regulatory pathway
- Blood vessels recovered with organs and used for organ transplantation only
- Autologous cells recovered and used in same surgical procedure

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)
  - The Establishment Registration, Donor Eligibility and Good Tissue Practice (GTP) final rules comprise 21 CFR Part 1271
- 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, 200, 312, 812)
  - Regulatory path: **Biologic** (IND/BLA) or **Device** (IDE/PMA)

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Cellular Therapies

- Regulated as HCT/P and subject to 1271 regulations
- Regulated as drugs and biologics and subject to premarket review requirements
- Clinical trials require an Investigational New Drug Application (IND)
  - A formal document with defined structure and content
  - Purpose is to request exemption from premarketing requirements and to allow lawful shipment of drug for clinical investigation.
  - Regulations (21 CFR 312) outline requirements for:
    - Use of investigational drug
    - Submission of application to FDA
    - Review by FDA

Regulation of Cell Therapies Under the 1271 Tissue Rules

HCT/P's regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 ONLY IF ALL FOUR of the following are met:

- Minimally Manipulated: Relevant biologic characteristic(s) are not altered by processing.
- Homologous Use Only: The HCT/P performs the same basic function in the recipient as in the donor.
- Production of the HCT/P does not involve combination of cells with another article (with limited exceptions and on the condition that addition of the excepted article does not raise new clinical safety concerns).
- Does not have a systemic effect, is not dependent upon the metabolic activity of living cells for primary function: exceptions for (a) autologous use, (b) first- or second-degree blood relatives, or (c) reproductive use.

More than Minimal Manipulation

- Risk of adventitious virus introduction during manufacturing
  - Reagents
  - Operators
  - Environment
- Risk of alteration of biological properties
  - Manufacturing is a novel, non physiological microenvironment

Risk/Benefit Considerations

- Protect patients from unreasonable risk
- Case-by-case
  - Patient population
    - Age
    - Medical condition
    - Availability of other treatment
    - Previous experience with similar products
  - Clinical Trial Design
  - Preclinical Information
  - Product Characteristics and Characterization

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Team Approach to Regulation of Regenerative Medicine Products

- Review Team
  - Product
  - Clinical
  - Pharm/Tox
  - Statistician
  - Regulatory Project Manager
  - Consult reviewer(s)
- CBER Research/Reviewer Model
  - Scientists/Clinicians: research-reviewers and full time review staff