

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

## Small Entity Compliance Guide

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### 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](mailto: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**

**Contains Nonbinding Recommendations**

**Table of Contents**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>QUESTIONS AND ANSWERS.....</b>	<b>2</b>
	<b>A. GENERAL.....</b>	<b>2</b>
	<b>B. REGISTRATION AND LISTING.....</b>	<b>4</b>
	<b>C. DONOR ELIGIBILITY.....</b>	<b>9</b>
	<b>D. CURRENT GOOD TISSUE PRACTICE.....</b>	<b>10</b>
	<b>E. FDA INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 21 CFR 1271.10.....</b>	<b>13</b>
<b>III.</b>	<b>REFERENCES.....</b>	<b>18</b>

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### Guidance for Industry

*This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

#### 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<sup>1</sup> human cells, tissues, or cellular or tissue-based products (HCT/Ps) better understand the comprehensive regulatory framework for HCT/Ps, set forth in Title 21 of the Code of Federal Regulations, part 1271 (21 CFR 1271).<sup>2</sup> Section 21 CFR 1271.3 provides definitions for important terms used in 21 CFR 1271.

This guidance document supersedes the guidance of the same title dated August 2007.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> "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(e)).

<sup>2</sup> See "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing;" Final Rule, 66 FR 5447 (January 19, 2001); "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products;" Final Rule, 69 FR 29786 (May 25, 2004); "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement;" Final Rule, 69 FR 68612 (November 24, 2004).

## Contains Nonbinding Recommendations

### II. QUESTIONS AND ANSWERS

#### A. GENERAL

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

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 the criteria in 21 CFR 1271.10(a) are subject only to regulation under section 361 of the Public Health Service Act (PHS Act) and the regulations in 21 CFR part 1271. An HCT/P that falls into this category is sometimes referred to as a "361 HCT/P" and no premarket authorization is required.

If an HCT/P does not meet all the criteria set out in 21 CFR 1271.10(a), and the establishment that manufactures the HCT/P does not qualify for any of the exceptions listed in 21 CFR 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act (FD&C Act), and applicable regulations, including 21 CFR part 1271, and premarket review will generally be required.

Please note, the regulatory status of products identified as not being HCT/Ps (see 21 CFR part 1271.3(d)(1)-(8)) is beyond the scope of this guidance.

##### **2. How can HCT/P manufacturers get more information about the appropriate regulatory considerations for their HCT/P?**

To further assist HCT/P manufacturers, FDA issued the Guidance for Industry, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use", dated November 2017 and updated July 2020 (Ref.1). This guidance is intended to improve stakeholders' understanding of the definitions of minimal manipulation in 21 CFR 1271.3(f) and homologous use in 21 CFR 1271.3(c). This guidance is also intended to facilitate stakeholders' understanding of how the regulatory criteria in 21 CFR 1271.10(a)(1) and (2) apply to their HCT/Ps.

In addition, FDA published the Guidance for Industry, "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception", dated November 2017 (SSPE Guidance) (Ref. 2). This guidance is intended to provide stakeholders with the FDA's current thinking on the scope of the exception set forth in 21 CFR 1271.15(b). If the exception in 21 CFR 1271.15(b) applies, the establishment is not required to comply with the requirements of 21 CFR part 1271.

FDA provides two mechanisms through which a manufacturer may obtain a recommendation or decision regarding the classification of an HCT/P:

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- 1) The Tissue Reference Group (TRG), which includes representatives from CBER and CDRH, provides product sponsors with an informal process through which they may obtain an Agency recommendation regarding the application of the criteria in 21 CFR 1271.10(a) to their HCT/Ps for a given indication. Information about this process as well as what you may want to include to facilitate review of your request can be found at: <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group>.
- 2) A Request for Designation (RFD) may be submitted to the Office of Combination Products (OCP) to obtain a formal Agency decision regarding the regulatory identity or classification of an HCT/P (21 CFR part 3). A description of that process and information on how to submit an RFD can be found at: <https://www.fda.gov/combination-products/rfd-process>. Additional information may be found in FDA's Guidance for Industry, "How to Write a Request for Designation," dated April 2011, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd>. You may also submit a Pre-RFD to OCP to obtain preliminary, feedback on the classification for your HCT/P. A description of the Pre-RFD process as well as assistance on how to prepare a Pre-RFD may be found in FDA's Guidance for Industry, "How to Prepare a Pre-Request for Designation (Pre-RFD)," <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd>.

