21 CFR Part 1271
HCT/P Regulatory Framework - Part 1

FDA Small Business Regulatory Education for Industry (REdI)
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Learning Objectives

- Understand events that led to promulgation of regulations to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps.
- List general requirements for manufacturers to meet the scope and purpose of the regulations of title 21 of the Code of Federal Regulations in part 1271.
- Correlate criteria and definitions in 21 CFR part 1271 regulations to understand how an HCT/P should be appropriately regulated.

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

Pre-regulation History

- 1974 - Creutzfeldt-Jakob Disease (**CJD)** after cornea transplant
- 1980s - **CJD** transmissions from use of human growth hormone (pituitary hGH) (1985) and human dura mater (1987); pooling from many donors
- 1985 - Transmission of **HIV** by artificial insemination; donor testing for HIV not available, semen donation occurred earlier
- 1986 - Transmission of **HIV** from an organ donor (no tissue); “hemodilution” of donor blood sample used for testing
- 1987 - Transmission of **HBV** by artificial insemination; screening minimal, testing not performed

Pre-regulation History

- 1988 - Transmission of **HIV** from a surgical bone femoral head; no donor testing or tissue processing; donation occurred in 1984
- 1990 - **Pneumococcal endophthalmitis** via cornea transplant
- 1991 - Transmission of **HIV** from organs and processed tissue (frozen bone and bone/ligament/bone allografts); tissue recovery occurred in 1985; HTLV-III Ab testing negative x 2 but donor in “window period”
- 1993 - Intercepted brokers attempting to sell unprocessed human tissue to US tissue banks; donors from Russia, Eastern Europe, and Central and South America; no donor records, donor testing questionable (HBV +)

Relevant History

- 1993 - Interim Final Rule, Human Tissue for Transplantation
- 1995 - Guidance Concerning Application, Testing, & High Risk Criteria for HIV and Hepatitis for Banked Human Tissue
- 1997 - GAO publishes report: “Human Tissue Banks: FDA Taking Steps to Improve Safety, But Some Concerns Remain”
- 1997 - ***Candida albicans*** infection from cryopreserved allograft heart valve; culture method deficiency
- 1997 - Final Rule, Human Tissue Intended for Transplantation (21 CFR part 1270)
  - Final Guidance, Screening & Testing Donors of Human Tissue Intended for Transplantation

Relevant History

- 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.

Relevant History

- Proposed Rules (21 CFR part 1271)
  - 1998 - Establishment Registration and Listing
  - 1999 - Suitability Determination for Donors of Human Cellular and Tissue-Based Products
  - 2001 - Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement
- 2001 - DHHS OIG publishes report: “Oversight of Tissue Banking”
- 2001 - ***Clostridium sordellii*** infection from cryopreserved femoral condyle allograft (recipient death)

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

21 CFR part 1271

21 CFR Part 1271	Issues Addressed
Subpart A: General Provisions	Definitions, criteria for regulatory pathways determination (e.g., 361 tissue vs. 351 biologic)
Subpart B: Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules, requirements for registering and listing establishments/products
Subpart C: Donor Eligibility	Requirements for donor screening and testing for “relevant communicable disease agents and diseases”
Subpart D: Current Good Tissue Practice (CGTP)	Handling and process controls to prevent contamination and introduction, transmission, or spread of communicable diseases
Subpart E: Additional requirements	Adverse reactions and deviation reporting and labeling
Subpart F: Inspection and enforcement	Inspection, importation, orders of retention, recall, destruction and cessation of manufacturing

Note: Subparts C and D also apply to HCT/Ps regulated as drugs, devices, and/or biologics

What is an HCT/P?

Definition: Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient (21 CFR 1271.3 (d))

HCT/P Examples	Not an HCT/P
Musculoskeletal tissue	Vascularized human organs for transplant
Cardiovascular tissue	Whole blood or blood components
Skin	Secreted or extracted human products such as milk, collagen, and cell factors; except that semen is considered an HCT/P
Dura mater	Minimally manipulated bone marrow, for homologous use and not combined with another article (except as described in 21 CFR 1271.3(d)(4)
Amniotic membrane	Non-human cells, tissues, or organs
Reproductive Cells & Tissue	In-vitro diagnostic products as defined in 21 CFR 809.3(a)
Cellular-derived therapeutic products (e.g., pancreatic islets, mesenchymal/stromal cells, fibroblasts)	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."
Hematopoietic Stem/Progenitor Cells (HPCs) derived from peripheral or umbilical cord blood	Ancillary products used in the manufacture of HCT/P

21 CFR 1271.10(a) Criteria

To be regulated solely under section 361 of the PHS Act, HCT/Ps must meet all of the following criteria (21 CFR part 1271.10(a)):

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, 1st or 2nd degree blood relative, or reproductive use

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

Two Regulatory Tiers for HCT/Ps

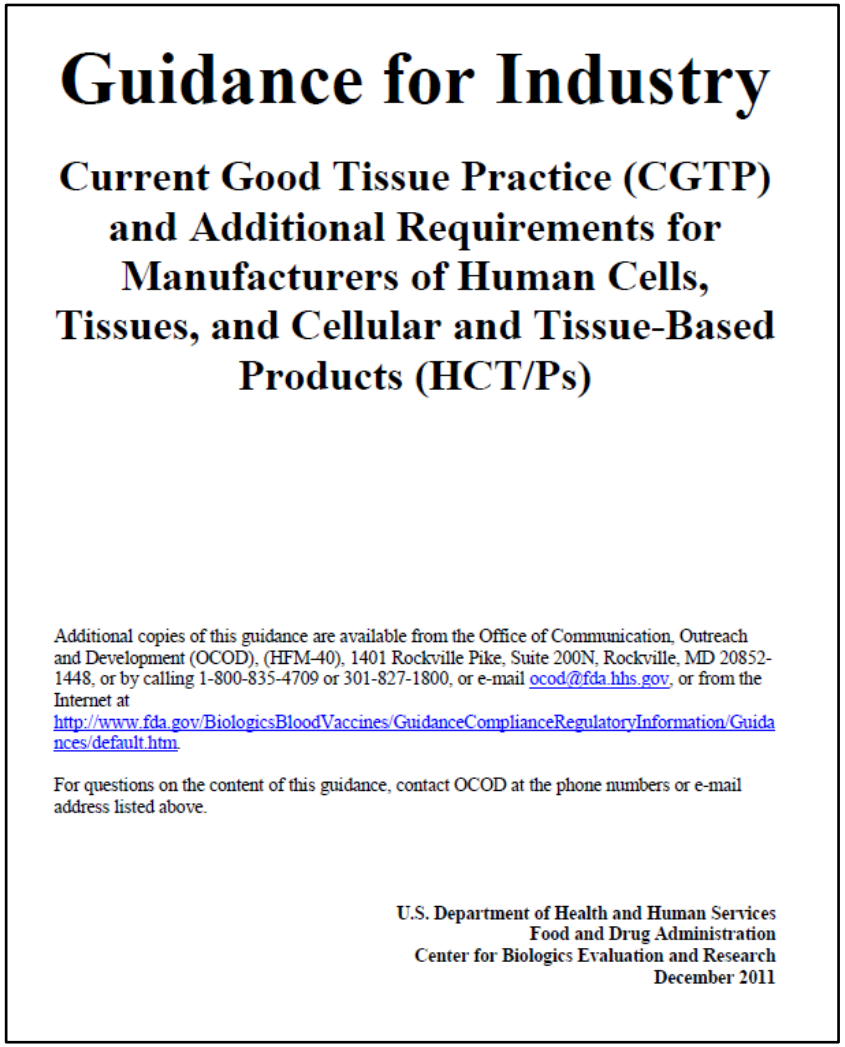
- 361 HCT/P
  - Regulated solely under authority of section 361 of the Public Health Service (PHS) Act
  - Subject to "Tissue Regulations" (21 CFR part 1271)
  - Premarket review and approval **not required**
- Drugs, devices, biological products (351 HCT/Ps)
  - Regulated under authority of section 361 and section 351 of the PHS Act and/or the Federal Food, Drug, & Cosmetic Act, and applicable regulations
  - Premarket review and approval **required**

Current Good Tissue Practice (CGTP)

III. CGTP REQUIREMENTS (§ 1271.150)

E. Do I Have to Follow CGTP Requirements if My HCT/Ps Are Also Regulated as a Biological Product, Drug, or Device?

Yes, CGTP requirements as well as drug current good manufacturing practice (CGMP) requirements or device quality system (QS) regulation requirements apply. The current CGMP regulations in 21 CFR Parts 210 and 211 or the QS regulation in 21 CFR Part 820 apply to an HCT/P depending upon whether the product is regulated as a drug, device or biological product (§ 1271.150(d)) (see especially, §§ 210.1(c), 210.2, 211.1, and 820.1). These CGMP and QS regulations supplement the CGTP requirements, and in the event that a regulation in Part 1271 is in conflict with a requirement in Parts 210, 211, or 820, the regulations more specifically applicable to the product in question will supersede the more general.



Guidance for Industry

Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

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 1-800-835-4709 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.

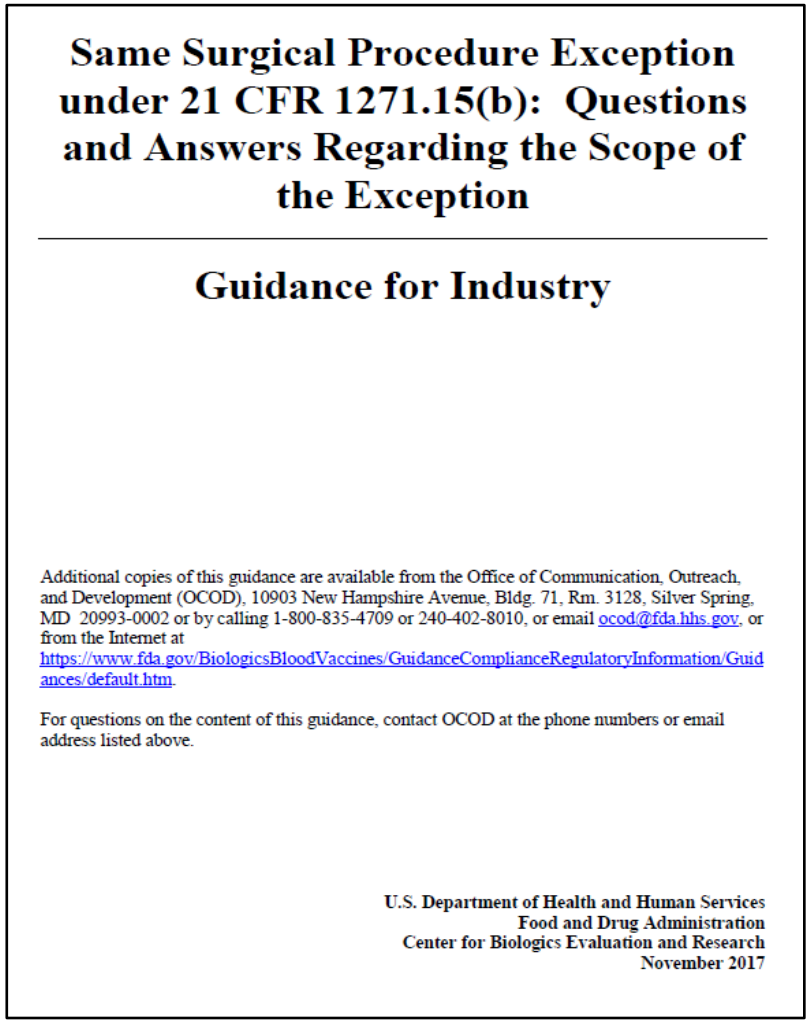
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2011

Exceptions to 21 CFR part 1271 Regulations

- 21 CFR 1271.15
  - Limited situations in which certain entities are not required to comply with the regulations in part 1271, unless noted otherwise
- **21 CFR 1271.15(b)**
  - You are not required to comply with the requirements of this part if you are an establishment that removes HCT/Ps from an individual and implants ***such HCT/Ps*** into the same individual during the same surgical procedure.

Same Surgical Procedure Exception (SSPE)

- Issued November 2017
- What is the relationship between the exception in 21 CFR 1271.15(b) and the four criteria in 21 CFR 1271.10(a)
- Types of procedures generally considered the same surgical procedure
- What processing steps can be performed that meet the exception



Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

Guidance for Industry

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 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://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
November 2017

When does the exception in 21 CFR 1271.15(b) apply?

- For the exception to apply, an establishment must:
  - remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use)
  - implant the HCT/Ps within the same surgical procedure; and
  - the HCT/Ps remain "such HCT/Ps"
- An HCT/P remains "such HCT/P" when it is in its original form. Generally, the only processing steps that will allow an HCT/P to remain "such HCT/P" are rinsing, cleansing, sizing, and shaping

Note: FDA considers the same surgical procedure exception to be a narrow exception to regulation under 21 CFR part 1271

Minimal Manipulation (MM)

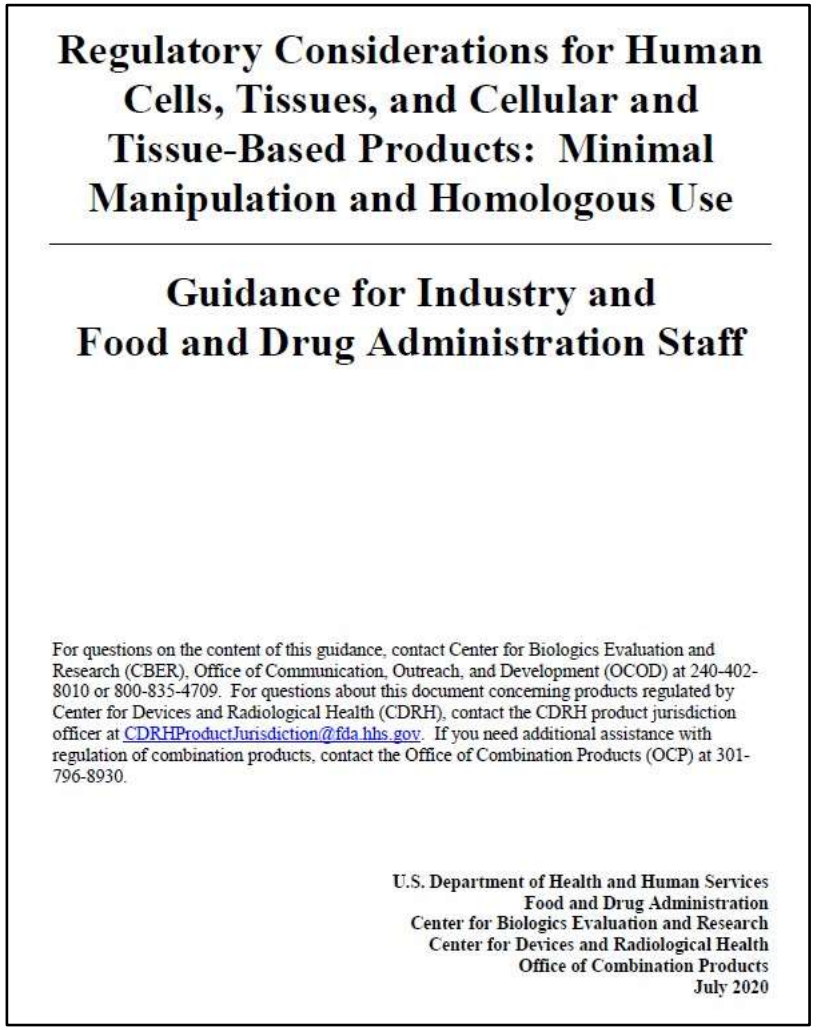
- Defined in 21 CFR 1271.3(f)
- For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement
- For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues
- Criterion relates to how the HCT/P functioned in the donor

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

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)
- Clarifies that MM and HU are distinct concepts
- 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)



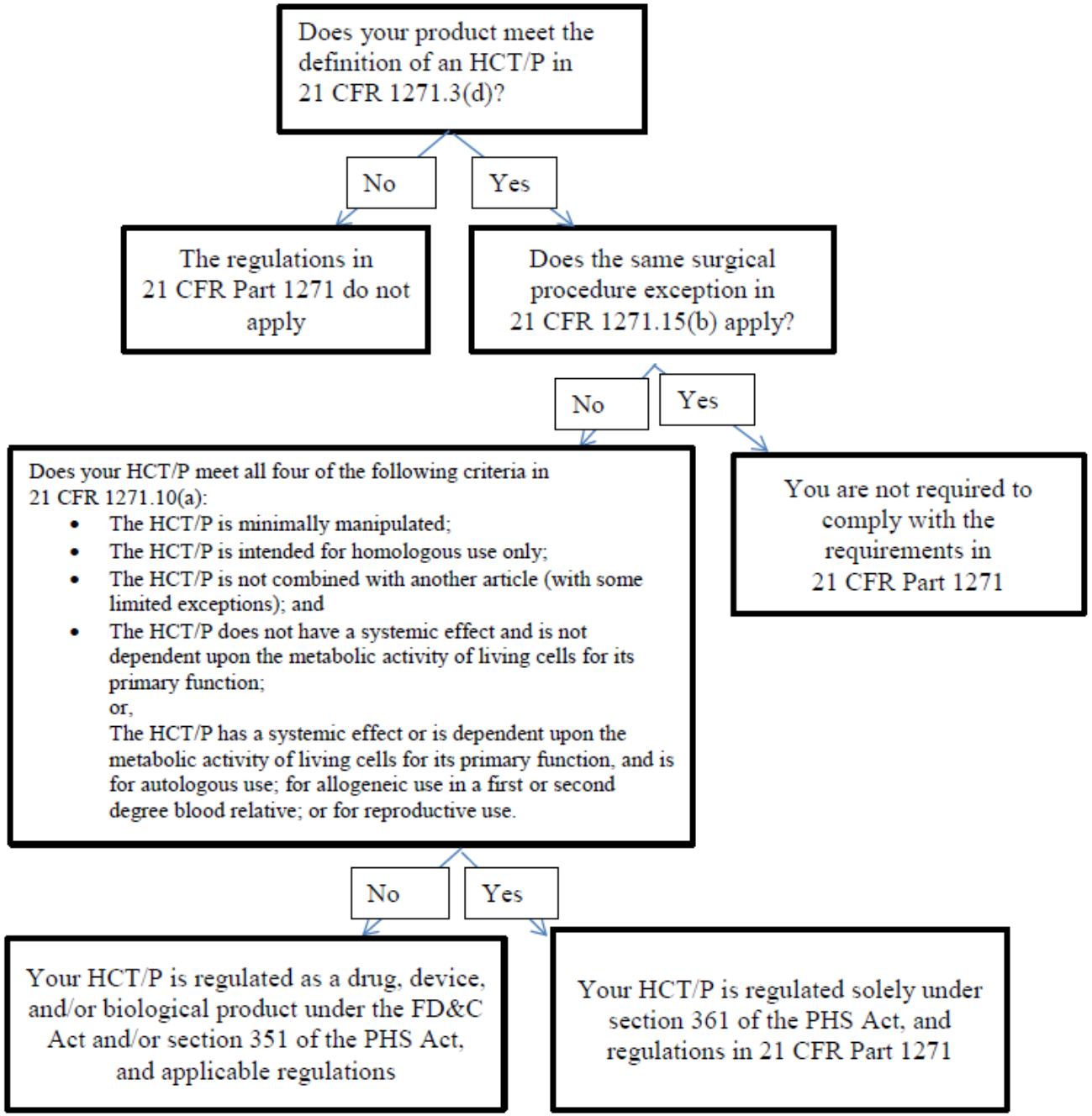
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

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

Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(b) and 1271.10(a)



Compliance and Enforcement Policy

- To give manufacturers **time to determine if they need to submit an IND [Investigational New Drug Application] or marketing application … and, if such an application is needed, to prepare the IND or marketing application,** the guidance describes a period of enforcement discretion for products based on a determination of the risk to public health
  - May 31, 2021 was the last day of "Period of Enforcement Discretion"
- A product that requires but lacks premarket approval may not be lawfully marketed, including when a sponsor has an IND or is pursuing a Biological License Application (BLA)

Options for Obtaining Regulatory Classification

- Obtain a Recommendation
  - Tissue Reference Group (TRG)

