Introduction to Cell Therapy Product Regulations

ISCT Somatic Cell Therapy Meeting

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Ellen Lazarus, M.D.

Medical Officer

Division of Human Tissues

Office of Cellular, Tissue, and Gene Therapies
FDA Proposed Approach to regulation of cell and tissue products

- Announced February 1997
- Tiered, risk-based approach addressing a broad range of products
- Level and type of regulation commensurate with the risk posed by the product
- Like products should be treated alike
- FDA exercises regulatory oversight only to degree appropriate to protect public health
FDA Proposed Approach – Three Main Goals

1. Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
2. Prevent improper handling or processing that might contaminate or damage tissues
3. Ensure that clinical safety and effectiveness is demonstrated for most tissues that are highly processed, used for non-natural purposes, combined with non-tissue components, or that have systemic effects
Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
- Musculoskeletal tissue and skin
- Ocular tissue
- Cellular therapy products
  - Hematopoietic stem/progenitor cells
  - Therapeutic cells (DLI)
  - Somatic cells
- Reproductive tissue
- Combination tissue/device; tissue/drug
- Human heart valve allografts
- Human dura mater
FDA Proposed Approach - Excluded Products

- Vascularized organs - HRSA
- Minimally manipulated bone marrow - HRSA
- Xenografts - separate FDA regulatory pathway
- Blood and blood products – separate regulatory pathway (OBRR)
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products used in manufacture
- In vitro diagnostic products
How are cell therapies regulated within this framework?

- Cell therapy products including hematopoietic stem/progenitor cells and somatic cells are “human cells, tissues, or cellular or tissue-based products” (HCT/P)
- Regulations at 21 CFR Part 1271 apply to all HCT/P
- Certain cell therapy products are subject to additional regulation, including CGMP and biological product licensing requirements
Two Regulatory Tiers

- Products regulated solely under HCT/P rules if *ALL* “kick down” factors apply
  - Regulatory authority derived from Section 361 of the PHS Act

- Products regulated under HCT/P rules *AND* premarket review requirements, etc. if product does not meet all “kick down” factors
  - Authority derived from FFDCA and PHS Act, sections 351 and 361
“Kick Down” Factors
21 CFR 1271.10(a)

- Minimally manipulated
- Intended for homologous use only, as reflected by labeling, advertising, or manufacturer’s objective intent
- Not combined with another article
  - Exceptions: sterilizing, preserving, storage agents that do not raise new safety concerns
- Does not have systemic effect
  - Exceptions: autologous use, use in first or second degree blood relative, reproductive use
The “Tissue Rules” apply to all 351 cell therapy products*

<table>
<thead>
<tr>
<th>21 CFR 1271</th>
<th>Covers</th>
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<tbody>
<tr>
<td>Subpart A</td>
<td>Scope; Definitions</td>
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<tr>
<td>Subpart B</td>
<td>Procedures for Registration and Listing</td>
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<tr>
<td>Subpart C</td>
<td>Donor Eligibility</td>
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<td>Subpart D</td>
<td>Current Good Tissue Practices (CGTP)</td>
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<tr>
<td>Subpart E</td>
<td>*Additional Requirements</td>
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<td>Subpart F</td>
<td>*Inspection and Enforcement</td>
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*Subparts E and F only apply to establishments described in 1271.10 (HCT/Ps regulated solely under section 361 of the PHS Act)
Which HPC are also regulated as biological products?

- All allogeneic, unrelated HPC from cord and peripheral blood

- HPC (including bone marrow) that are:
  - More than minimally manipulated
    - Examples: expanded, activated, genetically modified
  - Combined with another article - some exceptions
  - Intended for non-homologous use
    - Example: HPC for cardiac repair
Somatic Cell Therapy Products
Definition

“autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries”*

*October 14, 1993. 58 FR
## Examples of Somatic Cell Therapy Products

<table>
<thead>
<tr>
<th>Cellular product</th>
<th>Tissue source</th>
<th>Function/Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrocytes – more than min. manipulated</td>
<td>Cartilage biopsy</td>
<td>Cartilage repair</td>
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<tr>
<td>Pancreatic islets</td>
<td>Cadaveric donor pancreas</td>
<td>Produce insulin in type I diabetics</td>
</tr>
<tr>
<td>Embryonic stem cells</td>
<td>embryo</td>
<td>Broad potential uses</td>
</tr>
<tr>
<td>Cells combined with biomaterial matrix</td>
<td>Chondrocytes, epithelial cells, fibroblasts; with collagen, etc</td>
<td>Structural repair, etc</td>
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</table>
### Examples of Somatic Cell Therapy Products - continued

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<th>Cellular product</th>
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<th>Function/Use</th>
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</thead>
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<tr>
<td>Tumor Vaccines</td>
<td>Tumor cells or lysates</td>
<td>Elicit immune response to tumor</td>
</tr>
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<td></td>
<td>Antigen presenting cells from PBMC</td>
<td></td>
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<tr>
<td></td>
<td>Antigen-specific immune cells (from PBMC, TIL)</td>
<td>Kill tumor cells, stimulate other cells</td>
</tr>
</tbody>
</table>
Which cell products are currently subject to IND/BLA requirements?

Those that are:
- More than minimally manipulated
- Intended for non-homologous use
- Combined with another article (some exceptions)
Some cell products are subject to phase-in of approval requirements

- Unrelated allogeneic minimally manipulated HPC, A and HPC,C for homologous use are subject to biological product requirements, including licensure

- However, FDA is not currently enforcing IND/BLA requirements for these HPC pending development of a regulatory approach to licensure
Regulations applicable to cell therapy products under IND

- 21 CFR Part 312 - Investigational New Drug (IND) Application
- 21 CFR Parts 210/211 – Current Good Manufacturing Practices and statutory CGMPs (i.e., FDC Act)
- 21 CFR Parts 50 (protection of human subjects) and 56 (institutional review boards)
- 21 CFR Part 1271, subparts A, C and D (registration and listing are not required until products licensed)
Regulations that apply to licensed cell therapy products

- 21 CFR Part 201 - Labeling
- 21 CFR Part 202 - Advertising
- 21 CFR Part 210/211 - CGMP
- 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
- 21 CFR 1271 - Subparts A, B, C and D

- Applies only to unrelated allogeneic minimally manipulated HPC for hematopoietic reconstitution
- Requested submission of comments
  - Establishment controls
  - CMC
  - Processing & product standards

Data received in docket for cord blood - Draft guidance published January 2007
AC meeting March 30, 2007

Evaluating comments and additional data received in docket

When guidance is finalized, will have implementation date

Guidance for Industry

Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFD-400), Food and Drug Administration, 1660 Clifton Road, Room 1028A, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/comments. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturer Assistance (OCTMA-46), 1431 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-427-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact Ellen Laramie, M.D., at 301-427-6031.

U.S. Department of Health and Human Services;
Food and Drug Administration;
Center for Biologics Evaluation and Research;
December 2006.