Current US FDA Regulation of Cell Therapy

Andra Miller, Ph.D.
Director, Cell and Gene Therapies
Biologics Consulting Group
amiller@bcg-usa.com
Overview

- FDA Organization
- HCT/P Definition
- Tissue Rules (TR)
- Products regulated only under TR (1271)
- Products also regulated under IND/BLA
  - Preclinical, Product & Quality Expectations
- New Guidance Documents
FDA Review of Medicinal Products

Public Health Service Act

Food, Drug & Cosmetic Act

CBER
Center for Biologics Evaluation & Research

CDRH
Center for Devices and Radiological Health

CDER
Center for Drug Evaluation & Research
### Center for Biologics Evaluation and Research (CBER)

<table>
<thead>
<tr>
<th>OBRR</th>
<th>OCTGT</th>
<th>OVRR</th>
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</table>
| • Whole blood  
• Blood components  
• Blood fractionation  
• Donor Screening Test Kits | • Human tissues  
• Cellular therapies  
• Gene therapies  
• Combination products  
• Xenotransplantation  
• Devices used for cells & tissues | • Prophylactic vaccines  
• Anti-toxins  
• Allergenics  
• Adjuvants |
Food and Drug Administration: Regulatory Authority

Laws
- Statutes enacted by Congress outlining binding conduct or practice in the community
  - The Public Health Service Act (PHS Act)
    - Sections 351 and 361
  - The Food Drug and Cosmetic Act (FD&C Act)

Regulations
- Interpretation of Laws (21CFR)
  - Rules for daily business, binding like laws
  - Part 1271 Tissue Rules
  - Part 312 INDs
  - Parts 210 and 211 cGMP

Guidance
- Describes agency’s policy and regulatory approach to a specific area or issue
  - Not binding on industry, but usually binding on agency
Regulations for Cell Therapy

Referred to as “Tissue Rules”

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<th>Covers</th>
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<td>Subpart B</td>
<td>Procedures for Registration and Listing</td>
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<td>Subpart C</td>
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<td>Current Good Tissue Practices (cGTP)</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 (regulated solely by the Tissue Rules)
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What are: Human cells, tissues, or cellular or tissue-based products (HCT/Ps)?

• Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
Examples of HCT/Ps:

- Musculoskeletal
- Skin
- Ocular tissue
- Reproductive tissue
- Heart valves
- Dura mater

- Cellular therapies
- Hematopoietic stem/progenitor cells
- Cells + biomaterials
- Autologous manipulated chondrocytes
Not Classified as HCT/Ps

- Vascularized organs for transplant
- Minimally manipulated bone marrow for homologous use
- Cells, tissues, organs derived from other than human (xenografts)
- Blood and Blood Products
- Secreted or extracted products e.g. human milk, collagen, cell factors
- Ancillary products used in manufacture of HCT/P
- In vitro diagnostic products
Framework for Regulation of HCT/P’s

Two options and one exception based on risk presented by product:

1. Regulated Solely by Tissue Rules (361 Products)
2. Higher risk products regulated in addition as drug, device or biologic product (351 Products)
3. Exception
Exception: HCT/Ps not Regulated by U.S. FDA

Autologous cells if cells are obtained and returned to patient during same surgical procedure
21 CFR 1271.15(b)
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# The “Tissue Rules”

<table>
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<tr>
<th>Tissue Rule</th>
<th>Describes</th>
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<td>Establishment Registration and Listing</td>
<td>Which establishments must register and list products; Lists criteria for levels of FDA regulation</td>
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<tr>
<td>Eligibility Determination for Donors</td>
<td>Communicable disease test requirements and medical screening requirements</td>
</tr>
<tr>
<td>Current Good Tissue Practice (GTP)</td>
<td>Handling and process controls to prevent contamination and preserve integrity of cells; requirements for manufacturing</td>
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</table>
Establishment Registration & Listing

- Form FDA 3356
  - Can be done online at: http://www.fda.gov/cber/tissue/tisreg.htm.
- Must register within 5 days after beginning operations or subsequent ownership or location change
- An annual update is required in December
- Changes in HCT/P listing within 6 months of the change
Establishment Registration & Listing

• Establishments that perform donor testing or HCT/P testing must also register even if do not manufacture cells or tissue products