### **3. Which subparts of 21 CFR part 1271 apply to HCT/Ps<sup>3</sup> regulated solely under section 361 of the PHS Act?**

For HCT/Ps regulated solely under section 361 of the PHS act, 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 non-reproductive 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 non-reproductive 361 HCT/Ps; and,
- subpart F applies to all 361 HCT/Ps.

### **4. Which subparts of 21 CFR part 1271 apply to HCT/Ps regulated as drugs, devices, and/or biological products?**

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

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<sup>3</sup> Subparts C through F of 21 CFR part 1271 do not apply to HCT/Ps recovered before May 25, 2005.

## Contains Nonbinding Recommendations

- subparts A, C, and D apply to all these HCT/Ps; and,
- subparts B, E, and F do not apply.

### **5. For an establishment that manufactures an HCT/P regulated as a drug, device, and/or biological product, 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 addition to current good tissue practice (CGTP) requirements in 21 CFR part 1271, subpart D, current good manufacturing practice (CGMP) requirements in 21 CFR parts 210 and 211 for drugs and biological products, or quality system (QS) regulation requirements in 21 CFR part 820 for devices apply to an HCT/P regulated as a drug, device, and/or biological product, as appropriate. 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)).

For additional information about the CGTP requirements that would not be partly or completely covered by a corresponding CGMP regulation or QS regulation requiring the same practice, see the 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)” dated December 2011 (CGTP Guidance) (Ref. 3).

## **B. REGISTRATION AND LISTING**

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

All establishments that manufacture 361 HCT/Ps (361 HCT/P establishments) must register and list their HCT/Ps with FDA (see 21 CFR 1271.1(b)(1), 1271.10(b), and 1271.21). Manufacturers of HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the FD&C Act and applicable regulations, must register and list their products in accordance with 21 CFR part 207<sup>4</sup> or 807<sup>5</sup>, as applicable, rather than 21 CFR part 1271 (21 CFR 1271.1(b)(2)).<sup>6</sup>

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<sup>4</sup> See FDA’s Drug Registration and Listing webpage (available at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-registration-and-listing-system-drls-and-edrls>) for more information.

<sup>5</sup> See FDA’s Device Registration and Listing webpage (available at <https://www.fda.gov/medical-devices/how-study-and-market-your-device/device-registration-and-listing>) for more information.

<sup>6</sup> In 2016, FDA revised 21 CFR 1271.1(b)(2) and 1271.20 to require establishments that manufacture HCT/Ps regulated as drugs and/or biological products to register and list following the procedures in 21 CFR part 207 and establishments that manufacture HCT/Ps regulated as devices to register and list following the procedures in 21 CFR part 807. (see 81 FR 60169, 60223, August 31, 2016). However, the agency inadvertently omitted a conforming amendment to 21 CFR 807.20(d) to reflect those changes. The agency intends to update its regulations to correct the error.

## Contains Nonbinding Recommendations

FDA does not require establishments that manufacture HCT/Ps regulated as drugs, devices, and/or biological products that are only for use in research 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 those HCT/Ps in accordance with 21 CFR part 207 or 807 if they do not engage in other activities that would require them to register (21 CFR 207.13(e), 807.65(f) and 812.1).

### **2. Must foreign establishments that manufacture HCT/Ps imported for distribution in the United States register and list their HCT/Ps?**

Yes. All foreign establishments manufacturing 361 HCT/Ps that are imported or offered for import into the United States (U.S.) must register and list their 361 HCT/Ps with FDA (see 21 CFR 1271.1(b)(1), 1271.10(b), and 1271.21). It is a requirement for such foreign establishments to submit certain information described in 21 CFR 1271.25(a)(5)-(6), including the name, address, phone number, and email address of the U.S. agent(s) (someone located in the United States as a contact for inspection and other purposes) and of each importer that is known to the establishment at the time of initial registration or when submitting the annual registration update. If the HCT/Ps being imported or offered for import into the U.S. are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the FD&C Act, the foreign establishment must register and list in accordance with 21 CFR part 207 or part 807, as applicable (see 21 CFR 1271.1(b)(2)).

### **3. Which establishments are excepted 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. For HCT/Ps regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the FD&C Act, exemptions from registration and listing requirements are set forth in section 510(g) of the FD&C Act, 21 CFR 207.13, and 21 CFR 807.65, as applicable.

