

# **Guidance for Industry**

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

### **Small Entity Compliance Guide**

**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 written comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact the Office of Communication, Training and Manufacturers Assistance at 1-800-835-4709 or 301-827-1800.

**U.S. Department of Health and Human Services  
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**Contains Nonbinding Recommendations**

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## Small Entity Compliance Guide

*This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

### I. INTRODUCTION

The Food and Drug Administration (FDA) has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). It is intended to help small entity establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps) better understand and comply with the comprehensive regulatory framework for HCT/Ps, set forth in Title 21 of the Code of Federal Regulations, Part 1271 (21 CFR Part 1271). Title 21 CFR 1271.3 provides definitions for important terms used in 21 CFR Part 1271.

Previously, FDA issued questions and answers regarding the regulations in 21 CFR Part 1271. These questions and answers, along with other guidances and rulemakings pertaining to 21 CFR Part 1271, can be found at <http://www.fda.gov/cber/tissue/docs.htm>, and will not be covered in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

### II. BACKGROUND

Historically, the approach to regulating human cellular and tissue-based products (now called human cells, tissues, and cellular and tissue-based products or HCT/Ps) was highly fragmented. In 1997, FDA proposed a new approach to the regulation of HCT/Ps.<sup>1</sup> This approach would

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<sup>1</sup> 62 FR 9721, March 4, 1997.

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establish in 21 CFR Part 1271 a comprehensive regulatory program for HCT/Ps. In accordance with the tiered, risk-based approach that FDA proposed, some HCT/Ps would be regulated only under those new regulations and section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264), while others would be regulated as drugs, devices, and/or biological products under section 351 of the PHS Act (42 U.S.C. 262) and/or the Federal Food, Drug, and Cosmetic Act (the act). FDA requested written comments on the proposed approach and, on March 17, 1997, held a public meeting.<sup>2</sup>

FDA published three final rules and two interim final rules, outlined below, to implement the proposed approach.

1. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (registration final rule) (66 FR 5447, January 19, 2001). These provisions:
  - set forth 21 CFR Part 1271, Subpart A (general provisions pertaining to the scope and purpose of 21 CFR Part 1271, as well as definitions), and 21 CFR Part 1271, Subpart B (registration and listing procedures);
  - became effective in two stages:
    - the first effective date, April 4, 2001, applied to establishments whose products were already regulated under section 361 of the PHS Act and the regulations in 21 CFR Part 1270.
    - the second effective date was originally January 21, 2003, and applied to establishments that manufacture HCT/Ps currently regulated as biological products, drugs, or devices; hematopoietic stem cells from peripheral and cord blood; and reproductive cells and tissues. However, FDA delayed the second effective date until January 21, 2004.<sup>3</sup>
2. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (interim final rule) (69 FR 3823, January 27, 2004).
  - Excepted human dura mater and human heart valve allografts from the scope of the definition of HCT/Ps until the rulemaking for all of 21 CFR Part 1271 was completed.
  - Effective date – January 23, 2004 (compliance date – March 29, 2004).
3. “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products” (donor eligibility final rule) (69 FR 29786, May 25, 2004).
  - Set forth 21 CFR Part 1271, Subpart C (provisions for the screening and testing of donors to determine their eligibility).
  - Effective date – May 25, 2005.

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<sup>2</sup> Id.

<sup>3</sup> 68 FR 2689, January 21, 2003.

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4. “Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments, Inspection and Enforcement” (CGTP final rule) (69 FR 68612, November 24, 2004).
  - Set forth 21 CFR Part 1271, Subpart D (CGTP requirements), Subpart E (additional requirements for establishments described in 21 CFR 1271.10), and Subpart F (inspection and enforcement provisions for establishments described in 21 CFR 1271.10).
  - Effective date – May 25, 2005.
  - Subparts D (with some exceptions) and E do not apply to reproductive HCT/Ps at this time.
5. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling” (interim final rule) (70 FR 29949, May 25, 2005).
  - Revised certain regulations regarding the screening and testing of HCT/P donors and related labeling.
  - Effective date – May 25, 2005.

On June 19, 2007 (72 FR 33667), FDA adopted as a final rule, without change, the provisions of the May 25, 2005, interim final rule.

FDA believes that these regulations will increase the safety of HCT/Ps, and public confidence in their safety, by preventing the introduction, transmission and spread of communicable disease. The agency’s actions are intended to improve protection of the public health while minimizing regulatory burden, which in turn would encourage significant innovation.