• Establishments that only manufacture HCT/P under an IND or IDE don’t have to register and list until product is approved for commercial use (351 products)

• Foreign establishments importing HCT/Ps into the US must register
## Example of Form 3356

### Establishment Functions
- Recovery
- Test
- Process
- Label
- Screen
- Package
- Store
- Distribute

### Establishment HCT/P Listing

<table>
<thead>
<tr>
<th>Types of HCT/P's</th>
<th>HCT/P's Described in 21 CFR 1271.10</th>
<th>HCT/P's Regulated as Medical Devices, Drugs or Biological Drugs</th>
<th>Proprietary Names</th>
</tr>
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<tbody>
<tr>
<td>a. Bone</td>
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<td>b. Cartilage</td>
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<td>c. Cornea</td>
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<tr>
<td>d. Dura Mater</td>
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<tr>
<td>e. Embryo</td>
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<td>f. Fascia</td>
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<tr>
<td>g. Heart Valve</td>
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<tr>
<td>h. Ligament</td>
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<td></td>
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<tr>
<td>i. Cocyle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j. Pericardium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k. Peripheral Blood Stem Cells</td>
<td>✓</td>
<td>📅 HCT/P's Regulated as Medical Devices, Drugs or Biological Drugs</td>
<td></td>
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<tr>
<td>l. Sclera</td>
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<td>m. Semen</td>
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<tr>
<td>n. Skin</td>
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<tr>
<td>o. Somatic Cells</td>
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<tr>
<td>p. Tendon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q. Umbilical Cord Blood Stem Cells</td>
<td>✓</td>
<td>📅 HCT/P's Regulated as Medical Devices, Drugs or Biological Drugs</td>
<td></td>
</tr>
<tr>
<td>r. Vascular Graft</td>
<td></td>
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<td></td>
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<tr>
<td>s. TC, Apheresis</td>
<td>✗</td>
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Donor Eligibility

• Based on Donor Screening and Donor Testing for relevant communicable disease agents and disease
Donor Screening

• Review relevant medical records for risk factors for, and clinical evidence of:
  – relevant communicable disease agents and diseases;
  – risks associated with xenotransplantation

• Physical exam of donor for signs or symptoms of relevant communicable diseases

• Guidance Document:
  – Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Aug 8, 2007
Donor Testing

Relevant communicable disease agents or diseases

• All HCT/P Donors:
  – Human immunodeficiency virus, type 1 and type 2
  – Hepatitis B and C viruses
  – Treponema pallidum

• Viable leukocyte rich HCT/P, in addition to above:
  – Human T-lymphotropic virus, type I and type II
  – CMV

• Reproductive tissue, in addition to above:
  – Chlamydia trachomatis
  – Neisseria gonorrhea

• Additional relevant diseases:
  – West Nile Virus
  – Sepsis (screening only)
  – Vaccinia
GTP Requirements

- Govern the methods, the facilities and controls used for the manufacture of HCT/Ps
  - Prevent introduction, transmission and spread of infectious disease
  - Prevent mix-ups and cross-contamination
  - All steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution
  - Narrower focus than GMPs
GTP Requirements

• GTP’s ensure that the HCT/P do not:
  – Contain communicable disease agents
  – Are not contaminated and
  – Don’t become contaminated during manufacture
GTP Requirements

- Donor Screening & Testing
- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- Facilities
- Environmental Control and Monitoring
- Equipment
- Supplies/Reagents
- Recovery

- Processing and Process Controls
- Process Changes
- Process Validation
- Labeling Controls
- Storage
- Receipt, Pre-Distribution Shipment, Distribution
- Records
- Tracking
- Complaint File

= Core cGTPs
How to Comply with GTPs

- Register Establishment & List HCT/Ps
- Perform Donor Screening & Testing as applicable
- Ensure manufacturing facility and quality system address GTPs
- U.S. FDA verifies compliance by inspection as necessary
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Two Regulatory Tiers

- Tissue Rules
- Good Tissue Practices (GTP)
- Safety and Efficacy (IND/BLA)
- Good Manufacturing Practices (GMP)

U.S. FDA Regulatory Requirements

Risk

Low

High
Regulatory Requirements

• For HCT/Ps regulated only under Tissue Rules
  – No clinical safety or efficacy studies required
  – No premarket approval (BLA)
  – Emphasis is on preventing transmission or introduction of disease
  – An establishment must follow all of the cGTP requirements applicable to the operations that it performs
Classification as Lower Risk