### **4. How does a 361 HCT/P establishment submit their tissue establishment registration, and where can an establishment find more information on how to register and list HCT/Ps?**

HCT/P establishments that manufacture 361 HCT/Ps must register and list electronically under 21 CFR part 1271 using the electronic Human Cell and Tissue Establishment Registration System (eHCTERS)<sup>7</sup> to meet the requirement for electronic submission of establishment registration and product listing (21 CFR 1271.22). Establishments may request a waiver from the electronic

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<sup>7</sup> eHCTERS and instructions for use accessible at <https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/tissue-establishment-registration>.

## Contains Nonbinding Recommendations

submission requirement as described in 21 CFR 1271.23. HCT/P establishments may also submit questions about registration to [TissueReg@fda.hhs.gov](mailto:TissueReg@fda.hhs.gov).

### **5. When must new 361 HCT/P establishments register and list their HCT/Ps?**

New establishments must register and submit a list of their 361 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.

### **6. How will a 361 HCT/P establishment know when it is officially registered with FDA?**

FDA considers the establishment to be registered as soon as FDA receives the registration information submitted in eHCTERS. After FDA processes the establishment's registration, FDA will send to the Reporting Official the Registration Summary Report, which includes the FDA Establishment Identifier (FEI) number. If an establishment already registered under separate requirements in 21 CFR parts 207, 607<sup>8</sup>, and/or 807, the establishment will generally retain the same FEI number.

When the establishment has submitted their HCT/P manufacturing registration information to the FDA, the registration status is identified as "Pre-registered" in eHCTERS until the FEI number is assigned. The establishment may contact FDA at [TissueReg@fda.hhs.gov](mailto:TissueReg@fda.hhs.gov) or access the Public Query Application to determine the status of their registration.<sup>9</sup> The establishment's status will change to "registered" after the FEI number has been assigned. An establishment may also use the Public Query Application to access a list of other 361 HCT/P establishments that are registered with the FDA.

### **7. Does registration mean an establishment is in compliance?**

No. FDA acceptance of an establishment registration and HCT/P listing form 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 (21 CFR 1271.27(b)).

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<sup>8</sup> Establishments that manufacture human blood and blood products and licensed devices must register and list under 21 CFR part 607.

<sup>9</sup> Public Query Application accessible at: <https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/human-cell-and-tissue-establishment-registration-hcters-public-query-application>.

## Contains Nonbinding Recommendations

### **8. What else will 361 HCT/P establishments have to do after the initial registration?**

Establishments must update their registration annually in December and submit changes in their HCT/P listing at the time of change or each June or December, whichever month occurs first after 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. The establishment's FEI number and last registration receipt date are needed to access their registration in eHCTERS. Establishments can find this information in their most recent Registration Summary Report. FDA currently sends in November a reminder via email to the Reporting Official regarding annual registration. If the ownership or location of the establishment changes or if there is a change in the United States agent's name, address, telephone number, or email address, the establishment must submit an amendment to the registration within 30 calendar days of the change (21 CFR 1271.26).

### **9. What would happen if an establishment required to register under 21 CFR part 207, 807, or 1271 does not register or forgets to submit the annual registration?**

The establishment would be in violation of the applicable registration regulations.

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

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

### **11. Must an establishment (laboratory) register if it only performs speciation of microorganisms already detected in a culture specimen from a 361 HCT/P?**

Yes. By definition, the term "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 further processed and/or distributed. If an establishment (laboratory) only performs speciation of microorganisms, the establishment must register because it is performing a processing step (21 CFR 1271.1(b)).

## Contains Nonbinding Recommendations

### **12. What is the process to inactivate registration if the establishment no longer manufactures 361 HCT/Ps or has gone out of business?**

The Reporting Official of the establishment may inactivate the establishment registration using eHCTERS.

### **13. Must a hospital have multiple registrations if it manufactures more than one type of 361 HCT/P (e.g., hematopoietic stem/progenitor cells, reproductive cells) or if it performs different manufacturing functions (e.g., recovery, processing, donor testing)?**

Each establishment will generally have only one registration number (FEI number) for any combination of HCT/P types manufactured and/or manufacturing functions. 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, FDA requires separate registrations for two or more business enterprises that manufacture 361 HCT/Ps and are separate legal entities with different management even if both use the same facility or the same address (see 21 CFR 1271.3(b), 1271.10(b), and 1271.21).