### III. QUESTIONS AND ANSWERS

#### A. GENERAL

##### 1. Where can an establishment find the criteria to determine how their HCT/Ps will be regulated?

Title 21 CFR 1271.10(a) sets out the criteria that form the foundation of FDA’s tiered, risk-based approach to regulating HCT/Ps. HCT/Ps that meet all of these criteria are subject only to regulation under section 361 of the PHS Act and the regulations in 21 CFR Part 1271. (An HCT/P that falls into this category is referred to as a “361 HCT/P”). No premarket approval is required.

If the HCT/Ps do not meet the criteria in 21 CFR 1271.10(a) for regulation solely as 361 HCT/Ps, and the establishment does not qualify for any of the exceptions listed in 21 CFR 1271.15, the HCT/Ps are regulated as drugs, devices, and/or biological products (21 CFR

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1271.20). These HCT/Ps are subject to section 351 of the PHS Act and/or the act, and applicable regulations in Title 21 of the CFR.<sup>4</sup>

### **2. For establishments that manufacture a drug, device or biological product that is considered an HCT/P, what must the establishment do if a requirement in 21 CFR Part 1271 conflicts with a requirement in 21 CFR Parts 210, 211, or 820?**

In the event that a regulation in 21 CFR Part 1271 is in conflict with a requirement in 21 CFR Parts 210, 211, or 820, the establishment must follow the requirements that are more specifically applicable to the product, rather than the more general requirements (21 CFR 1271.150(d)).

### **3. What are examples of some 361 HCT/Ps that meet the criteria in 21 CFR 1271.10(a)?**

- Amniotic membrane when used alone or without added cells
- Bone
- Cartilage
- Cornea
- Fascia
- Ligament
- Pericardium
- Peripheral or umbilical cord blood stem cells (for autologous use or use in a first or second degree blood relative)
- Sclera
- Skin
- Tendon
- Vascular graft
- Heart valves
- Dura mater
- Reproductive cells and tissues (e.g., semen, oocytes, embryos)

All of the above are minimally manipulated, intended for homologous use only, and not combined with another article, with some exceptions.

### **4. For HCT/Ps recovered before May 25, 2005, which subparts of 21 CFR Part 1271 apply?**

All HCT/Ps recovered before May 25, 2005 are subject to certain regulations in 21 CFR Part 1271, Subpart A (General Provisions) and Subpart B (Procedures for Registration and Listing), as appropriate. In addition, such HCT/Ps are subject to the regulations in 21 CFR Part 1270. The regulations in 21 CFR Part 1271, Subparts C through F do not apply to HCT/Ps recovered before May 25, 2005.

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<sup>4</sup> Applicable regulations include, but are not limited to, 21 CFR 207.20(f), 210.1(c), 210.2, 211.1(b), 807.20(d), and 820.1(a), which require establishments to follow the procedures in 21 CFR Part 1271, Subparts B, C, and D.

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### 5. For HCT/Ps recovered after May 25, 2005, which subparts of 21 CFR Part 1271 apply?

For 361 HCT/Ps, the subparts of 21 CFR Part 1271 apply as follows:

- Subparts A through C apply to all 361 HCT/Ps.
- Subpart D applies only to nonreproductive 361 HCT/Ps, with the exception of 21 CFR 1271.150(c) and 1271.155, which apply to all 361 HCT/Ps.
- Subpart E applies only to nonreproductive 361 HCT/Ps.
- Subpart F applies to all 361 HCT/Ps.

For HCT/Ps regulated as drugs, devices, and/or biological products, the subparts of 21 CFR Part 1271 apply as follows:

- Subparts A through D apply to all such HCT/Ps.
- Subparts E and F do not apply.

## B. REGISTRATION AND LISTING

### 1. Which establishments are required to register and list their HCT/Ps?

All establishments that manufacture 361 HCT/Ps must register and list their HCT/Ps with the Center for Biologics Evaluation and Research (CBER) (21 CFR 1271.1(b)(1); see 21 CFR 1271.10(b) and 1271.21). In addition, all establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act must register and list their HCT/Ps with CBER (21 CFR 1271.1(b)(2)).<sup>5</sup>

FDA does not require establishments that manufacture drugs and devices under an investigational new drug application (IND) (21 CFR Part 312) or an investigational device exemption (IDE) (21 CFR Part 812) to register and list their HCT/Ps with CBER until the products are approved; or, cleared for premarket notifications. Therefore, establishments that only manufacture HCT/Ps currently under an IND or IDE do not have to register and list their HCT/Ps until the investigational HCT/P is approved through a biologics license application (BLA), a new drug application (NDA), or a premarket approval application (PMA); or cleared through a premarket notification submission (510(k)).

