Regulation of Allograft Heart Valves

OPTN Operations and Safety Committee Meeting

July 27, 2023

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Office of Therapeutic Products
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U.S. Food and Drug Administration

Disclosures

- No financial disclosures (federal government employee)
- Relevant work experience
  - Hospital corpsman, clinical laboratory, blood banking, 1976 to 1986
  - Tissue banking/organ donation, 1986 to 2016
    - Virginia Tissue Bank/LifeNet Health
      - Supervisor of Cardiovascular Services, Procurement Relations Manager, Director of Tissue Recovery Services, Director of Technical Training and Education
    - Virginia's Organ Procurement Agency (VOPA), Board of Directors
    - Washington Regional Transplant Consortium (WRTC), Organ & Tissue Advisory Committee
    - American Association of Tissue Banks (AATB), Senior Vice President of Policy
    - Canadian Blood Services, Organ and Tissue Donation and Transplantation, Tissue Expert Committee, member
    - World Health Organization, Medical Products of Human Origin, NOTIFY Project/Library, Expert, Process Group Chair
  - FDA/CBER, Division of Human Tissues, Director, 2016 to present
    - CBER Tissue Safety Team, Chairperson
    - Tissue Reference Group, Chairperson
    - OPTN, Ad hoc Disease Transmission Advisory Committee (DTAC), *ex-officio* invited member, FDA liaison
    - HHS Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA), *ex-officio* member, FDA representative
    - HHS Advisory Committee on Organ Transplantation (ACOT), *ex-officio* member, FDA representative

Overview

- Disease transmission by tissue allografts
- FDA's regulatory authority and approach
- 21 CFR part 1271
  - Subparts, Definitions, Guidance documents, Certain requirements
- The "new" allograft heart valve protocol
- Resources

Note: Presentation does not include a complete list of regulatory requirements. Refer to 21 CFR part 1271 and applicable guidance documents.

Disease Transmission by "Tissue" Allografts

(1954 to 2011 … worldwide)

HIV-1	Fresh bone, Frozen tendon
HBV	Fresh cornea, Cryopreserved heart valve
HCV	Frozen bone, Frozen tendon, Cryopreserved vein, Cryopreserved cardiac patch
CMV	Fresh skin
EBV	Fresh nerve
HTLV-1	Frozen bone
Rabies	Fresh cornea, Fresh artery ("organ" use)
Herpes simplex	Fresh cornea
CJD	Fresh cornea, Freeze-dried dura mater
Tuberculosis	Frozen bone, Cryopreserved heart valve
Yeast, Fungus	Fresh cornea, Cryopreserved heart valve
Bacteria	Fresh cornea, Fresh skin, Fresh cartilage, Frozen tendon, Frozen bone, Frozen pericardium, Cryopreserved heart valve

Information collated from Chapter 4 authored by Ted Eastlund, MD & Ruth Warwick, MD in *Tissue & Cell Clinical Use: An Essential Guide*, Edited by RM Warwick, SA Brubaker, 2012, Blackwell Publishing Ltd.

1997 Proposed Approach to Regulation

- 1997 - Proposed Approach to the Regulation of Cellular and Tissue-Based Products
  - Tiered, risk-based approach to:
    - prevent unwitting use of contaminated tissues with the potential to transmit infectious disease;
    - prevent improper handling or processing that might contaminate or damage tissues; and
    - ensure clinical safety and effectiveness is demonstrated for tissues that are highly processed, used for non-natural purposes, are combined with non-tissue components, or that have systemic effects on the body.

Driving Forces & Challenges

- From one to 50, to more than 100 allografts, can be processed and distributed from one person's tissue donation
- New manufacturing technologies, degree of manipulation increasing
- New products (e.g., tissue engineered, stem cells)
- Increasing demand for cells & tissues
- Public confidence in products – expectation for safe & effective therapies
- Industry standards not always followed, not enforceable
- Increasing public health concern

Regulatory Authority

Section 361 of the PHS Act

- FDA is an agency within the Department of Health and Human Services (HHS) and, by delegation from the Surgeon General and the Secretary of HHS, has authority to create and enforce regulations as it deems necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from State to State (42 U.S.C. 264).
- Under this authority, FDA has promulgated regulations in Title 21 of the Code of Federal Regulations (CFR) part 1271, regarding human cells, tissues, or cellular or tissue-based products (HCT/Ps). Since HCT/Ps contain components from the human body, they pose some risk of carrying pathogens that could cause disease in health-care personnel, other handlers of tissue, recipients, and family members or other close contacts of recipients.

Two Regulatory Tiers for HCT/Ps

- "361 HCT/P"
  - Regulated solely under authority of section 361 of the Public Health Service (PHS) Act
  - Subject to "Tissue Regulations" (21 CFR part 1271)
  - No premarket review
- Drugs, devices, biological products ("351 HCT/Ps")
  - Regulated under authority of section 361 and section 351 of the PHS Act and/or the Federal Food, Drug, & Cosmetic Act, and applicable regulations
  - Premarket review

21 CFR part 1271

Subpart A: General Provisions	Definitions; criteria for regulatory pathway determination (e.g., 361 HCT/P vs. 351 HCT/P)
Subpart B: Procedures for Registration and Listing	Requirements for establishment registration and listing products they manufacture
Subpart C: Donor Eligibility	Requirements for donor screening and testing for "relevant communicable disease agents and diseases," and for making a donor eligibility determination
Subpart D: Current Good Tissue Practice	Handling and process controls to prevent the introduction, transmission, or spread of communicable diseases
Subpart E: Additional Requirements for Establishments Described in §1271.10	Reporting adverse reactions and HCT/P deviations; labeling
Subpart F: Inspection and Enforcement of Establishments Described in §1271.10	Inspection; import; orders of retention, recall, destruction, and cessation of manufacturing

Subparts D and E are not implemented for reproductive HCT/Ps except these in subpart D:
§1271.150(c) Compliance with applicable requirements and §1271.155 Exemptions and alternatives

What are HCT/Ps?

21 CFR 1271.3(d)

- 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 to a human recipient.
- Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

What are HCT/Ps?

- The following articles are **not** considered HCT/Ps:
  - (1) Vascularized human organs for transplantation;
  - (2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, 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 and not combined with another article *(with exceptions)*;
  - (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 § 809.3(a) of this chapter; 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.”

21 CFR 1271.10(a) Criteria

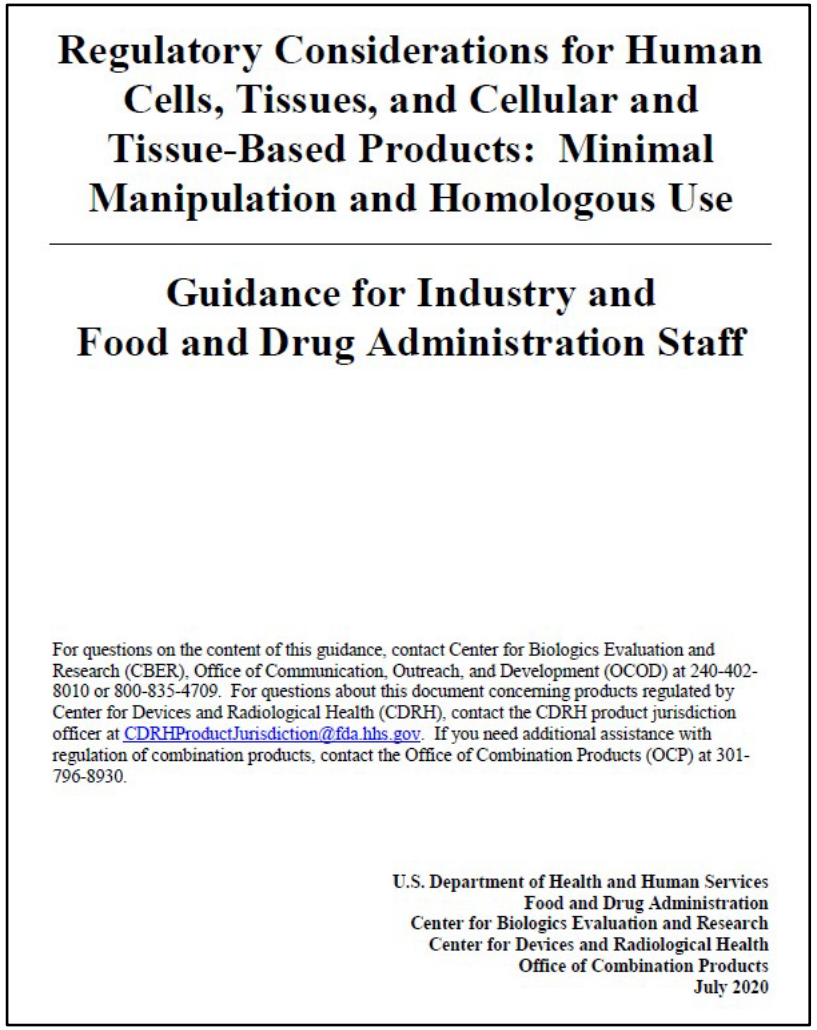
To be regulated solely under section 361 of the PHS Act and the regulations in part 1271, HCT/Ps must meet all of the following criteria:

1. Minimally manipulated (MM)*;
2. Intended for homologous use (HU)** only, as indicated by the manufacturer's objective intent;
3. Not combined with another article *(with some exceptions)*; AND
4. Either:
   i. Does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
   ii. Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use, allogeneic use in a 1st or 2nd degree blood relative, or for reproductive use.

*Defined in § 1271.3(f)
**Defined in § 1271.3(c)

MM/HU Final Guidance

- Issued jointly by CBER, CDRH, and OCP in November 2017; updated July 2020
- Provides recommendations for applying the criteria in 21 CFR 1271.10(a)(1)&(2)
- How to determine if an HCT/P is MM and intended for HU
- Compliance and Enforcement Policy
- Flowchart to illustrate how to apply the criteria in § 1271.15(b) and § 1271.10(a)



Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

Guidance for Industry and Food and Drug Administration Staff

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov. If you need additional assistance with regulation of combination products, contact the Office of Combination Products (OCP) at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
July 2020

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal

Minimal Manipulation (MM)

- Defined in 21 CFR 1271.3(f)
- 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
- Criterion relates to how the HCT/P functioned in the donor

MM/HU Final Guidance

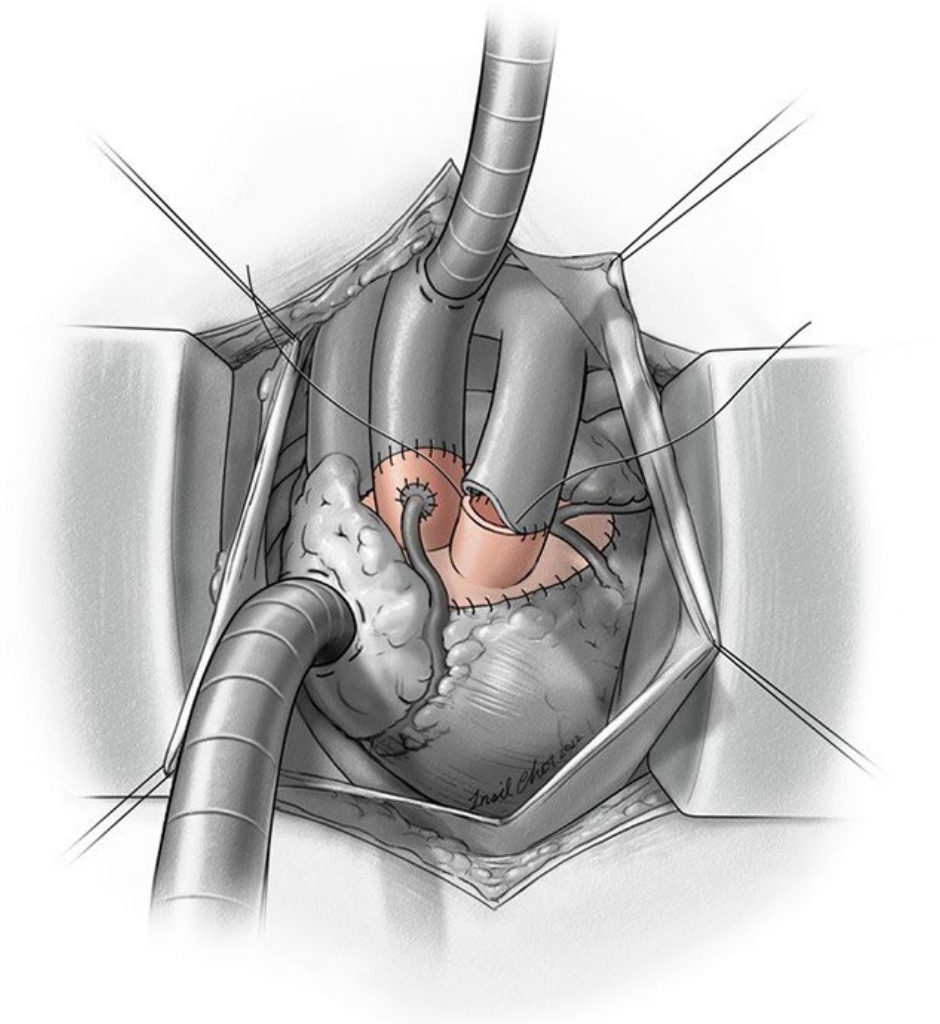
Excerpt from section III. QUESTIONS AND ANSWERS REGARDING MINIMAL MANIPULATION

Processing that alters the original characteristics of the HCT/P, raises increased safety and effectiveness concerns for the HCT/P because there would be less basis on which to predict the product's function after transplantation[11]. Thus, the determination of whether an HCT/P is minimally manipulated is based on the effect of manufacturing on the original relevant characteristics of the HCT/P as the HCT/P exists in the donor, and not based on the intended use of the HCT/P in the recipient.

[11] See the "Proposed Approach to Regulation of Cell and Tissue-Based Products" page 19. (1997 Proposed Approach)

Homologous Use (HU)

- Defined in 21 CFR 1271.3(c)
- 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
- Criterion relates to intended use of the HCT/P in the recipient



JTCVS Techniques, Volume 18 Pages 91-96 (April 2023), Copyright © 2023
T. Konrad Rajab, MD, Lillian Kang, MD, Kaila Hayden, BS, Nicholas D. Andersen, MD, Joseph W. Turek, MD, PhD, MBA
DOI: 10.1016/j.xjtc.2023.02.005

MM/HU Final Guidance

Excerpt from section IV. QUESTIONS AND ANSWERS REGARDING HOMOLOGOUS USE

Example 17-1: A heart valve is transplanted to replace a dysfunctional heart valve. This is homologous use because the donor heart valve performs the same basic function in the donor as in the recipient of ensuring unidirectional blood flow within the heart.

A heart valve is a structural tissue.
Primary function is ensuring unidirectional blood flow within the heart.

21 CFR 1271.10(a)(3)

The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

21 CFR 1271.10(a)(4)

Either:

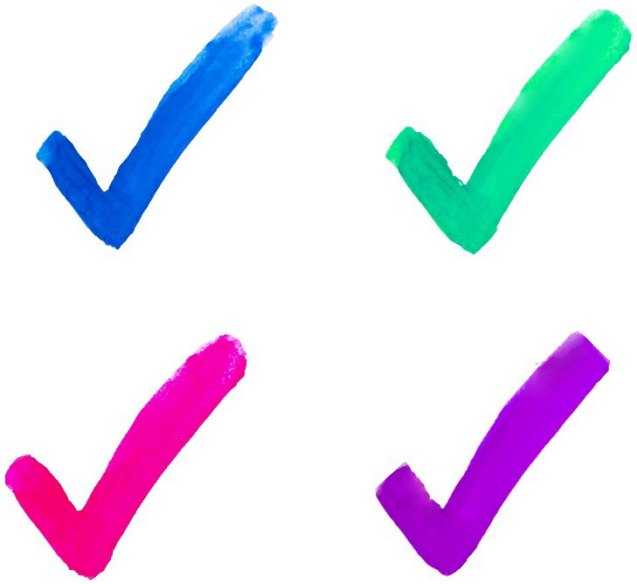
(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

  (a) Is for autologous use;

  (b) Is for allogeneic use in a first-degree or second-degree blood relative; or

  (c) Is for reproductive use.



21 CFR 1271.10(a)(4)

Also see "HCT/P Establishment Registration & Listing Final Rule," dated January 2001, at the top of page 5460, in response to Comment 31 concerning § 1271.10(a)(4):

> "In contrast, some HCT/P's (such as corneas, skin, or osteochondral allografts) may contain living cells, but do not depend on them for their primary function, which is structural."

https://www.federalregister.gov/documents/2001/01/19/01-1126/human-cells-tissues-and-cellular-and-tissue-based-products-establishment-registration-and-listing

The “new” allograft heart valve protocol

- Infant identified with congenital heart defects (i.e., Tetralogy of Fallot, Truncus arteriosus) who presents with life-threatening valvar stenosis or insufficiency that requires reconstructive procedures to repair ventricular outflow
- Donor size limit criteria includes an age and weight range, ABO matching may be optional
- Pediatric donor identified, authorization/consent obtained, donor screening and donor testing performed
- Heart procurement/recovery takes place (cardiectomy; standard fashion)
- Heart packaged in isotonic solution to maintain a cold environment and shipped to transplant center’s operating room (OR)
- Aortic and pulmonary heart valves/outflow tracts prepared by isolation [dissection; standard fashion] in the OR for immediate implantation according to standard surgical technique for a double root replacement

Subpart C - Donor Eligibility

Selections are limited

More Definitions

21 CFR 1271.3(e)
Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

21 CFR 1271.3(t)
Responsible person means a person who is authorized to perform designated functions for which he or she is trained and qualified.

21 CFR 1271.3(u)
Urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P.

Donor Eligibility

§ 1271.45 What requirements does this subpart contain?

(b) Donor-eligibility determination required.

A donor-eligibility determination, based on donor screening and testing for relevant communicable disease agents and diseases, is required for all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90. In the case of an embryo …

Note that § 1271.90 includes exceptions for autologous use and for reproductive use.

Donor Eligibility

§ 1271.45 What requirements does this subpart contain?

(c) Prohibition on use.

An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, except as provided under §§ 1271.60(d), 1271.65(b), and 1271.90 of this subpart.

Note that § 1271.60(d) includes use in cases of 'urgent medical need' and § 1271.65(b) includes limited uses of HCT/Ps from an ineligible donor.

Donor Eligibility

§ 1271.50 How do I determine whether a donor is eligible?

(a) Determination based on screening and testing.

If you are the establishment responsible for making the donor-eligibility determination, you must determine whether a donor is eligible based upon the results of donor screening in accordance with § 1271.75 and donor testing in accordance with §§ 1271.80 and 1271.85. A responsible person, as defined in § 1271.3(t), must determine and document the eligibility of a cell or tissue donor.

Donor Eligibility

§ 1271.55 What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain?

(a) *Accompanying records.* Once a donor-eligibility determination has been made, the following must accompany the HCT/P at all times:

(1) A distinct identification code affixed to the HCT/P container, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P …

(2) A statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and

(3) A summary of the records …

RCDADs

- Relevant communicable disease agents or diseases (RCDADs) specifically listed in § 1271.3(r)(1)

- Relevant communicable disease agents or diseases that meet certain criteria described in § 1271.3(r)(2) are added through guidance

RCDADs

For all HCT/Ps:

- Human immunodeficiency virus, types 1 and 2 (HIV-1/2)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Human transmissible spongiform encephalopathy (hTSE), including Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD)
- *Treponema pallidum* (agent that causes syphilis)
- Vaccinia**
- Sepsis**
- West Nile Virus (WNV)**
- Zika virus (ZIKV)**

** These were not considered RCDADs at the time of publication of the Tissue Regulations in 2004. They were added to the list of RCDADs through publication of the 2007 DE Guidance (vaccinia, sepsis, WNV) and 2018 Zika Guidance (ZIKV).

For viable, leukocyte-rich cells and tissues:

- Human T-lymphotropic virus, type I and type II (HTLV-I/II)

For reproductive cells and tissues:

- *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG)

Donor Screening

§ 1271.75 How do I screen a donor?

(a) All donors.

Except as provided under § 1271.90, if you are the establishment that performs donor screening, you must screen a donor of cells or tissue by reviewing the donor's relevant medical records for:

(1) Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, … and,

(2) Communicable disease risks associated with xenotransplantation

Donor Testing

§ 1271.80 What are the general requirements for donor testing?

(a) *Testing for relevant communicable diseases is required.*

(b) *Timing of specimen collection.*

(c) *Tests.*

(d) *Ineligible donors.*

§ 1271.85 What donor testing is required for different types of cells and tissues?

(a) *All donors.*

(b) *Donors of viable, leukocyte-rich cells or tissue.*

(c) *Donors of reproductive cells or tissue.*

(d) *Retesting of anonymous semen donors.*

(e) *Dura mater.*

Donor Screening and Testing

Agent	Required for	Screening	Testing*
HIV 1/2	All HCT/Ps	X	X
HBV	All HCT/Ps	X	X
HCV	All HCT/Ps	X	X
Treponema pallidum	All HCT/Ps	X	X
TSE	All HCT/Ps	X	
WNV	HCT/Ps	X	X *(living donors only)*
Sepsis	All HCT/Ps	X	
Vaccinia	All HCT/Ps	X	
ZIKV	All HCT/Ps	X	
HTLV I/II	Viable, leukocyte-rich HCT/Ps	X	X
CMV	Viable, leukocyte-rich HCT/Ps		X
Chlamydia trachomatis	Reproductive HCT/Ps	X	X
Neisseria gonorrhoeae	Reproductive HCT/Ps	X	X

* More than one test may be necessary to adequately and appropriately test for a single agent (i.e., serology and NAT).

Adequate and Appropriate Tests

HIV-1 FDA licensed donor screening test: • Anti-HIV-1 or combo test for anti-HIV-1 and anti-HIV-2, AND • NAT test for HIV-1 or combination NAT test	**HIV-2** FDA licensed donor screening test: • Anti-HIV-2 or combo test for anti-HIV-1 and anti-HIV-2	**HBV** FDA licensed donor screening test: • Hepatitis B surface antigen (HBsAg), • Total antibody to Hepatitis B core antigen (IgG & IgM; anti-HBc), AND • NAT test for HBV	**HCV** FDA licensed donor screening test: • Anti-HCV, AND • NAT test for HCV or combination test
Treponema pallidum FDA cleared donor screening test: • Nontreponemal or treponemal	**WNV** FDA licensed donor screening test: • NAT test for WNV	**HTLV-I/II** FDA licensed donor screening test: • Anti-HTLV-I/II	**CMV** FDA cleared donor screening test: • Anti-CMV, total IgG and IgM
Chlamydia trachomatis FDA cleared diagnostic test: • NAT test for CT in an asymptomatic, low-prevalence population	***Neisseria gonorrhoeae*** FDA cleared diagnostic test: • NAT test for NG in an asymptomatic, low-prevalence population		

- 2007 DE Guidance, sections VI.A-B.
- 2015 Syphilis Tests Guidance
- 2016 WNV NAT Guidance
- 2016 HBV NAT Guidance

DE Related Guidance

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007)
- Use of Donor Screening Tests to Test Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products for Infection with *Treponema pallidum* (Syphilis); Guidance for Industry (September 2015)
- Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry (August 2016)

DE Related Guidance

- Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Guidance for Industry (September 2016)
- Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human-Derived Clotting Factor Concentrates; Guidance for Industry (November 2016)
- Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry (March 2016, updated May 2018)

Subpart D –
Current Good Tissue Practice

Selections are limited

Recovery

§ 1271.215 Recovery.

If you are an establishment that recovers HCT/Ps, you must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

21 CFR 1271.3(ii)

Recovery means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

Packaging and Shipping

§ 1271.265 Receipt, predistribution shipment, and distribution of an HCT/P.

(d) Packaging and shipping.

Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination. For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit.

Tracking

§ 1271.290 Tracking.