- For a lower level of regulation, HCT/P must meet all the specified criteria
  - If ‘yes’ to all criteria: regulated under TR
  - No: clinical studies for safety and efficacy (IND)
  - No: premarket approval (BLA)
4 Criteria for Lower Level of HCT/P Regulation

The cells/tissues are:

1. Not more than minimal manipulation
2. Not combined with another article – drug, device, biologic or tissue
3. Intended for homologous clinical use
4. Primary function in recipient is not systemic or dependent upon the metabolic activity of the cells – Unless for autologous or family-related, or reproductive uses
Two Regulatory Tiers

- Tissue Rules
- Good Tissue Practices (GTP)

- Safety and Efficacy (IND/BLA)
- Good Manufacturing Practices (GMP)

U.S. FDA Regulatory Requirements

Risks:
- Tissue Rules
  - Good Tissue Practices (GTP)
- Meet Criteria
- Fail Criteria
Definition of HCT/P Terms

• Minimal manipulation
  – What it is
  – What it is not

• Homologous use
  – What it is
  – What it is not
Minimal Manipulation - Defined

• 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

• For **cells or nonstructural tissues**, processing that does not alter the relevant biological characteristics of cells or tissues.
Minimal Manipulation – Examples
Structural

• Fascia or dermis processed into particulate form
• Dehydrated and decellularized amniotic membrane intended for wound covering
• Cutting, grinding, shaping of bone
Minimal Manipulation – Examples Non-structural

• CD 34+ selection of peripheral blood stem cells (PBSCs)
• Density gradient separation to remove a particular type of cell from a mixture of cells
Not Minimal Manipulation –
Examples

• Decellularization of human arteries, veins, heart valves, or valve conduits
  – Regulated as medical devices
• Dehydrated and decellularized amniotic membrane intended for wound healing
• Culture expansion of cells
  – Autologous or allogeneic
• Genetic modification of cells
Homologous Use - Defined

• 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.
Homologous Use - Examples

• Demineralized bone matrix used as a void filler during orthopedic surgery
• Bone recovered from a limb, used as a bone dowel for spinal surgery
• Allogeneic cord blood used for hematopoietic reconstitution
• Pancreatic islet cells used for treatment of type 1 diabetes
Non-Homologous Use - Examples

• 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
• Autologous bone marrow cells used for myocardial repair
• Nasal mucosal cells used to regenerate nerve tissue
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Which HCT/Ps are also Regulated as Biological Products?

• More than minimally manipulated
  – Examples: Cells/tissues from human organs that have been expanded or activated (islets, hepatocytes)

• Genetically modified cells

• Intended for Non-homologous use
  – Example: HPC for cardiac repair

• Combined with another article
  – Examples: drugs, devices “Combination Products”
## Examples of HCT/P Also Regulated as Biological Products

<table>
<thead>
<tr>
<th>Cellular Product</th>
<th>Tissue Source</th>
<th>Function/Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrocytes more than MM</td>
<td>Cartilage biopsy</td>
<td>Cartilage repair</td>
</tr>
<tr>
<td>Pancreatic islets- more than MM</td>
<td>Cadaveric donor pancreas</td>
<td>Produce insulin in type 1 diabetics</td>
</tr>
<tr>
<td>Cells combined with biomaterial matrix \ (Combination Product)</td>
<td>Chondrocytes, epithelial cells, fibroblasts (with collagen matrix)</td>
<td>Structural repair</td>
</tr>
<tr>
<td>HPC</td>
<td>BM, cord or peripheral blood</td>
<td>• Allogeneic, unrelated transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Expanded, activated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gene modified</td>
</tr>
<tr>
<td>Gene modified smooth muscles cells</td>
<td>Vein segment</td>
<td>Angiogenesis</td>
</tr>
</tbody>
</table>
HCT/P Also Regulated as Biological Products

- Require pre-market approval by US FDA
- Data are submitted in a Biologics License Application (BLA)
- Approval based on data from US (IND) or foreign studies that are:
  - Well designed
  - Performed by qualified investigators
  - Conducted in accordance with ethical principles
- Data must demonstrate safety & efficacy
Investigational New Drug (IND) Application