### 2. When must new establishments register and list their HCT/Ps?

New establishments must register and list their HCT/Ps within 5 days after beginning operations (21 CFR 1271.21(a)). The establishment should also appoint a Reporting Official who will be responsible for registration and listing updates and/or changes and who will serve as the contact for all registration related communication.

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<sup>5</sup> Specifically, 21 CFR 1271.1(b)(2) states that if an establishment manufactures HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act, 21 CFR 207.20(f) and 807.20(d) require such an establishment to register and list its HCT/Ps with CBER, following the procedures in 21 CFR Part 1271, Subpart B.

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### **3. Which establishments are exempt from HCT/P registration and listing?**

If an establishment qualifies for any of the exceptions listed in 21 CFR 1271.15, the establishment does not have to register and list their HCT/Ps with CBER.

### **4. What else will establishments have to do after the initial registration?**

Establishments must update their registration annually in December and submit changes in HCT/P listing within 6 months of the change (21 CFR 1271.21). Even if there are no changes or updates to an establishment's HCT/P listing, the establishment must still register annually. We recommend that establishments keep a record on file containing the field establishment identifier number (FEI #) and validation date of the registration as this information is necessary to make changes and updates electronically. If the ownership or location of the establishment changes, the establishment must submit an amended registration form within 5 days of the change (21 CFR 1271.26). FDA currently notifies the Reporting Official listed on Form FDA 3356 in November regarding the annual registration.

### **5. What would happen if an establishment does not register or forgets to submit the annual registration?**

The establishment is in violation of the regulations.

### **6. How will an establishment know when it is officially registered with FDA?**

FDA considers the establishment to be registered and in compliance with 21 CFR Part 1271 requirements as soon as FDA receives the Form FDA 3356 (registration form). After FDA processes the establishment's registration form, FDA will send to the Reporting Official a validated form, which includes the registration number (FEI #). If the establishment already registered under 21 CFR Parts 207, 607, or 807, the establishment will retain the same FEI #.

If the establishment has not received its validation form confirming its "registered" status and needs to know its registration status as "pre-registered", the establishment may contact FDA at [tissureg@fda.hhs.gov](mailto:tissureg@fda.hhs.gov) or access the Public Query Application (<http://www.fda.gov/cber/tissue/tissregdata.htm>). The status will change to "registered" when the FEI # has been generated. An establishment may also use the Public Query Application to access a list of other establishments that are registered with the FDA.

When an establishment updates the registration form from "registered" to "inactive", FDA considers the status changed as soon as FDA receives the form.

### **7. Where can an establishment find more information on how to register and list HCT/Ps?**

- <http://www.fda.gov/cber/tissue/tisreg.htm> – provides access to the establishment registration form (Form FDA 3356), instructions for completing the form (paper and electronic form), and other information on the Electronic Human Cell and Tissue Establishment Registration (eHCTERS).

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- <http://www.fda.gov/cber/tissue/tisregcontact.htm> – provides contact information for the CBER Tissue Establishment Registration Coordinator.

### **8. Must an individual or company register if it only obtains blood samples from donors and sends the samples to a registered establishment (e.g., an independent laboratory or a recovery establishment) for testing?**

No. If an individual or company is simply obtaining a blood sample from a donor and sending the blood sample to a registered testing laboratory or to a registered recovery establishment, then the individual or company is not required to register. Obtaining a blood sample is not considered part of manufacturing.

### **9. Must an establishment (laboratory) register if it only performs speciation of microorganisms already detected in an HCT/P culture specimen?**

Yes. By definition, manufacture includes processing, and processing includes testing for microorganisms (21 CFR 1271.3(e) and (ff)). Testing for microorganisms generally includes sampling, culturing and identifying the microorganisms present in the sample (speciation). FDA is aware that HCT/P manufacturers use this information in a number of ways, including determining whether an HCT/P may be processed and/or distributed. If an establishment (laboratory) only performs speciation of microorganisms, the establishment (laboratory) must register as it is performing a processing step (21 CFR 1271.1(b)).

### **10. What is the process to cancel registration if the establishment no longer manufactures HCT/Ps?**

The Reporting Official listed on the Form FDA 3356 may submit a revised Form FDA 3356 (paper or electronic form), marking “inactive” in box 2, to inactivate the registration.