### **14. Must a hospital be registered if the only functions performed there with respect to HCT/Ps are surgical removal and temporary storage of autologous HCT/Ps prior to their implantation?**

An establishment that only removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure is not required to comply with the requirements of 21 CFR part 1271, including registration and listing (21 CFR 1271.15(b)). For additional information on FDA's current thinking on the scope of the exception set forth in 21 CFR 1271.15(b), including the types of procedures that may be considered the same surgical procedure, see the SSPE Guidance (Ref. 2).

### **15. Must a hospital register and list with respect to 361 HCT/Ps that it receives, stores, and routinely shares with other hospitals?**

Yes. Hospitals that receive 361 HCT/Ps and make them available for distribution to other establishments (e.g., hospitals) are performing the manufacturing steps of storage and distribution and therefore must register and list those 361 HCT/Ps (21 CFR 1271.3(e), 1271.10(b), and 1271.21). An establishment is not required to

## **Contains Nonbinding Recommendations**

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)).

### **16. Must an establishment be registered if it recovers HCT/Ps for teaching and nonclinical research purposes only?**

No. According to 21 CFR 1271.15(a), if your establishment only recovers HCT/Ps that are used solely for nonclinical scientific or educational purposes, you are not required to comply with the requirements of 21 CFR part 1271, including registration and listing.

## **C. DONOR ELIGIBILITY**

### **1. What are the donor eligibility (DE) requirements for HCT/Ps?**

The DE requirements are outlined in title 21 CFR part 1271, subpart C. A DE determination is required for all donors of cells or tissue used in HCT/Ps, recovered on or after May 25, 2005,<sup>10</sup> except as provided under 21 CFR 1271.90 and must be based on donor screening and testing for relevant communicable disease agents and diseases (RCDADs) (21 CFR 1271.45(b)). An HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible, except as provided under 21 CFR 1271.60(d), 1271.65(b), and 1271.90 (21 CFR 1271.45(c)). A DE determination is a determination of whether a donor is eligible based on the results of donor screening in accordance with 21 CFR 1271.75 and donor testing in accordance with 21 CFR 1271.80 and 1271.85 (21 CFR 1271.50(a)).

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

An establishment can find more comprehensive information on DE by accessing FDA's "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 2007 (2007 DE Guidance) (Ref. 4) 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," dated April 2008 (Ref. 5).

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<sup>10</sup> 69 FR 29786 (May 25, 2004).

## Contains Nonbinding Recommendations

FDA has issued guidance documents<sup>11</sup> that notified establishments of a new RCDAD and/or recommended specific donor screening and testing measures, which serve to supplement recommendations in certain sections of the 2007 DE Guidance.

### **D. CURRENT GOOD TISSUE PRACTICE**

#### **1. What are current good tissue practice (CGTP) requirements?**

CGTP requirements are the requirements in 21 CFR part 1271, subpart C and subpart 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, packaging, and distribution (21 CFR 1271.150(a)). The CGTP Guidance (Ref. 3) provides HCT/P establishments with recommendations for complying with CGTP requirements under 21 CFR part 1271, subpart D and additional requirements under subpart E. For additional information on subpart C, refer to the 2007 DE Guidance (Ref. 4).

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

The CGTP 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.

#### **3. Who must comply with the CGTP requirements if one establishment engages another establishment (e.g., a contract establishment) to perform certain steps in manufacture of HCT/Ps, 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 manufacturing 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)(1)(iii)). For further information, see “Guidance for Industry: Compliance with 21 CFR part 1271.150(c)(1) – Manufacturing Arrangements”, dated September 2006 (Ref. 6).

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<sup>11</sup> All FDA guidance documents related to DE requirements for HCT/Ps may be found at: <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances>.

## Contains Nonbinding Recommendations

### 4. How does an HCT/P establishment request an exemption or an alternative to a requirement?

Under 21 CFR 1271.155, an establishment may request an exemption from or alternative to any requirement in subpart C (Donor Eligibility) or subpart D (Current Good Tissue Practice) of 21 CFR part 1271. Note that on June 22, 2016, FDA published a final rule, entitled “Revisions to Exceptions Applicable to Certain Human Cells, Tissues, and Cellular and Tissue-Based Products” (81 FR 40512, June 22, 2016), which revised 21 CFR part 1271 to clarify that if an embryo was originally intended for reproductive use for a specific individual or couple, its subsequent directed or anonymous donation for reproductive use would not be prohibited under 21 CFR 1271.45(c), even when the applicable donor eligibility requirements under part 1271, subpart C, are not met (see 21 CFR 1271.90(b)).