(a) *General.*

If you perform any step in the manufacture of an HCT/P in which you handle the HCT/P, you must track each such HCT/P in accordance with this section, to facilitate the investigation of actual or suspected transmission of communicable disease and take appropriate and timely corrective action.

(b) *System of HCT/P tracking.*

(c) *Distinct identification code.*

Subpart E – Additional Requirements for Establishments Described in § 1271.10

Selections are limited

Adverse Reaction Reports

§ 1271.350 Reporting.

(a) *Adverse reaction reports.*

(1) You must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. You must report to FDA an adverse reaction involving a communicable disease if it:

(i) Is fatal;

(ii) Is life-threatening;

(iii) Results in permanent impairment of a body function or permanent damage to body structure; or

(iv) Necessitates medical or surgical intervention, including hospitalization

Adverse Reaction Reports

§ 1271.350 Reporting.

(a) *Adverse reaction reports.*

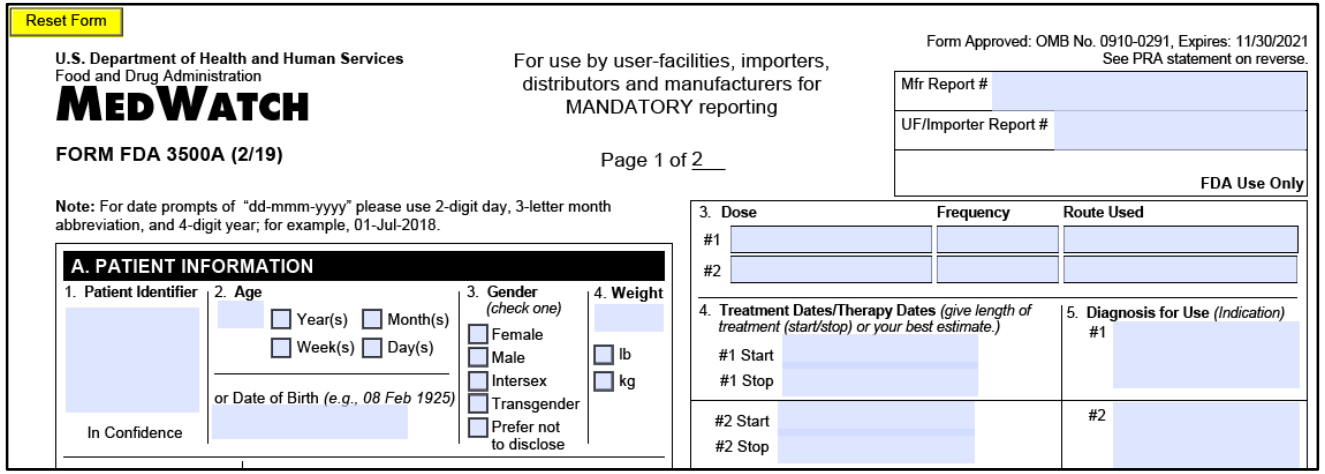
(2) You must submit each report on a Form FDA–3500A to the address in paragraph (a)(5) of this section within 15 calendar days of initial receipt of the information.

(3) You must, as soon as practical, investigate all adverse reactions that are the subject of these 15-day reports and must submit followup reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

Adverse Reaction Reports

21 CFR 1271.3(y)

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.



Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (2/19)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Form Approved: OMB No. 0910-0291, Expires: 11/30/2021
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2018.

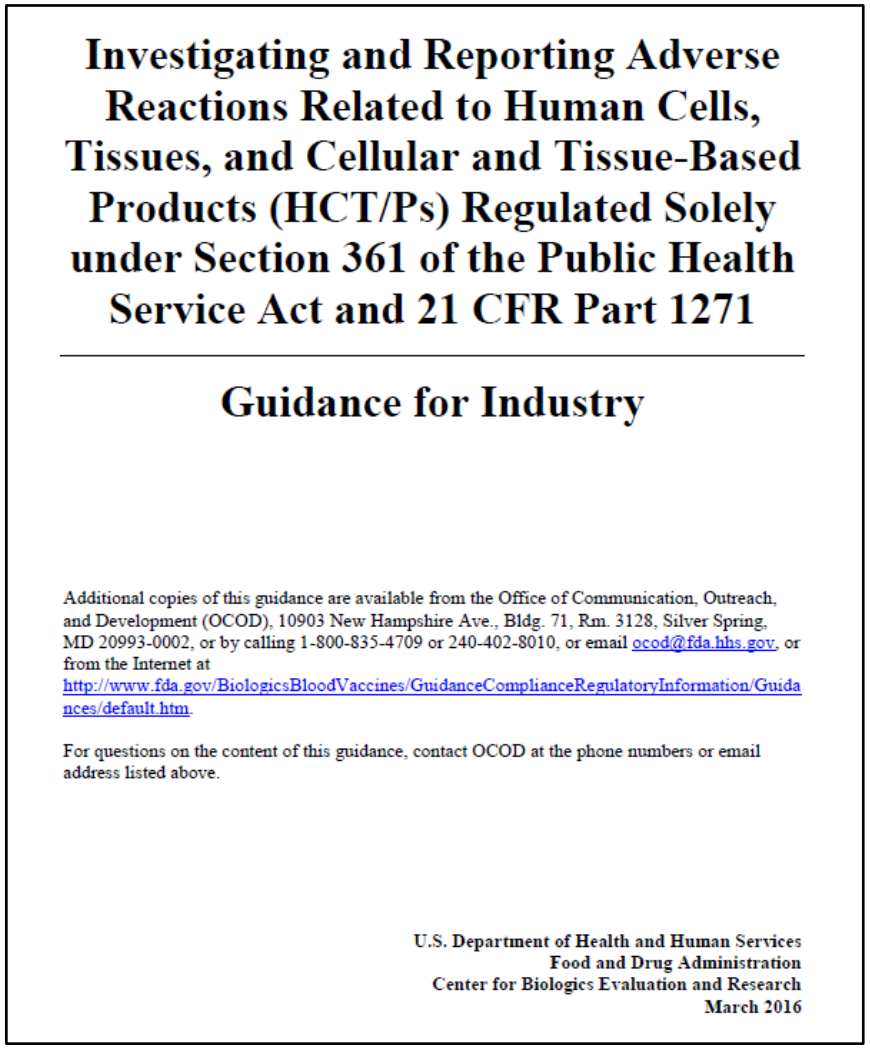
A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Day(s) — or Date of Birth *(e.g., 08 Feb 1925)*
3. Gender *(check one)* — Female, Male, Intersex, Transgender, Prefer not to disclose
4. Weight — lb, kg

3. Dose	Frequency	Route Used
#1		
#2		

4. Treatment Dates/Therapy Dates *(give length of treatment (start/stop) or your best estimate.)*
#1 Start / #1 Stop
#2 Start / #2 Stop

5. Diagnosis for Use *(Indication)*
#1
#2



Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely under Section 361 of the Public Health Service Act and 21 CFR Part 1271

Guidance for Industry

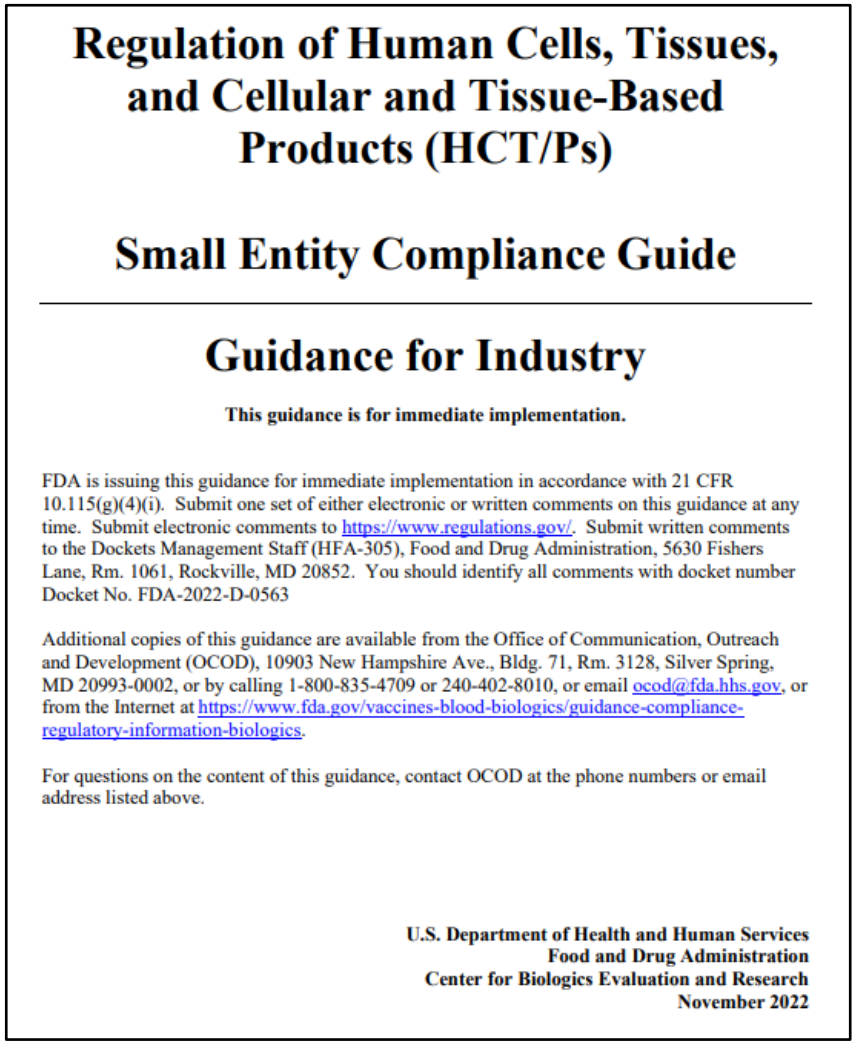
Additional copies of this guidance are available from the Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2016

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigating-and-reporting-adverse-reactions-related-human-cells-tissues-and-cellular-and-tissue

Resources



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

Small Entity Compliance Guide

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number Docket No. FDA-2022-D-0563

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2022

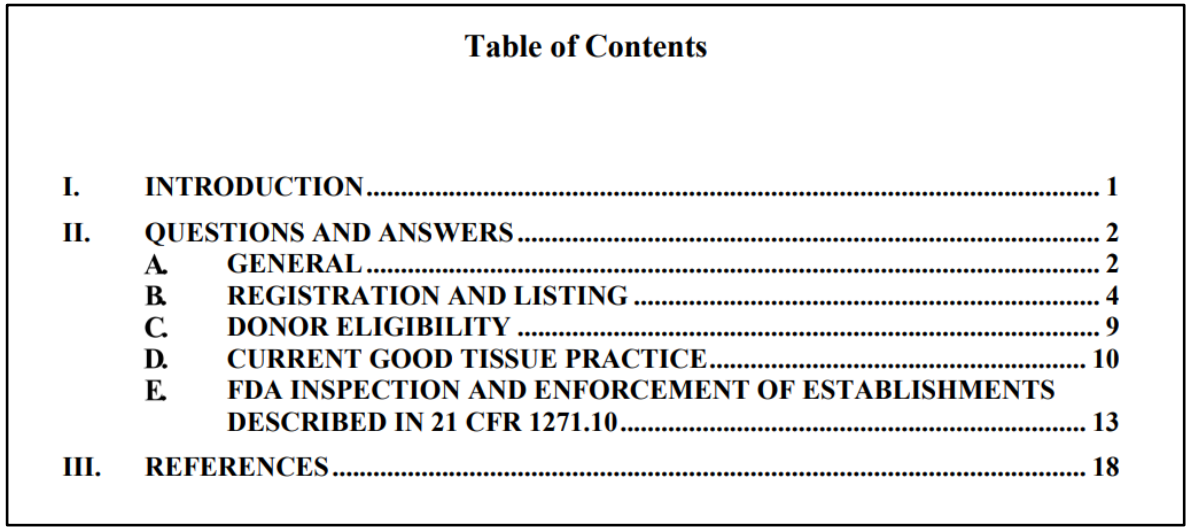


Table of Contents

- Question and answer format related to all subparts in 21 CFR part 1271
- Intended to help small entity establishments that manufacture HCT/Ps better understand the comprehensive regulatory framework for HCT/Ps, set forth in 21 CFR part 1271 and comply with certain HCT/P related final rules

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-small-entity-compliance

Resources

21 CFR part 1271
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271

Tissue and Tissue Products (homepage)
https://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm

Tissue Guidances
https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances

Safety & Availability (Biologics)
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics

HCT/P Donor Testing
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable#approved

HCT/P Adverse Reaction Reporting
https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/human-cell-tissue-products-hctp-adverse-reaction-reporting

Resources

Subscribe for CBER Updates

https://www.fda.gov/vaccines-blood-biologics/news-events-biologics#subscribe

CBER Contacts For HCT/P Manufacturers

Manufacturers Assistance and Technical Training Branch (MATTB)
industry.biologics@fda.hhs.gov
1-800-835-4709 or 240-402-8010
https://www.fda.gov/vaccines-blood-biologics/industry-biologics/manufacturers-assistance-and-technical-training-branch-mattb

Contacts in the Center for Biologics Evaluation & Research (CBER)
https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/contacts-center-biologics-evaluation-research-cber

OTP Contact Information

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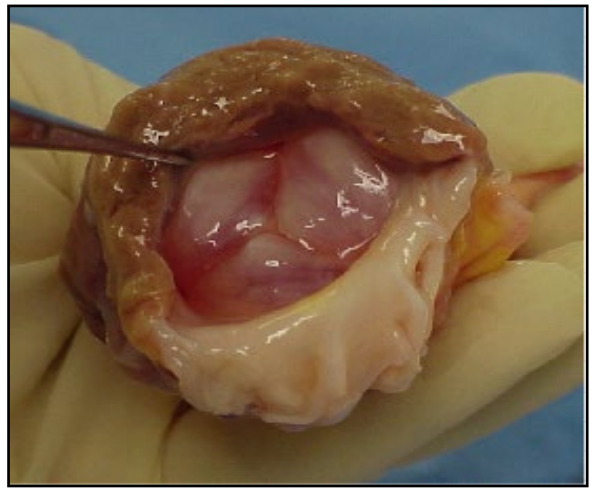
Regulatory Questions
Contact the Regulatory Management Staff at:
OTPRPMS@fda.hhs.gov
240-402-8190



OTP Learn Webinar Series https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otp-learn

CBER website
http://www.fda.gov/BiologicsBloodVaccines

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