### **11. Must a hospital that manufactures more than one type of HCT/P (e.g., hematopoietic stem/progenitor cells, reproductive cells) and/or that performs different manufacturing functions (e.g., recovery, processing, donor testing) have multiple registrations?**

Each physical location will generally have only one registration number (FEI #) for any combination of HCT/P types and/or functions unless the individual establishments are under different corporate entities. An establishment means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps (21 CFR 1271.3(b)). One general physical location could be reasonably construed to include separate buildings within close proximity provided that the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and capable of being inspected at the same time. For example, a hospital administrator could facilitate one registration of multiple laboratories under the same management. However, we recommend separate registrations for two or more business enterprises that are separate legal entities with different management even if both use the same facility or the same address.<sup>6</sup>

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<sup>6</sup> See [http://www.fda.gov/ora/inspect\\_ref/fmd/fmd130.html](http://www.fda.gov/ora/inspect_ref/fmd/fmd130.html).

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### **12. Must hospitals that surgically remove and temporarily store autologous HCT/Ps prior to implanting the HCT/Ps register and list such HCT/Ps?**

No. We consider this to be the same surgical procedure, even though the storage time and future replacement surgery may be a number of days apart. Therefore, such hospitals would qualify for the exemption listed in 21 CFR 1271.15(b) as long as they do no additional manufacturing to the HCT/Ps.

### **13. Must hospitals that receive, store, and routinely share qualified HCT/Ps with other hospitals register and list such HCT/Ps?**

Yes. An establishment is not required to comply with the requirements of 21 CFR Part 1271 if the establishment does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within its facility (21 CFR 1271.15(d)). Hospitals that receive HCT/Ps and make them available for distribution to other hospitals are performing the manufacturing steps of storage and distribution and therefore must register and list such HCT/Ps with CBER (21 CFR 1271.21; see 21 CFR 1271.3(e)).

### **14. Must foreign establishments that import HCT/Ps for distribution in the United States register and list such HCT/Ps?**

Yes. All foreign establishments importing or offering for import HCT/Ps into the United States must register and list such HCT/Ps with CBER.<sup>7</sup> If such HCT/Ps are 361 HCT/Ps, the foreign establishment should indicate the name, address, and phone number of its U.S. agent (someone located in the United States as a contact for inspection purposes) on the initial and updated registration form. If such HCT/Ps are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act, the foreign establishment must submit the name, address, and phone number of its U.S. agent on the initial and updated registration form; the U.S. agent must reside or maintain a place of business in the United States (see 21 CFR 207.40(c) and 807.40(b)). Foreign establishments may submit Form FDA 3356 via mail, facsimile, or electronically.

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<sup>7</sup> Foreign establishments manufacturing 361 HCT/Ps must register and list such HCT/Ps with CBER (21 CFR 1271.10(b); see 21 CFR 1271.1(b)(1) and 1271.21). Foreign establishments importing or offering for import drugs and/or devices into the United States must comply with the registration and listing requirements in 21 CFR Part 207, Subpart C, and Part 807, Subpart B (21 CFR 207.40(a) and 807.40(a)). Foreign biological establishments would also be subject to 21 CFR 207.40(a) and 807.40(a) because biological products meet the definition of “drug” or “device” under the act. As discussed in footnote 5, 21 CFR 207.20(f) and 807.20(d) require drug, device, and biological establishments to register and list their HCT/Ps with CBER, following procedures in 21 CFR Part 1271, Subpart B. Therefore, foreign establishments whose HCT/Ps are regulated as drugs, devices, and/or biological products and are imported or offered for import into the United States must register and list such HCT/Ps with CBER.

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### C. DONOR ELIGIBILITY

#### 1. How do the donor eligibility requirements under 21 CFR Part 1271, Subpart C, differ from the donor suitability requirements under 21 CFR Part 1270?

Title 21 CFR Part 1270 applies only to certain human tissue intended for transplantation (musculoskeletal, skin, and ocular), recovered before May 25, 2005, and requires donor screening and testing for only certain diseases (HIV, hepatitis B, and hepatitis C). Title 21 CFR Part 1271, Subpart C, applies to donors of additional cells and tissues, recovered on or after May 25, 2005, and requires screening and testing of these donors for additional relevant communicable diseases. For example, 21 CFR Part 1271, Subpart C, applies to donors of hematopoietic stem/progenitor cells derived from peripheral and umbilical cord blood (e.g., cord blood), reproductive cells and tissue (e.g., semen, oocyte, embryo), human dura mater, and human heart valves, in addition to donors of musculoskeletal, skin, and ocular tissue. Title 21 CFR Part 1271 also applies to HCT/Ps regulated as drugs, devices, or biological products, whereas 21 CFR Part 1270, does not.

#### 2. Where can an establishment find more information on donor eligibility?

An establishment can find more comprehensive information on donor eligibility by accessing FDA's "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" and "Guidance for Industry: Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donors Who Were Tested For Communicable Diseases Using Pooled Specimens or Diagnostic Tests" at <http://www.fda.gov/cber/tissue/docs.htm>.

### D. CURRENT GOOD TISSUE PRACTICE

#### 1. What are current good tissue practice requirements?

Current good tissue practice (CGTP) requirements are the requirements in 21 CFR Part 1271, Subparts C and D, that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packing, and distribution (21 CFR 1271.150(a)).

#### 2. What is the purpose of the CGTP requirements?

The requirements aim to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps by reducing the risk that the HCT/Ps contain communicable disease agents (e.g., viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents), and by preventing contamination during manufacturing.

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### **3. If an establishment only performs certain activities in the manufacture of HCT/Ps, must the establishment follow all CGTP requirements?**

An establishment need only comply with those requirements applicable to the operations that it performs (21 CFR 1271.150(c)(1)(i)). For example, a laboratory that performs communicable disease tests but does not store HCT/Ps would not have to meet HCT/P storage requirements.

### **4. What are “core CGTP requirements”? Is an HCT/P establishment only required to follow core CGTP requirements and not other CGTP requirements?**

Core CGTP requirements (21 CFR 1271.150(b)) are those requirements that directly relate to preventing the introduction, transmission, or spread of communicable diseases by HCT/Ps. They include requirements for facilities, environmental control, equipment, supplies and reagents, recovery, processing, process controls, labeling controls, storage, receipt, predistribution shipment, distribution, and donor screening and testing. Other CGTP requirements support the core CGTP requirements (e.g., requirements for procedures and recordkeeping). An establishment must follow all of the CGTP requirements applicable to the operations that it performs, whether or not they are considered core requirements. See 21 CFR 1271.150(c)(1)(i).

### **5. What if one establishment engages another establishment (e.g., a contract establishment) to perform certain steps in manufacture, under a contract, agreement, or other arrangement?**

The contract establishment must comply with those CGTP requirements applicable to the manufacturing step(s) that it performs under a contract, agreement, or other arrangement (21 CFR 1271.150(c)(1)(ii)). The establishment that is contracting for outside work must ensure that the contract establishment complies with applicable CGTP requirements before entering into the contract, agreement, or arrangement (21 CFR 1271.150(c)(iii)). If, after entering into the contract, agreement, or arrangement, that establishment becomes aware of information suggesting that the contract establishment may no longer be in compliance, the establishment that is contracting for outside work must either: (a) investigate and take reasonable steps to ensure that the contract establishment complies, or (b) terminate the contract, agreement, or arrangement with the non-compliant firm (21 CFR 1271.150(c)(1)(iii)). For further information, see “Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements” available at <http://www.fda.gov/cber/tissue/docs.htm>.

### **6. What does an establishment do if it has questions about the CGTP regulations?**

FDA previously issued questions and answers regarding the regulations in 21 CFR Part 1271, which include the CGTP regulations. These questions and answers can be found at <http://www.fda.gov/cber/tissue/docs.htm>. If an establishment has specific questions about the CGTP regulations, please contact the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852, 1-800-835-4709 or 301-827-1800. Questions may also be submitted via email to: [matt@cber.fda.gov](mailto:matt@cber.fda.gov) (industry) or [octma@cber.fda.gov](mailto:octma@cber.fda.gov) (consumers and health care professionals).

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### **E. FDA INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 21 CFR 1271.10**

#### **1. What does an FDA inspection involve?**

An FDA inspection will be conducted as necessary in the judgment of FDA to determine compliance with the applicable provisions in 21 CFR Part 1271 (21 CFR 1271.400(a)). The FDA inspection may include, but is not limited to, an assessment of the establishment's facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers and controls required to be maintained under 21 CFR Part 1271.

FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel as necessary to determine compliance with the provisions of 21 CFR Part 1271 (21 CFR 1271.400(c)). FDA representatives may take samples, may review and copy any records required to be kept under 21 CFR Part 1271, and may use other appropriate means to record evidence of observations during inspections (21 CFR 1271.400(d)). Financial records and personnel records are not required records under 21 CFR Part 1271.

