FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Laura M. St. Martin, M.D., M.P.H.
Medical Officer, Division of Human Tissues
FDA/CBER/OCTGT
Division of Human Tissues

March 12, 2008

SCOPE OF TALK

- History of Tissue Regulation
- What are HCT/Ps
- Tissue Rules—Registration, DE, CGTP
- 351 vs. 361 Tissues

HISTORY OF TISSUE REGULATION

Brief History of Tissue Regulation

- Interim final rule, Human Tissues Intended for Transplantation—Published December 1993, Finalized July 1997 (21 CFR Part 1270)
  - First tissue rule; in response to infectious disease concerns
  - Donor suitability
  - Covered limited scope of tissues and diseases
- Legal Authority: Section 361 of Public Health Service (PHS) Act—prevent the introduction, transmission, or spread of communicable diseases

Brief History of Tissue Regulation (cont.)

- Proposed Approach to Regulation of Human Cells and Tissues—February 1997
  - Tiered risk-based approach
  - Broad scope of cells and tissues
- 21 CFR Part 1271 (current tissue rules)
  - Establishment Registration and Product Listing
  - Donor Eligibility
  - Current Good Tissue Practice

The “Tissue Rules”
(21 CFR 1271, Effective May 25, 2005)

Tissue Rule	Issues Addressed
Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing products
Donor Eligibility	Requirements for donor screening and testing for “relevant communicable disease agents and diseases”
Current Good Tissue Practice (CGTP)	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents; reporting; inspections

21 CFR Part 1271

- These three rules form the platform for regulation of all human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- For certain HCT/Ps (“361 HCT/Ps”), the new regulations comprise the sole regulatory requirements
- For HCT/Ps regulated as drugs, devices, and/or biological products, the new tissue regulations supplement other requirements (GMP/QSR)

HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/Ps)

“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

What is Included? Examples of HCT/Ps

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/device and other combination therapies

Not Included

- Vascularized human organs
- Minimally manipulated bone marrow
- Xenografts
- Blood products
- Secreted or extracted products; e.g., human milk, collagen, cell factors
- Ancillary products used in manufacture
- *In vitro* diagnostic products
- Blood vessels recovered with organs for use in organ transplantation

Federal Regulatory Responsibility

Government Agency	Products
Food and Drug Administration (Center for Biologics)	Blood and Blood Products Cellular Therapeutics Tissues Tissue Engineered Products Xenografts Gene Therapies Vaccines
Health Resources and Services Administration	•Bone Marrow for homologous use •Vascularized Human Organs •Blood Vessels recovered with organs •Cord Blood registry

Regulatory Framework
Goals

- Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
- Prevent improper handling or processing that might contaminate or damage tissues
- Ensure that clinical safety and effectiveness are demonstrated for cells and tissues that are highly processed, used for purposes other than replacement, combined with non-tissue components, or that have systemic effects

Regulatory Framework
Guiding Principles

- Risk-based approach includes a broad range of products
- The level and type of regulation is commensurate with the risk posed by the product characteristic
- Like products are treated alike
- FDA exercises regulatory oversight only to the degree appropriate to protect the public health

21 CFR Part 1271

- Subpart A—General Provisions
- Subpart B—Procedures for Registration and Listing
- Subpart C—Donor Eligibility
- Subpart D—Current Good Tissue Practice
- Subpart E—Additional Requirements for Establishments Described in 1271.10
- Subpart F—Inspection and Enforcement of Establishments Described in 1271.10

REGISTRATIONS FINAL RULE (SUBPARTS A and B)

Subpart A – General Provisions
Subpart B – Procedures for Registration and Listing

- Provides purpose and scope for all parts of the regulation
- Includes important definitions
- Includes criteria that need to be met to be regulated without pre-market approval
- Includes exceptions
- Procedures for registration and listing

Establishment Registration and Listing

- Any establishment that manufactures HCT/Ps must
  - Register and submit a list of every HCT/P it manufactures within 5 days of beginning operation
  - Re-register annually
  - Update if change in location or ownership
- All foreign establishments importing HCT/Ps to the US must register and list such HCT/Ps

Definition—Manufacture

- Manufacture means any or all steps in the recovery, processing, storage, labeling, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor

Establishment Registration and Listing (cont.)

- Establishment registration is not a pre-market review program
  - An establishment may begin to market its product once it registers (for 361 HCT/Ps)
  - There are periodic inspections, but distribution may begin before the establishment is inspected

Does my hospital have to register if…

- we only store HCT/Ps used for non-clinical scientific research?
  - No [21 CFR 1271.15(a)]
- surgeons at our hospital remove and re-implant tissue from the same individual, during the same surgical procedure?
  - No [21 CFR 1271.15(b)]
- we receive and store HCT/Ps only for use in our facility?
  - No [21 CFR 1271.15(d)]

Does my hospital have to register if…

- my hospital routinely sends tissue in our inventory to another hospital for use at that hospital?
  - Yes. You would be engaged in distribution, which is considered a part of manufacturing [21 CFR 1271.3(e)].
  - If a hospital sends tissue for use at another physical location or building that is not on the same campus, even if under the same management, that establishment is considered a distributor and must register.

Does my hospital have to register if…

- we store autologous calvarium sections (bone flaps) for possible future re-implantation?
  - No, as long as no further manufacturing occurs [21 CFR 1271.3(e)].
  - If you send the autologous tissue to another facility for storage prior to re-implantation at your facility, you do not have to register. However, the storage facility has to register.
  - If you send the autologous tissue to another hospital for re-implantation, this is distribution, and your hospital must register

DONOR ELIGIBILITY FINAL RULE (SUBPART C)

Subpart C – Donor Eligibility

- Requirements are a component of CGTP
- A donor-eligibility determination, based on donor screening and testing for relevant communicable disease agents and diseases, is required for all donors of HCT/Ps, with some exceptions*
- HCT/P must not be administered until the donor has been determined to be eligible, with some exceptions

DE Determination—Exceptions

- DE determination not required for
  - Cells and tissues for autologous use
  - Reproductive cells or tissues from sexually intimate partner
  - Certain cryopreserved reproductive cells or tissues
- Required labeling (as applicable)
  - “FOR AUTOLOGOUS USE ONLY ”
  - “NOT EVALUATED FOR INFECTIOUS SUBSTANCES”
  - “WARNING: Advise recipient of communicable disease risk”
  - Biohazard legend
  - “WARNING: Reactive test results for [name of RCDAD]

Determination of Donor Eligibility

- Made by a responsible person
- Based upon donor screening and testing for relevant communicable disease agents/diseases
- Donor is eligible if:
  - Donor screening indicates that donor is free from risk factors for, and clinical evidence of, relevant communicable diseases, and is free from communicable disease risks of xenotransplantation
  - Donor testing is negative or nonreactive

Relevant Communicable Disease Agent or Disease

- Risk of transmission by HCT/P because agent/disease is:
  - Potentially transmissible *and*
  - Either sufficient incidence/prevalence among potential donors, *or*
  - May have been released accidentally or intentionally in a manner that could place potential donors at risk of infection
- Significant health risk—morbidity/mortality
- Appropriate screening measures and/or screening test available

Relevant Communicable Disease Agent or Disease

- For all HCT/Ps:
  - HIV-1 and 2
  - HBV
  - HCV
  - Human transmissible spongiform encephalopathy (CJD)
  - *Treponema pallidum*
- For viable, leukocyte-rich cells/tissues:
  - HTLV I and II
- For reproductive cells/tissues:
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhea*

Additional RCDADs

- Listed in Donor Eligibility Guidance published February 27, 2007
  - West Nile Virus
  - Sepsis
  - Vaccinia
- FDA will add to list if an infectious disease meets definition of “relevant communicable disease” under 1271.3(r)(2)

Records to accompany HCT/P after DE determination is complete

- Distinct donor identification code (no personal identifying information)
  - Exception: Directed repro donor or blood relative
- Statement whether donor has been determined to be eligible or ineligible, based upon the results of screening and testing
- Summary of records used to make DE determination

Before DE determination is complete

- HCT/P kept in quarantine
- HCT/P may be shipped in quarantine, if clearly identified and accompanied by records:
  - Identifying the donor by distinct ID code
  - Stating that DE determination not completed
  - Stating that HCT/P must not be administered until DE determination complete unless documented urgent medical need

Definitions

- *QUARANTINE* – storage or identification of HCT/P to prevent improper release, in a physically separate area or through other procedures (e.g., automated designation)
- *URGENT MEDICAL NEED* – no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P

HCT/P from a donor determined to be ineligible

- Storage: Must store in a physically separate area or follow other procedures that prevent improper release, such as automated designation, until destruction or other disposition, e.g. nonclinical use
- Limited uses
  - Allogeneic use in a first or second-degree blood relative
  - Reproductive HCT/P from a directed reproductive donor
  - Documented urgent medical need

HCT/P from an ineligible donor – labeling and records

- Special labeling
  - Biohazard legend
  - “WARNING: Advise recipient of communicable disease risks”
  - “WARNING: Reactive test results for [name of RCDAD]” (if applicable)
- Accompanied by records of testing
- Notify physician using the HCT/P of results of donor screening and testing

CURRENT GOOD TISSUE PRACTICE FINAL RULE (SUBPARTS D, E, F)

Subpart D – Current Good Tissue Practice

- Methods, facilities, and controls for manufacturing to prevent communicable disease transmission
- Broad goals applicable to the wide range of HCT/Ps
- Establishments have the flexibility to determine how to meet goals through SOPs
- Narrower in scope than GMPs
- Requires a quality program to prevent, detect, and correct deficiencies that could increase communicable disease risk

Current Good Tissue Practice

- Recover, process, store, label, package, and distribute HCT/Ps, and screen/test donors, to prevent introduction, transmission, and spread of communicable disease
- Communicable diseases include viruses, bacteria, fungi, parasites, and TSE agents