    https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group

    Revised SOPP 8004 posted 1-16-2020

    https://www.fda.gov/media/85648/download
  - Pre-RFD

    Guidance for Industry: How to Prepare a Pre-Request for Designation

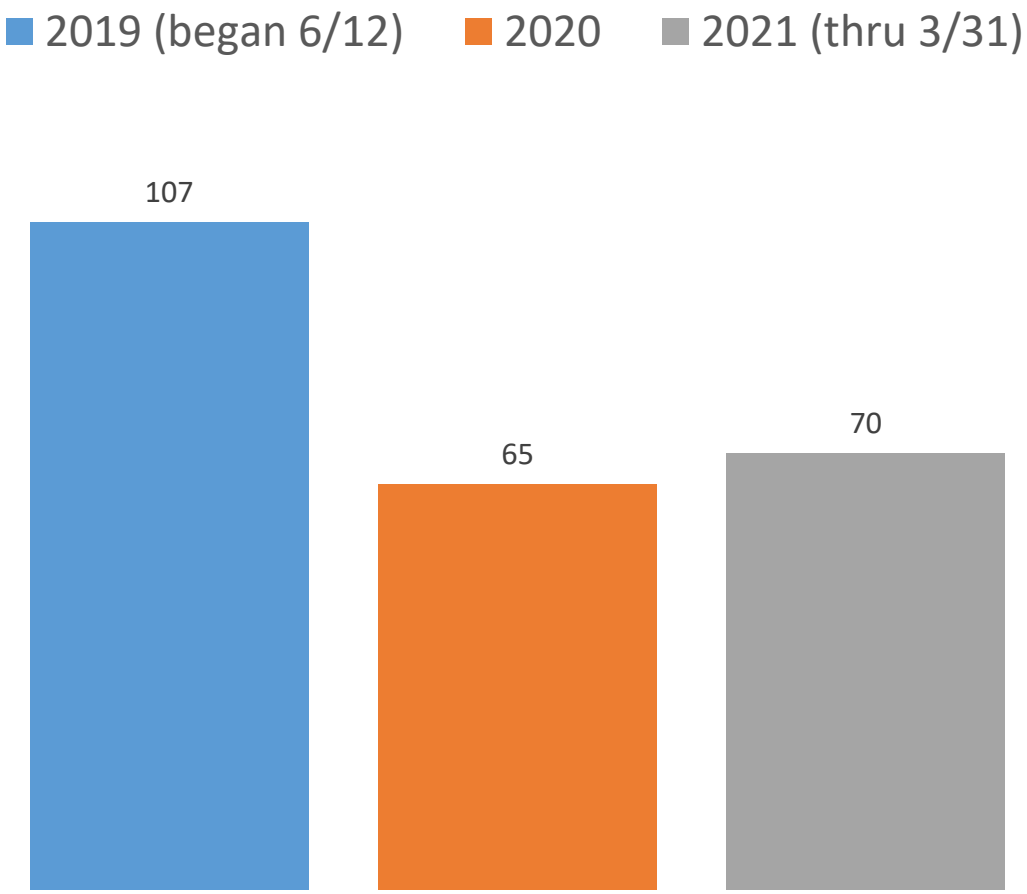
    https://www.fda.gov/media/102706/download
- Obtain a Decision
  - Request for Designation (RFD)

    https://www.fda.gov/CombinationProducts/RFDProcess/default.htm

TRG Rapid Inquiry Program (TRIP)

- Temporary program for providing a preliminary, informal, non-binding assessment from FDA's TRG as to how an HCT/P appears to be appropriately regulated
- Resources permitting, FDA will respond within one week to each inquiry that contains sufficient detail for evaluation
- Originally announced effective dates: June 12, 2019 to December 31, 2019
  - Program extended to March 31, 2020 (announced December 2019)
  - Program extended to October 31, 2020 (announced March 2020)
  - Program extended to **March 31, 2021 and ended** (announced July 2020)

TRIP Inquiries



242 TRIP inquiries received from manufacturers, consultants, law firms, practitioners, marketers, distributors, and other stakeholders

Knowledge Check 1

True or False:

History has shown us that communicable disease agents and diseases transmitted through use of HCT/Ps have been limited to viruses (e.g., HIV, HBV, HCV) derived from the donor.

Knowledge Check 2

Which options below are available to manufacturers to obtain from FDA a regulatory classification for their HCT/P?:

1. Request for Designation (RFD)
2. Pre-RFD
3. Tissue Reference Group (TRG)

Resources

21 CFR part 1271
https://www.ecfr.gov/cgi-bin/text-idx?SID=f6f44f140b31543c17e0a8974f1500fd&mc=true&node=pt21.8.1271&rgn=div5

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

Tissue Notices, Proposed and Final Rules
https://www.fda.gov/vaccines-blood-biologics/biologics-rules/tissue-notices-proposed-and-final-rules

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

Resources

Industry (Biologics)

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/default.htm

Tissue Establishment Registration

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/default.htm

> According to §1271.27(b), FDA acceptance of an establishment registration and HCT/P listing does not constitute a determination that an establishment is in compliance with applicable rules and regulations or that the HCT/P is licensed or approved by FDA.

Resources

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https://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/default.htm

Summary

- Use of HCT/Ps has led to risks to public health due to transmissions of disease.
- A tiered risk-based approach was used when promulgating regulations to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps.
- To understand how an HCT/P should be appropriately regulated, refer to criteria and definitions in 21 CFR part 1271 regulations that pertain to how the product is manufactured and how it is intended to be used.

Thank you for your kind attention!

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