For reproductive establishments, inspections will be limited to determining compliance with applicable provisions contained in 21 CFR Part 1271, Subparts A, B, and C; and 21 CFR 1271.150(c)(1) and 1271.155 of Subpart D. For information about compliance and surveillance activities relating to 361 HCT/Ps, see the Compliance Program Guidance Manual, Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), 7341.002, at <http://www.fda.gov/cber/cpg/7341002tis.htm>.

#### **2. When will an FDA inspection be performed?**

An FDA inspection will ordinarily be performed during regular business hours and may be made with or without prior notification (21 CFR 1271.400(a)). The frequency of inspection will be at FDA's discretion (21 CFR 1271.400(b)).

#### **3. What enforcement actions can FDA take to prevent the introduction, transmission, or spread of communicable diseases for 361 HCT/Ps?**

For 361 HCT/Ps, the advisory, administrative and judicial actions include an Untitled Letter; Warning Letter; Orders of Retention, Recall, Destruction, and Cessation of Manufacturing; and Prosecution.<sup>8</sup>

An Untitled Letter is a correspondence with regulated industry that cites violations that do not meet the threshold of regulatory significance for a Warning Letter. A Warning Letter is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other

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<sup>8</sup> See FDA's Compliance Program Guidance Manual, Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 7341.002, Part V – Regulatory/Administrative Strategy.

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activities to be in violation of statutes or their implementing regulations. Warning Letters are only issued for violations of regulatory significance (i.e., those that may lead to an enforcement action if the documented violations are not promptly and adequately corrected).

Under 21 CFR 1271.440, FDA may issue orders for retention, recall, destruction, and/or cessation of manufacturing. FDA may take one or more of these actions upon an agency finding that there are reasonable grounds to believe the following: (a) an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in 21 CFR Part 1271 and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or (b) the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or (c) an establishment is in violation of the regulations in 21 CFR Part 1271 and, therefore, does not provide adequate protections against the risks of communicable disease transmission.

FDA may pursue prosecution for gross, flagrant or intentional violations, fraud, danger to health, or a continued or repeated course of violative conduct.<sup>9</sup>

#### **4. When would an FDA order for cessation of manufacturing go into immediate effect?**

The FDA order for cessation of manufacturing will go into immediate effect only when FDA determines that there are reasonable grounds to believe that there is a danger to health if the establishment continues to manufacture (see 21 CFR 1271.440(a)(3)).

#### **5. Are there any exceptions to the enforcement provisions in 21 CFR Part 1271, Subpart F?**

Yes. In 21 CFR 1271.440(f), FDA will not issue an order for the destruction of reproductive tissue, nor will it carry out such destruction itself.

#### **6. What are the requirements for importing 361 HCT/Ps?**

With two exceptions (certain reproductive HCT/Ps and peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act), when an HCT/P is offered for import, the importer of record must notify, either before or at the time of importation, the director of the FDA district having jurisdiction over the port of entry through which the HCT/P is imported or offered for import. Additionally, the importer of record must provide sufficient information for FDA to make an admissibility decision (see 21 CFR 1271.420(a)). For additional information, see [http://www.fda.gov/ora/inspect\\_ref/iom/IOMORADIR.html](http://www.fda.gov/ora/inspect_ref/iom/IOMORADIR.html) and <http://www.fda.gov/cber/cpg/7342007tis.htm>.

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<sup>9</sup> Sections 3559 and 3571(c) of Title 18, U.S.C., and section 368 of the PHS Act (42 U.S.C. 271) are the applicable statutes when pursuing prosecution for violating regulations promulgated under section 361 of the PHS Act. Under section 368(a) of the PHS Act, any individual who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Additionally, individuals may be punished by a fine of up to \$100,000 if death has not resulted from a violation of the regulations or up to \$250,000 if death has resulted.

## **Contains Nonbinding Recommendations**

### **7. What are the exceptions for 361 HCT/Ps offered for import?**

The import provisions in 21 CFR 1271.420 do not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in 21 CFR Part 1271, and donated by a sexually intimate partner of the recipient for reproductive use (21 CFR 1271.420(c)). In addition, such import provisions do not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in 21 CFR Part 1271, except when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission. In such circumstances, 21 CFR 1271.420(a) and (b) apply (21 CFR 1271.420(d)).