Core CGTPs

- Requirements most directly related to preventing introduction/transmission/spread of communicable disease
- Certain requirements (e.g., records management system) limited in applicability to core CGTPs

Requirements

- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- ***Facilities***
- ***Environmental Control*** and Monitoring
- ***Equipment***
- ***Supplies and Reagents***
- ***Recovery***
- ***Processing and Process Controls***
- Process Changes
- Process Validation
- ***Labeling Controls***

Requirements (continued)

- ***Storage***
- ***Receipt, Pre-distribution Shipment, and Distribution***
- Records
- Tracking
- Complaint File
- ***Donor eligibility determinations***

Tracking of HCT/Ps (21 CFR 1271.290)

- Manufacturer is required to:
  - Establish and maintain a system to track each HCT/P
  - Inform consignee of the tracking system it has established
- Distinct HCT/P identification code

Blood Bank—Potential Role

- Blood bank sometimes is responsible for tissue hospital receives from tissue bank
- Hospital can facilitate investigation and/or recall if:
  - Returns implant card
  - Keeps record of:
    - Tissue identification code
    - Source tissue bank
    - Type of tissue
    - Surgeon’s name
    - Patient identification

Compliance with Parts 210, 211, and 820

- For HCT/Ps that are also drugs, biological products, or devices, CGTPs supplement, but do not supercede, GMP and QSR regulations
- In the event of a conflict, the regulations more specifically applicable to the product in question will supercede the more general

Subpart E – Additional Requirements

for Establishments Described in Sec. 1271.10

- Applicable to non-reproductive HCT/Ps that are regulated solely under Part 1271
- Reporting
- Labeling

Adverse Reaction Reports (21 CFR 1271.350)

- Manufacturers must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution
- Manufacturers must report to FDA an adverse reaction involving a communicable disease if
  - Fatal
  - Life-threatening
  - Permanent damage
  - Necessitates medical or surgical intervention

FDA's Reporting Requirements

- *Adverse reaction* means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response
- To report adverse reactions, manufacturers must submit a MedWatch 3500A to FDA within 15 days of receipt of information
- And submit follow-up MedWatch report within 15 days of receipt of new information from the investigation

Reports of HCT/P Deviations

- Investigate all deviations related to a distributed HCT/P
- Report deviations relating to core CGTP
- Report within 45 days of discovery using Form FDA-3486
- Reports include information on follow-up actions

Labeling

- Information on HCT/P label
  - Distinct ID code
  - Description of the type of HCT/P
  - Expiration date, if any
  - Required warnings, if applicable
- Information on either label or package insert
  - Name and address of establishment that makes the HCT/P available for distribution
  - Storage temperature
  - Other warnings, where appropriate
  - Instructions for use related to prevention of transmission of communicable disease

Subpart F – Inspection and Enforcement
of Establishments Described in Sec. 1271.10

- Applicable to all HCT/Ps regulated solely under Part 1271
- Inspections
- Import
- Orders of retention, recall, destruction, and cessation of manufacturing

Inspections

- FDA representative may inspect establishments, including facilities under contract, at any reasonable time and in reasonable manner
- With or without prior notice
- Frequency of inspection at FDA’s discretion
- Seek the most responsible person available
- May question personnel
- May take samples, review and copy records

Imports

- Importer must notify FDA
- Importer must hold the HCT/P intact
- May be transported under quarantine to consignee before admissibility decision
- Does not apply to reproductive HCT/Ps and to peripheral blood stem/progenitor cells regulated solely under section 361

Enforcement Orders

- FDA may order retention, recall, destruction, or cessation of manufacturing
- Establishments may request a hearing under Part 16
- FDA will not issue order of destruction for reproductive tissue

“361” vs. “351” HCT/Ps OVERVIEW

“361” HCT/Ps

- Regulated solely under 361 of PHS Act
- 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/Ps

- 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 Part 1271.10—Criteria for Regulation Solely Under 361 of the PHS Act

- Minimally manipulated
- Intended for homologous use
- Not combined with another article; and
- No systemic effect and not dependent on metabolic activity of living cells
  - Exceptions: autologous use; use in a first- or second-degree blood relative; or reproductive use

Minimal Manipulation

- 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
- 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…

Statutes that apply to “351” HCT/Ps (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

Statutes that apply to “351” HCT/Ps (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)
- 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.

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

Information Available

- Website at www.fda.gov/cber/tiss.htm
  - Published documents
  - Registration information – including Form 3356 and electronic access
  - E-mail address for registration questions tissuereg@cber.fda.gov
  - Links to BPD Reporting and Adverse Reactions Reporting Guidance

CBER INFORMATION

- Web site
  - http://www.fda.gov/cber
- E-mail
  - Manufacturers: matt@cber.fda.gov
  - Consumers, health care: octma@cber.fda.gov
- Phone
  - 301-827-1800