You must ordinarily request an exemption or alternative under 21 CFR 1271.155(d) in writing (hardcopy or electronically). However, you may request an exemption orally if circumstances make it difficult (e.g., there is inadequate time) to submit your request in writing. You must follow an oral request with an immediate written request (21 CFR 1271.155(d)). Requests for exemptions or alternative methods must be submitted to the appropriate Center (21 CFR 1271.155(b)).

As stated in 21 CFR 1271.155(b), the request must be accompanied by supporting documentation, including all relevant valid scientific data. More information on the criteria for granting exemptions and alternatives and the supporting documentation required may be found at: <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/exemptions-and-alternatives>.

If the HCT/P is regulated solely under section 361 of the PHS Act and regulations in part 1271, or as a biological product or medical device regulated by CBER, requests should be sent to:

Director, Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave  
Document Control Center  
WO71-G112  
Silver Spring, MD 20993-0002

If you have questions concerning these requests, need to orally request an exemption or alternative, or wish to submit a request electronically, please refer to the Exemptions and Alternatives website above.

## Contains Nonbinding Recommendations

If the HCT/P is regulated as a medical device by CDRH, the request should be sent to:

Combination Product Jurisdiction Officer  
Center for Devices and Radiological Health  
Food and Drug Administration  
10903 New Hampshire Ave  
Document Control Center  
WO66-G609  
Silver Spring, MD 20993-0002

If you have questions concerning these requests or need to orally request an exemption or alternative, please refer to the Exemptions and Alternatives website above.

### **5. Is an HCT/P establishment required to investigate and report adverse reactions related to 361 HCT/Ps?**

Establishments that make nonreproductive 361 HCT/Ps available for distribution are required to investigate adverse reactions involving a communicable disease related to those 361 HCT/Ps (21 CFR 1271.350(a)(1)). In addition, the establishments must report to FDA such adverse reactions that meet any of the criteria under 21 CFR 1271.350(a)(1)(i)-(iv). FDA issued a guidance entitled “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”, dated March 2016 (Ref. 7) with recommendations for complying with the requirements under 21 CFR part 1271, subparts D and E, for investigating and reporting of complaints of adverse reactions involving communicable disease in recipients of 361 HCT/Ps. That guidance provides updated information specific to reporting adverse reactions related to HCT/Ps, to supplement the general instructions accompanying the MedWatch mandatory reporting form, Form FDA 3500A, and supplements section XXII of the CGTP Guidance (Ref. 3).

### **6. Is an HCT/P establishment required to investigate and report deviations for 361 HCT/Ps?**

Establishments that manufacture nonreproductive 361 HCT/Ps are required to investigate all HCT/P deviations related to distributed 361 HCT/Ps for which they performed a manufacturing step (21 CFR 1271.350(b)(1)). Under 21 CFR 1271.350(b)(2), the establishment must report to FDA any such HCT/P deviation relating to the core CGTP requirements defined in 21 CFR 1271.150(b), if the HCT/P deviation occurred in its facility or in a facility that performed a manufacturing step for the establishment under contract, agreement, or other arrangement. FDA issued the guidance, “Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section

## Contains Nonbinding Recommendations

361 of the Public Health Service Act and 21 CFR Part 1271” dated September 2017 (Ref. 8) to provide establishments that manufacture non-reproductive 361 HCT/Ps, with recommendations and relevant examples for complying with the requirements under 21 CFR 1271.350(b) to investigate and report HCT/P deviations.

The guidance also supplements sections V. and XXII. of the CGTP Guidance (Ref. 3), by providing additional recommendations specific to an establishment’s responsibilities to investigate HCT/P deviations concerning 361 HCT/Ps under 21 CFR 1271.160(b)(6) and 1271.350(b).

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

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

An FDA inspection of an establishment that manufactures 361 HCT/Ps 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 (21 CFR 1271.400(a)).

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)).

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 (see 21 CFR 1271.150(c)(3) and 1271.330).

As of May 15, 2017, as part of the broader agency Program Alignment initiative, FDA’s Office of Regulatory Affairs (ORA) implemented a program-based management structure that aligns staff, including inspection staff, by FDA-regulated product. This organizational approach replaced a management structure based on geographic regions. The goal is to improve our public health response in a way that keeps pace with the acceleration of scientific innovation, global expansion of markets, and modern legal authorities.<sup>12</sup>

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<sup>12</sup> See FDA’s Program Alignment and ORA webpage at <https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora> for more details.

