

“FDA Regulatory Pathway”

**2nd Annual FDA and the Changing
Paradigm for Tissue Regulation**

2-8-06

Las Vegas, Nevada

Outline

- **“361” vs. “351” HCT/Ps**
- **21 CFR 1271.10**
- **Statutes that apply**
- **Regulations that apply**
- **Examples of jurisdictional recommendations and decisions**
- **Questions and Answers**

“361” HCT/Ps

- **No pre-market review--no application to FDA is required**
- **Meet all criteria in 1271.10**
- **Compliance determined at FDA inspections**
- **Examples—musculoskeletal tissue; skin; cornea; reproductive cells (subparts D and E do not currently apply); minimally manipulated cellular therapies for homologous use in the donor/patient or in a first- or second-degree blood relative**

“351” HCT/P

- **Pre-market review and approval**
 - **IND/BLA—biological products**
 - **IND/NDA--drug**
 - **IDE/PMA or 510(k)--device**
- **Do not meet one or more criteria in 1271.10**
- **Pre-license/approval inspection**
- **Routine FDA inspections**
- **Examples--cellular therapies for unrelated allogeneic use (regardless of whether or not minimally manipulated or for homologous use); amniotic membrane seeded with limbal stem cells**

21 CFR 1271.10

- **HCT/P regulated solely under section 361 of PHS Act and regulations in part 1271 if it meets all of the following criteria:**
 - **(1) HCT/P is minimally manipulated**
 - **(2) HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent**

continued

- (3) Manufacture of HCT/P does not involve the combination of the cell or tissue with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P**

continued

– **(4) Either:**

- **(I) HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or**
- **(ii) HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for:**
 - **(a) autologous use**
 - **(b) allogeneic use in a first-degree or second-degree blood relative, or**
 - **(c) reproductive use**

Minimal Manipulation

- (1) For structural tissue, processing that *does not alter the original relevant characteristics* of the tissue relating to the tissue's *utility* for reconstruction, repair, or replacement; and
- (2) For cells or nonstructural tissues, processing that *does not alter the relevant biological characteristics* of the cells or tissues

Homologous Use

- **The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the *same basic function* or functions in the *recipient* as in the *donor*.**

Statutes that apply to “361” HCT/Ps

- **Section 361 of Public Health Service Act**
- **“The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such *regulations* as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.**

Statutes that apply to “351” HCT/Ps

- **PHS Act—sections 361 and 351**
- **Section 351. Regulation of Biological Products.**
- **(a) No person shall sell, barter, or exchange ..in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus....or analogous product...**

continued

- **applicable to the prevention, treatment, or cure of diseases or injuries of man, unless such product has been propagated or manufactured and prepared at *an establishment holding an unsuspended and unrevoked license*, issued by the Secretary**

continued

- **Federal Food, Drug, and Cosmetic Act**
- **Biological products meet the definition of “drug” in section 201((g)(1)**
- **Interstate commerce**
- **Prohibited acts—(1) adulteration; (2) misbranding; penalties**

Regulations that apply to “361” HCT/Ps

- **21 CFR part 1270 (recovered before 5/25/05)
and 1271 (recovered on or after 5/25/05)**
- **Part 1271**
 - **Subpart A-General Provisions; definitions**
 - **Subpart B-Registration and Listing**
 - **Subpart C-Donor Eligibility**
 - **Subpart D-Current Good Tissue Practice (not repro)**
 - **Subpart E—Additional Requirements: Reporting, Labeling (not repro)**
 - **Subpart F—Inspection and Enforcement**

Regulations that apply to “351” Biological Products that are also HCT/Ps while under IND

- **21 CFR part 1271**
 - **Subpart A**
 - **Subpart B**
 - **Subpart C**
 - **Subpart D—however, for those sections that are subsumed by CGMPs in 210/211, if you comply with CGMPs, you would likely be in compliance with CGTPs.**

INDs

- **21 CFR Part 312—Investigational New Drug Application**
- **21 CFR Parts 210/211—Good Manufacturing Practice and statutory CGMPs (i.e., FDC Act)—to be discussed further in Mary Malarkey’s talks**
- **21 CFR Parts 50 (protection of human subjects) and 56 (institutional review boards)**

Regulations that apply to “351” Licensed Biological Products that are also HCT/Ps

- **21 CFR part 1271**
 - **Subpart A**
 - **Subpart B**
 - **Subpart C**
 - **Subpart D—however, for those sections that are subsumed by CGMPs in 210/211, if you comply with CGMPs, you would likely be in compliance with CGTPs.**

continued

- **21 CFR Part 201—Labeling**
- **21 CFR Part 202—Advertising**
- **21 CFR Part 210/211—Good Manufacturing Practice**
- **21 CFR Part 600—Biological Products; General (includes Reporting of Adverse Experiences and Biological Deviations)**
- **21 CFR Part 601—Licensing**
- **21 CFR 610—General Biologics Standards**

Jurisdictional Recommendations and Decisions

- **Tissue Reference Group (TRG)**
 - Recommendations to Center Directors
 - www.fda.gov/cber/tissue/trgfyrpts.htm
- **Office of Combination Products (OCP)**
 - Request for Designation (RFD)
 - Procedure in 21 CFR Part 3
 - www.fda.gov/oc/combination

Question can be sent to either one. If you disagree with the TRG recommendation, you can then submit an RFD

Example #1—Minimal Manipulation--structural

- **Fascia or dermis processed into particulate form**
- **Allogeneic dehydrated and decellularized amniotic membrane intended for wound covering**
- **Cutting, grinding, shaping of bone**

Example #2—Minimal Manipulation--cell

- **CD 34+ selection of allogeneic peripheral blood hematopoietic stem/progenitor cells**
- **Density gradient separation to remove a particular type of cell from a mixture of cells**

Example #3—More than minimal manipulation-- structural

- **Allogeneic, decellularized human arteries, veins, heart valves, or valve conduits intended to replace dysfunctional cardiovascular tissue**

Example #4—More than minimal manipulation--cell

- **Autologous cultured (expanded ex vivo) epithelial cells isolated from skin biopsies and intended to cover burns**
- **Gene therapy**

Example #5—Homologous use- -structural

- **Demineralized bone matrix used as a void filler during orthopedic surgery**
- **Bone recovered from a limb, used as a bone dowel for spinal surgery**

Example #6—Homologous use- -cell

- **Allogeneic placental/umbilical hematopoietic stem/progenitor cells used for hematopoietic reconstitution**
- **Pancreatic islet cells used for treatment of type 1 diabetes**

Example #7—Non-homologous use--structural

- **Allogeneic veins or arteries intended for use as arteriovenous access (A-V shunts) for hemodialysis**
- **Cartilage tissue used in the bladder for treatment of reflux**

Example #8—Non-homologous use--cell

- **Autologous bone marrow hematopoietic stem/progenitor cells used for myocardial repair**
- **Nasal mucosal cells used to regenerate nerve tissue**

Example #9—Combined with

- **Demineralized bone matrix combined with another article to create a paste or putty used to fill bone defects**
- **Tendon allograft combined with a suture for use in ligament reconstruction**

Example #10—Not combined with

- **Lyophilized pericardium and a vial of saline packaged together in a kit, for reconstitution by the physician**
- **Any HCT/P to which a sterilizing (e.g., antibiotic), preserving (e.g., Optisol), or storage (e.g., DMSO) agent is added**

Questions?

- **Contact information:**
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