Alternative Regulatory Framework for FMT: transplantation and implantation of human cells, tissues and cellular and tissue-based products (HCT/Ps)

Microbiota Transplantation: Recommendations for a Regulatory Framework
Working Group Meeting #1
December 4, 2015
University of Maryland Carey School of Law, Baltimore

Scott A. Brubaker, CTBS
Senior Vice President, Policy
Overview

- Federal regulatory framework for HCT/Ps
- Current Good Tissue Practice
  - Donor eligibility
- Designation & review of an HCT/P
- Draft and Final Guidance Documents of interest
HCT/P -- Definition

• *Human cells, tissues, or cellular and tissue-based products (HCT/Ps)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient … (21 CFR 1271.3(d)(2))
Biological Product -- Definition

• *Biological Product* means a virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product... applicable to the prevention, treatment, or cure of a disease or condition of human beings. (42 U.S.C. 262)

• Biological products are not manufactured to specifications
  – Need to pay careful attention to the entire process, including source, derivation, and facilities

*Information courtesy of Jill Hartzler Warner, J.D.*
FDA’s (Proposed) Approach to Regulate Cell & Tissue Products

- Announced February 1997
- Risk-based approach to include a broad range of products
- The level and type of regulation should be commensurate with the risk posed by the product characteristic
- Like products should be treated alike
- FDA should exercise regulatory oversight only to the degree appropriate to protect public health
- Areas of regulatory concerns
  - Prevent transmission of communicable disease
  - Safe processing & handling
  - Clinical safety & effectiveness, where appropriate
  - Promotional claims
  - Monitoring industry

Information courtesy of Jill Hartzler Warner, J.D.
Federal Regulations

• United States Congress
  – Enact laws and publish in the US Code
• Department of Health and Human Services (HHS)
• Food & Drug Administration (FDA)
  – Promulgate regulations via Rules and Guidance and publish in the Code of Federal Regulations
    • Proposed Rules and draft Guidance are issued for public comment before Final versions published
• Centers for Disease Control & Prevention (CDC)
  – Publish recommendations (not “regulations”)

[168x456]Federal Regulations
[34x380]•
[66x344]–
[89x199]•
[669x20]6
FDA’s Statutory Authorities

- Public Health Service Act, Section 351
  - Biological products must be shown to be safe, pure, and potent

- Federal Food, Drug, and Cosmetic Act, Section 201 (aka “FD&C Act”)
  - Drugs (including biological products) and devices must be shown to be safe and effective

- Public Health Service Act, Section 361
  - Prevention of the spread of communicable disease
Regulations and Guidance

• Code of Federal Regulations
  – FDA promulgates regulations to implement the statutes
  – Regulations have the force of law
  – FDA regulations are contained in Title 21

• Guidance
  – FDA issues guidance documents to interpret regulations or provide recommendations
  – Guidance is non-binding
  – Alternative approaches may be used if they meet the requirements of statutes and regulations

Slide courtesy of Jill Hartzler Warner, J.D.
FDA Oversight: Tissues & Cells

• Center for Biologics Evaluation and Research (CBER)
  – Office of Cellular, Tissue and Gene Therapies
    • Division of Human Tissues
    • Division of Cell and Gene Therapies
    • Division of Clinical Evaluation and Pharmacology/Toxicology
  – Office of Compliance and Biologics Quality
    • Division of Inspections and Surveillance
• Center for Devices and Radiological Health (CDRH)
  – Office of Device Evaluation
• Center for Drug Evaluation and Research (CDER)

Office of the Commissioner Office of Combination Products
FDA/CBER Regulation

Subparts (Final Rules) issued between 2001 - 2011

- 21 CFR Part 1271 – Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)
  (Intended for Implantation, Transplantation, Infusion or Transfer)
  - Subpart A – Scope, Purpose & Definitions (2001)
  - Subpart B – Establishment Registration & Product Listing (2001)
  - Subpart C – Eligibility Determination for Donors of HCT/Ps
    • + Final Guidance Document (2007)
  - Subpart D – Current Good Tissue Practice (CGTP)
    • + Final Guidance Document (2011)
  - Subpart E – Additional Requirements – Labeling & Reporting
  - Subpart F – Inspection

Subparts C, D, E, and F issued 2004 w/Effective date: May 25, 2005
“Manufacture HCT/Ps”

Definition found at §1271.3(e)

• “Manufacture” is a term that captures the many different functions that cell & tissue establishments might take in preparing cells & tissues for clinical use. Steps include:
  – Donor: screening & testing
  – HCT/P: recovery, processing, storage, packaging, labeling and/or distribution
A potentially infectious microorganism, virus, or other disease agent that may pose a risk of transmission to recipients of, or those who come in contact with, HCT/Ps. These disease agents/diseases:

1) have sufficient incidence and/or prevalence to affect the potential donor population;

2) could be fatal, life-threatening, result in permanent impairment, or necessitate medical or surgical intervention to preclude permanent impairment; and, 

3) for which appropriate screening measures have been developed or an appropriate screening test for donor specimens has been FDA cleared, approved, or licensed, and is available.

There can also be those disease agents or diseases that could place potential donors and/or recipients at risk for infection due to accidental or intentional release.
Donor Eligibility - RCDADs

- Relevant Communicable Disease Agents and Diseases
  - HIV-1 (includes group O)
  - HIV-2
  - HBV
  - HCV
  - Syphilis
  - Human TSEs (CJD, vCJD)
  - Sepsis
  - WNV
  - Vaccinia
  - Xenotransplantation
Required Donor Screening Tests - RCDADs

- HIV 1/2 Ab (best to use one with claim for HIV-1 Group O)
- HIV-1 NAT
- HBsAg
- HBcAb (total, meaning IgG plus IgM)
- HCV Ab
- HCV NAT + plasma dilution evaluation
- Syphilis
- HTLV I/II Ab – only required if tissue is deemed to be rich in viable leukocytes
- *Neisseria gonorrhea, Chlamydia trachomatis* – only required for reproductive HCT/Ps
- Must consider results of additional tests performed
## Current RCDADs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Required for</th>
<th>Screening</th>
<th>Testing*</th>
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<tr>
<td>HIV-1 and -2</td>
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<td>X</td>
</tr>
<tr>
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<tr>
<td>Hepatitis C</td>
<td>All</td>
<td>X</td>
<td>X</td>
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<tr>
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<td>X</td>
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</tr>
<tr>
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<td>All</td>
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<tr>
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<td>X</td>
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</tr>
<tr>
<td>Sepsis</td>
<td>All</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vaccinia (recent smallpox vaccination)</td>
<td>All</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

* More than one test may be necessary to adequately and appropriately test for a single RCDAD (e.g. anti-HCV and HCV NAT for Hepatitis C)
Donor Infectious Disease Testing

- **WNV NAT**
  - FDA draft guidance re-issued October 2013 (originally issued in 2008); no announcement to date
  - AATB pursuing relevancy studies w/CDC

- **HBV NAT**
  - Not required by any entity; routinely used by US tissue banks for >2 years
    - HIV-1 NAT, HCV NAT used since 2005

- **T. cruzi Ab**
  - FDA draft guidance issued in 2009; draft “withdrawn” in 2015
  - AATB w/CDC – relevancy studies with tissue ongoing

- **Syphilis Testing**
  - FDA final guidance issued September 2015
Donor Screening for Risk - AATB

• Additional AATB “relevant” diseases and adverse conditions. Consideration of:
  – Malignancy history
  – History of autoimmune disease
  – Ingestion or exposure to toxic substances
  – Malaria (Health Canada reg for tissues/cells), + malaria risk per Med Director
  – Rabies exposure (a New York State DoH requirement for tissue donation)
  – Gonorrhea in the past 12 months (HIV risk)
  – Unknown reason for being ineligible for blood donation

• Additional screening:
  – Undetermined Cause of Death with likelihood of other exclusionary criteria
  – Trauma to tissue to be recovered
  – Encephalitis, meningitis, clinically active tuberculosis
  – Tissue specific criteria (e.g., for musculoskeletal tissue - clinically significant metabolic bone disease, etc.)
“Donor Medical History Interview”

Described at 21 CFR 1271.3 (n), (n)(1), and (n)(2). This interview process also satisfies 21 CFR 1271.50 (a) and (b)(1)

AATB/AOPO/EBAA: “Donor Risk Assessment Interview”

A documented dialogue, whether in person or by telephone, with an individual or individuals who would be knowledgeable of the donor’s relevant medical history and social behavior. These include: the donor, if living; the next of kin; the nearest available relative; a member of the donor’s household; other individual with an affinity relationship (caretaker, friend, significant life partner); and/or the primary treating physician. Alternatively, a living donor may complete a written questionnaire. The relevant social history is elicited by questions regarding certain activities or behaviors that are considered to place such an individual at increased risk for a relevant communicable disease or disease agent.
Physical Examination

• Required for living donors of HCT/Ps; methods vary

• To assess:
  - general donor health; and
  - risks related to communicable disease
    o Donor Medical Hx Interview (medical, social, behavioral, and travel history) is conducted
      ▪ If any history is suspect, a directed exam of a body part or region may be indicated
Current Good Tissue Practice (CGTP)

- Methods, facilities, and controls for manufacturing to prevent contamination and cross-contamination
- Requires a quality program to prevent, detect, and correct deficiencies that could increase communicable disease risk
- Adverse reaction/deviation reporting and tracking requirement
- Includes donor eligibility requirements (screening & testing)
- Includes potential to request an exemption from or alternative to any requirement in subpart C or D (see 1271.155)
“Core CGTP”

• Requirements relating to:
  – facilities in 1271.190(a) and (b);
  – environmental control in 1271.195(a);
  – equipment in 1271.200(a);
  – supplies and reagents in 1271.210(a) and (b);
  – recovery in 1271.215;
  – processing and process controls in 1271.220;
  – labeling controls in 1271.250(a) and (b);
  – storage in 1271.260 (a) through (d);
  – receipt, predistribution shipment, and distribution of an HCT/P in 1271.265(a) through (d); and
  – donor eligibility determinations, donor screening, and donor testing in 1271.50, 1271.75, 1271.80, and 1271.85.
• Not “core” but required:
  – 1271.145 Prevention of the introduction, transmission, or spread of communicable diseases.
  – 1271.150 Current good tissue practice requirements.
  – 1271.155 Exemptions and alternatives.
  – 1271.160 Establishment and maintenance of a quality program.
  – 1271.170 Personnel.
  – 1271.180 Procedures.
  – 1271.225 Process changes.
  – 1271.230 Process validation.
  – 1271.260 Storage.
  – 1271.270 Records.
  – 1271.290 Tracking.
  – 1271.320 Complaint file.

1271.150 includes (c) Compliance with applicable requirements - (1) Manufacturing arrangements
Tissue Reference Group (TRG)

- Recommends designation of an HCT/P as regulated solely under Section 361 of the PHS Act (or more)
- Composition
  - 3 representatives each from CBER and CDRH
  - 1 rep from Office of Combination Products
  - 1 rep from Office of Chief Counsel
- Recommendations made to both CBER and CDRH Center Directors
- Summary of recommendations are posted online
HCT/P Designations & Regulatory Requirements

- Tissue Rules (GTP)
- Biologics Regs (GMP)
- Device Regs (QSR)

Pre-market approval

Marketing notification

Tissue
Cellular Therapeutic
Tissue Engineered

(IDE, BLA, IND)
Product Designation

• To be regulated solely under PHS Act 361, the tissue/cells must:
  • be minimally manipulated (processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement);
  • be intended for homologous use only, as reflected in the labeling, advertising, or other indications of the manufacturer’s objective intent;
  • not be combined with a drug or device, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of the water, crystalloids, or sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
  • not have a systemic effect and not be dependent on the metabolic activity of living cells for its primary function except if for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use.

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.
Not an HCT/P

(1) Vascularized human organs for transplantation;
(2) Whole blood or blood components or blood derivative products subject to listing under 21 CFR Parts 607 and 207, respectively;
(3) Secreted or extracted human products, such as milk, collagen, and cell factors, except that semen is considered an HCT/P;
(4) Minimally manipulated bone marrow for homologous use;
(5) Ancillary products used in the manufacture of HCT/P;
(6) Cells, tissues, and organs derived from animals other than humans;
(7) In vitro diagnostic products as defined in 21 CFR 809.3(a); and
(8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2 that are intended for use in organ transplantation and labeled “For use in organ transplantation only.”
HCT/P’s Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act

These HCT/P’s are regulated solely as "361 products" when they meet all of the criteria in 21 CFR 1271.10(a):

- BONE (including DEMINERALIZED BONE)
- LIGAMENTS
- TENDONS
- FASCIA
- CARTILAGE
- OCULAR TISSUES (CORNEAS & SCLERA)
- SKIN
- VASCULAR GRAFTS (VEINS & ARTERIES), except preserved umbilical cord veins
- PERICARDIUM
- AMNIOTIC MEMBRANE (when used alone (-without added cells-) for ocular repair)
- DURA MATER
- HEART VALVE ALLOGRAFTS
- HEMATOPOIETIC STEM CELLS DERIVED FROM PERIPHERAL OR UMBILICAL CORD BLOOD
- SEMEN
- OOCYTES
- EMBRYOS

“361 products” require CGTP
Controls to avoid transmission of communicable disease from donors to recipients
Granted “pre-market” approval
CBER

HUMAN SOMATIC CELL THERAPY AND GENE THERAPY PRODUCTS Regulated under Section 351 of the PHS Act and/or the FD&C Act

This grouping includes products that FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products.

- CULTURED CARTILAGE CELLS
- CULTURED NERVE CELLS
- LYMPHOCYTE IMMUNE THERAPY
- GENE THERAPY PRODUCTS
- HUMAN CLONING
- HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector)
- UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELLS
- UNRELATED DONOR LYMPHOCYTES FOR INFUSION

“351 products” additionally require CGMP
“Products” are licensed thru Biological License Application (BLA) process
Requires “safety and efficacy” to be able to market
Guidance for Industry and FDA Staff

Investigational New Drug Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-855-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologies Evaluation and Research
March 2014

• Specific HCT/P (a drug)
• Specific Intended Use is investigational
  – Requires clinical studies
• An IND allows the investigational product to be shipped across state lines with the intent of collecting safety and efficacy data in humans
  – Phase 1 clinical studies primarily focus on safety data
  – Phase 2 and 3 studies focus on safety and effectiveness data and human rights of subjects
Updates the October 2009 Guidance

If clinical studies in humans demonstrate the biological product is safe and effective and the relative benefits outweigh the risks, licensure can be sought.

These “HPC, Cord Blood” products also must be intended for hematopoietic reconstitution in patients with specific hematological malignancies, certain lysosomal storage and peroxisomal enzyme deficiency disorders.
“351 medical devices” additionally require Quality System Regulation (QSR). Requires safety, efficacy, and post-market surveillance.
Office of Combination Products (OCP)

COMBINATION PRODUCTS

- DEMINERALIZED BONE combined with HANDLING AGENTS (glycerol, sodium hyaluronate, calcium sulfate, gelatin, collagen) - are regulated as DEVICES
- BONE-SUTURE-TENDON ALLOGRAFTS - regulated as DEVICES
- CULTURED CELLS (fibroblasts/keratinocytes/nerve/ligament/bone marrow) on SYNTHETIC MEMBRANES or combined with COLLAGEN may be regulated as DEVICES or BIOLOGICAL PRODUCTS (these products are currently under review and may be regulated by CBER under either the device authorities or under section 351 of the PHS Act)
- ENCAPSULATED PANCREATIC ISLET CELLS are regulated as BIOLOGICAL PRODUCTS

Designated as “351 products” or fall under the “Food, Drug & Cosmetic Act (FD&C)”

Requires CGMP or QSR
Significant “Recent” Draft Guidance

Issued: October 2014, December 2014 (x2), February 2015, November 2015
Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. 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 guidance are available from the Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Avenue, Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002 or by calling 1-800-835-4709 or 240-402-7800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2014

• Exception defined; must meet 3 criteria:
  – Must be autologous use;
  – Re-implanted within the same surgical procedure; and
  – HCT/P remains in original form.4 The communicable disease risks, as well as safety risks, generally would be no different from those typically associated with surgery.
  – 4 allows HCT/P to be rinsed, cleaned, sized, or shaped
  – Further processing, or distribution, voids exception
Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

Draft Guidance for Industry and Food and Drug Administration Staff

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions on the content of this guidance, contact CBER, Office of Communication, Outreach, and Development (OCOD) at 240-402-7800 or 800-835-4709. For questions about this document concerning products regulated by CDRH, contact the Office of the Center Director at 301-796-5900. If you need additional assistance with regulation of combination products, contact the Office of Combination Products at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products in the Office of the Commissioner (OCP)
December 2014

• Clarifying (?) descriptions
  – Structural tissues
    • “Original relevant characteristics”
  – Cells or non-structural tissues
    • “Relevant biological characteristics”
• Examples
Clarifying (?) descriptions

- Minimal Manipulation
  - aliquoting, rinsing, removal of macroscopic debris, and freezing
  - More than MM = decellularization (?)

- Autologous use
  - Limited handling vs processing

- Exceptions

- Examples
Outlines regulatory requirements

Investigation
  – Information collection
    • Donor, Recovery, Processing, Environmental Control & Monitoring, Storage & Distribution, Tracking, Labeling, Complaint File
  – Information sharing

Reporting
  – Completion of MedWatch Form FDA 3500 A

Implementation
Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

Draft Guidance for Industry and FDA Staff

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)
October 2015

• Defines/Clarifies
  – Homologous Use
  – Repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues
  – “the same basic function or functions” in the definition of homologous use
  – Use in the same anatomic location (or not)
  – “Intended for homologous use only” as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent
  – “manufacturer’s objective intent”

• Examples
Homologous Use

- Used to repair, reconstruct, replace, or supplement:
  - Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,
  - Recipient cells that may not be identical to the donor’s cells, or recipient tissues that may not be identical to the donor’s tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

- Supplementation generally means to add to or complete.
Draft Guidance & Public Hearing

• Same Surgical Procedure Exception, Minimal Manipulation, Adipose Tissue/Regulatory Considerations, & Homologous Use all open or reopened for comment until **April 29, 2016**

• A public hearing will be held on **April 13, 2016** from 8 a.m. to 5 p.m. at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room. Register by **January 8, 2016**.
U.S. Dept. of Health & Human Services (HHS) Advisory Committees
(discuss cells/tissues for transplant and make recommendations)

- ACBTSA
  - Advisory Committee for Blood & Tissue Safety & Availability
- CTGTAC
  - Cell, Tissue, and Gene Therapies Advisory Committee
- BPAC
  - Blood Products Advisory Committee
- TSEAC
  - Transmissible Spongiform Encephalopathy Advisory Committee
Thank you for the opportunity.

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