• An application to test an unapproved drug or biologic in human clinical trials

• Three IND phases:
  – Phase I- initial introduction to humans, primary objective is safety
  – Phase II- optimize dose, route, regimen, patient population and endpoints, controlled
  – Phase III- pivotal safety and efficacy, randomized, controlled, support labeling claims
Investigational New Drug (IND) Application

• The IND must provide:
  – Preclinical Pharmacology/Toxicology data
  – Manufacturing description and product safety & characterization data
  – Clinical protocol and investigator information
Biological Product Development Process

Research → Non-clinical → IND → BLA → Approval

Phase I, II, III

Product/process
Non-clinical studies → Clinical studies
Non-clinical Studies Expectations

Support the safety and rationale for use of the product in humans

- **Efficacy/ Proof-of-concept**
  - Demonstrate ability to correct or alleviate target disease in relevant model

- **Safety/Toxicology**
  - Potential for adverse events
  - Escalating doses (MTD)
  - Delivery method

- Design of Non-clinical program based on clinical expectations
- GLP or “spirit of GLP”
Non-clinical Studies Expectations

• Cell Fate Post-transplant
  – Tumorigenicity
  – Cell migration and trafficking
  – Cellular differentiation
  – Persistence and cell survival
Manufacturing and Product Testing Expectations

- **Product Safety Testing**
  - Sterility, mycoplasma, endotoxin, adventitious virus
  - Must be assessed at all stages of product development

- **Product Characterization**
  - Purity, viability, identity, potency
  - Step-wise approach applies

- **Manufacture under GMP / GTP**

- **Process Control and Consistency**
  - Demonstrated based on accumulating data from product testing
HCT/P Lot Release Challenges

• Sterility
  – Result not available prior to release. Release based on 48-72 assay results & negative Gram Stain. May still need to obtain post-release results on sample of final product. Rapid test methods

• Mycoplasma
  – Result not available prior to release. May need to develop alternative test methods or procedures (PCR)

• Purity
  – Endotoxin/pyrogenicity - results typically obtained prior to release (LAL)

• Potency
  – Often a single quantitative assay is not possible for a cell product. Matrix of qualitative and quantitative assays can be used.
HCT/P Lot Release Challenges

• Identity
  – Assays should be product specific and may include phenotypic markers, morphology, specific staining

• Viability
  – Function of product depends upon living cells; recommend at least 70% viability

• When final lot release results are not available prior to use, in-process testing will be critical and may need to examine product after use to verify safety, function, performance, etc.
Quality Expectations

• GCP, GLP, GMP, GTP provide the framework (controls) for conduct of high quality:
  – Research
  – Pre-clinical safety studies
  – Product manufacture
  – Clinical trials
GCP, GLP, GMP/GTP

- Principles apply to the entire product/clinical development process
- For GMP level of compliance increases with phase of study
- For GTP 100% compliance is expected prior to manufacture
- Ensure integrity and quality of data/ product
- Very important for all:
  - DOCUMENTATION !!
GCP, GLP, GMP/GTP

• Good Clinical Practice (ICH E6)
  – Applies to design, conduct and reporting of clinical trials

• Good Laboratory Practice
  – Applies to nonclinical laboratory studies that are intended to support an investigational or marketing permit
  – Not to manufacturing or quality of test material used in preclinical studies
    • GMP not GLP
GCP, GLP, GMP/GTP

• **Good Manufacturing Practice**
  – Applies to the manufacturing process and the facility for HCT/P regulated as biological products, QC activities

• **Good Tissue Practice**
  – Applies to all human cellular and tissue-based products
  – Supplements but does not supersede GMPs
Quality Expectations for Biologics

Research → Non-clinical → IND → BLA → Approval

Phase I, II, III Clinical studies

GLP

GCP

GMP/GTP
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CBER Guidelines

- http://www.fda.gov/cber/guidelines.htm
- Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide August 2007
- Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs) July 2007
- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
Summary

• HCT/P are regulated under 21 CFR 1271, referred to as Tissue Rules
• Tissue rules consist of instructions for:
  – Establishment Registration
  – Donor Eligibility
  – Good Tissue Practices
• 4 criteria define the level of potential product risk
• Low risk products follow TR only
• Higher risk products follow TR + Biologics Regulations (IND/BLA, GMP)