U.S. Food and Drug Administration Regulation of Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/Ps)

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Tissue Rules

Brief History of Tissue Regulation

- First tissue rule published in December 1993 in response to infectious disease concerns
- Legal Authority: Section 361 of Public Health Service (PHS) Act—prevent the introduction, transmission, or spread of communicable diseases
- Approach to regulation of Human Cells, Tissues, or Cellular or Tissue-Based Products (HCT/P)
  - Tiered risk-based approach
  - Broad scope of cells and tissues
  - Implemented through rulemaking

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, are not contaminated, and do not become contaminated

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 (minimally manipulated) ▪Vascularized Human Organs ▪Cord blood registry

Human Cells, Tissues, or Cellular or 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?

Human Cells, Tissues or Cellular or Tissue-Based Products (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

Establishment Registration and Product Listing

Establishment Registration and Listing

- Any establishment that manufactures HCT/Ps must register with FDA and submit a list of every HCT/P it manufactures
  - Manufacture = 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
- All foreign establishments importing HCT/Ps to the US must register and list such HCT/Ps

Establishment Registration and Listing (cont.)

- Establishment registration is not a pre-market review program
  - You may begin to market your product once you register
  - There are periodic inspections, but distribution may begin before you are 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.

Donor Eligibility

Donor Eligibility Rules and Guidance for HCT/Ps Recovered on or After May 25, 2005

- Donor Eligibility Final Rule (21 CFR Part 1271, Subpart C)
  - Published 1999; Final 2004; Effective May 25, 2005
- Guidance for Industry: Eligibility Determination for Donors of HCT/Ps
  - Published February 27, 2007; Implementation by August 27, 2007
  - Finalizes Draft Donor Eligibility Guidance published May 2004 and Draft CJD/vCJD Guidance published June 2002

Donor Eligibility Requirement

- 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 (e.g., autologous use)

Determination of Donor Eligibility

- 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, and
  - Donor testing is negative or nonreactive

Relevant Communicable Disease Agent or Disease

- Two groups of Relevant Communicable Disease Agents or Diseases :
  - Those that are specifically listed in the tissue rule
  - Those that meet certain criteria and may be added later through guidance

Specific Relevant Communicable Disease Agents or Diseases

- For all human cells and tissues:
  - HIV-1 and 2
  - Hepatitis B
  - Hepatitis C
  - Human TSE, including CJD
  - Treponema pallidum
- For viable, leukocyte-rich cells, also:
  - HTLV-I and II
- For reproductive cells or tissues, also:
  - Chlamydia trachomatis
  - Neisseria gonorrhea

Other Relevant Communicable Disease Agents or Diseases—Criteria

- Risk of transmission by HCT/P
  - Potential for transmission *and*
  - Sufficient incidence/prevalence, or risk of infection among potential donors
- Significant health risk—morbidity/mortality
- Appropriate screening measures and/or screening test available

Additional Relevant Communicable Disease Agents or Diseases

- Listed in the Donor Eligibility Guidance published February 27, 2007
  - West Nile Virus
  - Sepsis
  - Vaccinia

Adverse Reaction Reporting and Investigation

What is an Adverse Reaction? [21 CFR 1271.3(y)]

- a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response

FDA's Reporting Requirement [21 CFR Part 1271.350)]

- Manufacturers must ***investigate:***
  - ***Any*** adverse reaction involving a ***communicable disease*** related to an HCT/P that they made available for distribution.
- Manufacturers must ***report*** to FDA (Form **FDA 3500A**):
  - An adverse reaction involving a communicable disease if it:
    - Is fatal
    - Is life-threatening
    - Results in permanent impairment of function or permanent damage to body structure; or
    - Necessitates medical or surgical intervention

Voluntary Reporting of Adverse Reactions to FDA

- FDA encourages voluntary reporting of adverse reactions
- If you are a **Voluntary** reporter (e.g. healthcare professional, end user):
  - Use Form **FDA 3500**
  - Also promptly report to HCT/P establishment

What Happens to Adverse Reaction Reports Submitted to FDA?

- FDA's Tissue Safety Team (TST) receives and reviews each report
- Conducts follow-up investigation
  - May contact manufacturer
    - Processing records/cultures reports, environmental records, donor records/autopsy reports
  - May contact hospital and/or clinician
    - hospital infectious disease surveillance, pre-implant cultures, recipient's medical history and clinical course
- May collaborate with CDC
  - Laboratory testing of retained samples, tracing of donors and recipients

Potential Actions

- Close case if no further action indicated
- Notification of consignees
- Recall
- Regulatory action (Order of retention, recall, destruction, and cessation of manufacturing)
- Public notification; press release
- Enforcement activities to assure that the manufacturer carries out corrective actions

Product Recall and Withdrawal

What is a recall? [21 CFR 7.3(g)]

- **Recall** means a firm's removal or correction of a product that FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure.
  - **Correction** includes patient monitoring, without removal of the product [21 CFR 7.3(h)]
- The **recalling firm** is the firm that initiates a recall, or in the case of a FDA-requested recall, the firm that has the primary responsibility for the manufacture and marketing of the product.

What is a market withdrawal? [21 CFR 7.3(j)]

- Market withdrawal means a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation.
- FDA determines when a firm's action is a recall and when it is a withdrawal.

What should I do when one of our tissue suppliers notifies us of a recall or market withdrawal?

- Follow the tissue supplier's instructions for quarantine and return of unused tissue.
- Provide the tissue supplier with information about the disposition of all affected tissue.
- The tissue supplier may recommend that you (the transplant facility) identify which patient(s) received affected tissue and notify their transplant physician(s) of the recall.
- Communicate any recipient adverse reaction information that becomes available to you to the tissue supplier.

Tracking of HCT/Ps

Tracking of HCT/Ps (21 CFR 1271.290)

- If you perform any step in the manufacture of an HCT/P, you must track each HCT/P
- Distinct HCT/P identification code
- Tracking from consignee to donor
- Tracking from donor to consignee or final disposition

FDA Rules and The Joint Commission Standards

FDA & The Joint Commission—Complementary Requirements

- FDA requires manufacturer to report adverse reactions to FDA; TJC requires organization to report to source facility
- FDA requires manufacturer to investigate adverse reactions; TJC requires organization to investigate
- FDA requires tracking to consignee; TJC requires tracking to recipient

Current Activities and Future Opportunities

Current Activities

- Human Tissue Task Force (HTTF)
  - recent release of report with recommendations
- MedSun Tissue and Cell Pilot Project
  - surveillance for tissue & cell transplant adverse events
  - >50 hospitals, >100 hospital personnel trained
- Transplantation Transmission Sentinel Network (TTSN)
  - Tissue and organ common donor ID, adverse event reporting
- Collaboration with HRSA
  - Advisory Committee on Organ Transplantation, policy issues
- PHS Advisory Committee on Blood Safety and Availability
  - Expansion of Charter, includes tissues and organs
  - Biovigilance focus

Future Goals

- Enhance processes for adverse reaction report investigation and evaluation
- Expand MedSun Tissue Pilot Project
- Increase collaboration with professional organizations and State public health authorities
- Improve outreach to consumers and health care providers
  - Encourage reporting, educate on tissue safety

Helpful Websites

- www.fda.gov/cber/tiss.htm
- www.fda.gov/cber/regsopp/8508.htm
- www.fda.gov/medwatch

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