## Contains Nonbinding Recommendations

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

An FDA inspection of an establishment that manufactures 361 HCT/Ps 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 compliance or enforcement actions can FDA take to prevent the introduction, transmission, or spread of communicable diseases for 361 HCT/Ps?

For 361 HCT/Ps, advisory, administrative and judicial actions that FDA may take in response to violations of 21 CFR part 1271 include an Untitled Letter; Warning Letter; Orders of Retention, Recall, Destruction, and/or Cessation of Manufacturing; and prosecution.

A Warning Letter is a correspondence that notifies regulated industry about violations that FDA has identified during its inspections or other investigations to provide an opportunity to take prompt, voluntary corrective action. Typically, a Warning Letter notifies a responsible individual or establishment that FDA considers one or more products, practices, processes, or other 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). 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.

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 in certain circumstances, such as when there are gross, flagrant or intentional violations, fraud, danger to health, or a continued or repeated course of violative conduct. Because 21 CFR part 1271 was promulgated pursuant to section 361 of the PHS Act (42 U.S.C. 264), there are criminal penalties found in 42 U.S.C. 271(a) that may apply: "Any person who violates any regulation prescribed under [42 U.S.C. 264] . . . shall be punished by a fine of not more than \$1,000 or by imprisonment for not more than one year, or

## **Contains Nonbinding Recommendations**

both.” However, Title 18 of the United States Code (U.S.C.) contains superseding penalties provisions for federal crimes. Under 18 U.S.C. 3551, “a defendant who has been found guilty of an offense described in any Federal statute” is governed by the sentencing provisions of 18 U.S.C. Chapter 227 (18 USC 3551-3586). Under 18 U.S.C. 3559(a)(6), any federal criminal offense which carries a possible maximum sentence of one year or less, but more than six months, is a Class A misdemeanor. The statutory fines for Class A misdemeanor federal offenses are, for individuals, for a violation resulting in death, not more than \$250,000; otherwise, not more than \$100,000 (18 U.S.C. 3571(b)(4) and (5)). For organizations, including corporations, for a violation resulting in death, not more than \$500,000; otherwise, not more than \$200,000 (18 U.S.C. 3571(c)(4) and (5)).

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

An 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. As described 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 361 HCT/Ps offered for import?**

Under 21 CFR 1271.420(a), when an HCT/P (except for certain reproductive HCT/Ps and peripheral blood stem/progenitor cells as described in 21 CFR 1271(c) and(d)) is offered for import, the importer of record must notify the FDA Director (or designee) of the district that covers the port of entry before or at the time of importation and provide sufficient information for FDA to make an admissibility decision. HCT/Ps offered for import must be held intact by the importer of record or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA (21 CFR 1271.420(b)). Due to the perishable nature of most HCT/Ps, an HCT/P may be transported under quarantine to the consignee while FDA is determining admissibility of the HCT/P (21 CFR 1271.420(b)).

The “FDA Investigations Operations Manual 2021 (IOM)” (Ref. 9) is the primary operational reference for FDA employees who perform field investigational activities in support of the agency’s public health mission and has more information on inspectional and import activities.

**Contains Nonbinding Recommendations**

## **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 PHS 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 PHS 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 indicating the need to review the information referenced in 21 CFR 1271.420(a). In such circumstances, 21 CFR 1271.420(a) and (b) apply (21 CFR 1271.420(d)).

## Contains Nonbinding Recommendations

### III. REFERENCES

1. Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, November 2017 and Corrected July 2020, available at: <https://www.fda.gov/media/109176/download>
2. Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception, November 2017, available at: <https://www.fda.gov/media/89920/download>
3. 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), December 2011, available at: <https://www.fda.gov/media/82724/download>
4. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007, available at: <https://www.fda.gov/media/73072/download>
5. 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, April 2008, available at <https://www.fda.gov/media/70696/download>
6. Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements”, September 2006, available at: <https://www.fda.gov/media/70696/download>
7. FDA Guidance: 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, March 2016, available at: <https://www.fda.gov/media/91082/download>
8. FDA Guidance: Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271, September 2017, available at: <https://www.fda.gov/media/107703/download>
9. **FDA Investigations Operations Manual, 2021**, available at: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual>