

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

Guidance for Industry

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Contains Nonbinding Recommendations

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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

We, the Food and Drug Administration (FDA), are issuing this guidance to provide you, establishments that manufacture non-reproductive human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are regulated solely under section 361 of the Public Health Service Act (PHS Act) and the regulations under Title 21 of the Code of Federal Regulations (CFR) Part 1271, with recommendations and relevant examples for complying with the requirements under 21 CFR 1271.350(b) to investigate and report HCT/P deviations. The examples provided in this guidance have been chosen to illustrate those HCT/P deviations that have been most frequently reported to FDA's Center for Biologics Evaluation and Research (CBER).¹

This guidance document does not apply to reproductive HCT/Ps² or to HCT/Ps regulated under 21 CFR Part 1270 and recovered before May 25, 2005. Furthermore, this guidance does not apply to healthcare professionals who implant, transplant, infuse, or transfer HCT/Ps into recipients.³

¹ See FDA's Annual Report Summaries at <https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/ucm129757.htm>.

² See 21 CFR 1271.150(c)(3).

³ See 21 CFR 1271.15(d). However, FDA notes that healthcare professionals have an important role in identifying HCT/P deviations and reporting HCT/P deviations to manufacturers of HCT/Ps. Further, manufacturers may seek to obtain additional information from healthcare professionals such as recipient culture reports or recipient clinical records when investigating the possible transmission of communicable disease related to HCT/Ps that the manufacturer made available for distribution.

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This guidance document also does not apply to HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act, nor does it apply to investigational HCT/Ps subject to an investigational new drug (IND) application or an investigational device exemption (IDE). This guidance finalizes the draft guidance of the same title dated December 2015.

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

On November 24, 2004, FDA published in the *Federal Register* the final rule entitled "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement" (69 FR 68612).⁴ This rule, which became effective on May 25, 2005, requires HCT/P establishments to follow current good tissue practice (CGTP), which governs the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps; recordkeeping; and the establishment of a quality program. The rule also established certain "core CGTP requirements" under 21 CFR 1271.150(b) that are directly related to preventing the introduction, transmission, or spread of communicable diseases. In addition, certain requirements in subparts D and E of 21 CFR Part 1271 were limited in their applicability to these core CGTP requirements, including the requirement under 21 CFR 1271.350(b) to report HCT/P deviations to FDA.

An HCT/P is regulated solely under section 361 of the PHS Act and the regulations under 21 CFR Part 1271 if it meets all of the following criteria under 21 CFR 1271.10(a):

1. The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; **AND**

⁴ Available at

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ActsRulesRegulations/TissueProposedFinalRules/default.htm>.

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4. Either:
 - i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; **OR**
 - ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function; **AND**
 - a) Is for autologous use;
 - b) Is for allogeneic use in a first-degree or second-degree blood relative; **OR**
 - c) Is for reproductive use.

Under 21 CFR 1271.350(b), an establishment that manufactures non-reproductive HCT/Ps⁵ that meet all of the above criteria must investigate all HCT/P deviations related to a distributed HCT/P for which the establishment performed a manufacturing step. Such establishment must report, to FDA, within 45 days of the discovery of the event, any such HCT/P deviation relating to the core CGTP requirements, if the HCT/P deviation occurred in their facility or in a facility that performed a manufacturing step under contract, agreement, or other arrangement.

As noted above, and discussed in more detail in a separate guidance,⁶ all core CGTP requirements found at 21 CFR 1271.150(b) directly relate to preventing the introduction, transmission, or spread of communicable diseases by HCT/Ps. The following are core CGTP requirements:

- Donor-eligibility determinations, donor screening, and donor testing (21 CFR 1271.50, 1271.75, 1271.80, and 1271.85);
- Facilities (21 CFR 1271.190(a) and (b));
- Environmental control (21 CFR 1271.195(a));
- Equipment (21 CFR 1271.200(a));
- Supplies and reagents (21 CFR 1271.210(a) and (b));
- Recovery (21 CFR 1271.215);
- Processing and process controls (21 CFR 1271.220);
- Labeling controls (21 CFR 1271.250(a) and (b));
- Storage (21 CFR 1271.260(a) through (d)); and
- Receipt, predistribution shipment, and distribution of an HCT/P (21 CFR 1271.265(a) through (d)).

Under 21 CFR 1271.150(a), you must follow CGTP requirements to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing). Communicable diseases include, but are not

⁵ See 21 CFR 1271.330.

⁶ See FDA's "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 available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>.

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limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. In addition, under 21 CFR 1271.180, HCT/P establishments must establish and maintain procedures appropriate to meet core CGTP requirements.

III. HCT/P DEVIATION REPORTING

A. What is an HCT/P Deviation?

The term “HCT/P deviation” is defined in 21 CFR 1271.3(dd) as an event:

1. That represents a deviation from applicable regulations in 21 CFR Part 1271 or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination;
or
2. That is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

B. Who Must Investigate and Report an HCT/P Deviation?

Under 21 CFR 1271.350(b)(1), an establishment must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step. “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)). “Distribution” means any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor (21 CFR 1271.3(bb)).

Under 21 CFR 1271.350(b)(2), you must report to FDA any such HCT/P deviation relating to the core CGTP requirements, if the HCT/P deviation occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement. We recommend that the HCT/P establishment that makes the HCT/P available for distribution be responsible for reporting HCT/P deviations related to distributed products to FDA. “Available for distribution” means that the HCT/P has been determined to meet all release criteria (21 CFR 1271.3(z)). If the distributing HCT/P establishment has notified the contract facility that it has filed a deviation report, FDA does not intend to enforce any requirement for the contract facility to submit a second, duplicative HCT/P deviation report. However, the contract facility would be required to investigate the deviation in accordance with 21 CFR 1271.350(b)(1) and 21 CFR 1271.160(b)(6), as also discussed below.

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Although 21 CFR 1271.350(b)(1) requires you to investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step, we remind all establishments, including contract facilities, that, as described in 21 CFR 1271.160(b)(2), a quality program for all establishments involved in manufacturing HCT/Ps must ensure that procedures exist for receiving, investigating, evaluating and documenting information relating to core CGTP requirements, including complaints, and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with other establishments and consignees. Complete details regarding “other establishments” and “consignees” are provided in the provision under 21 CFR 1271.160(b)(2)(i) through (iii). In addition, we remind all establishments, including contract facilities, that 21 CFR 1271.160(b)(6) requires establishments to investigate and document HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and making reports if required under 21 CFR 1271.350(b) or other applicable regulations.

C. What are Some Examples of Who Must Report an HCT/P Deviation?

Because timely and accurate reporting of HCT/P deviations has been of considerable interest to industry stakeholders, we explain who is responsible to report an HCT/P deviation to FDA based on the following event scenarios:

1. You are an establishment that has a contract, agreement, or other arrangement with another establishment to perform donor screening for you. Based on the review of the relevant medical records you received from the contract establishment that performed the donor screening, you determined the donor to be eligible and distributed the HCT/P. Subsequently, the contract donor screening establishment notified you that during an internal audit, they discovered

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that some of the questions related to risk factors for a relevant communicable disease agent or disease (RCDAD)^{7,8,9,10} were not answered when the donor medical history interview was conducted.

Who must report: Under 21 CFR 1271.350(b)(1), you must investigate the HCT/P deviation related to a distributed HCT/P. In addition, under 21 CFR 1271.160(b)(6), the contract establishment is responsible for investigating and documenting the HCT/P deviation and, under 21 CFR 1271.160(b)(2)(ii), they are responsible for notifying you of the event and providing details about the investigation. We recommend that, you, the establishment that distributed the HCT/P, submit the report required under 21 CFR 1271.350(b)(2) because the HCT/P deviation is related to core CGTP requirements (specifically,

⁷ Under 21 CFR 1271.3(r), “relevant communicable disease agent or disease” (RCDAD) for non-reproductive HCT/Ps includes the following:

- Human immunodeficiency virus (HIV), types 1 and 2;
- Hepatitis B virus (HBV);
- Hepatitis C virus (HCV);
- Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD);
- Human T-lymphotropic virus (HTLV), types I and II (for viable, leukocyte-rich cells and tissues);
- *Treponema pallidum* (syphilis);
- West Nile virus;
- Sepsis;
- Vaccinia; and
- Zika virus

⁸ West Nile virus, sepsis, vaccinia, and Zika virus are communicable disease agents or diseases, not specifically listed under 21 CFR 1271.3(r)(1), but determined to be relevant communicable disease agents or diseases under 21 CFR 1271.3(r)(2). More information regarding these additional relevant communicable disease agents or diseases can be found at FDA’s Tissue Guidances page at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/default.htm>.

⁹ See “Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry,” dated March 2016; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf>.

¹⁰ See the following guidance documents for recommendations for nucleic acid testing to reduce the risk of West Nile virus and Hepatitis B virus, and other screening tests recommended for *Treponema pallidum* (Syphilis):

- “Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps),” dated September 2016; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM372084.pdf>;
- “Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products,” dated August 2016; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM516650.pdf>;
- “Guidance for Industry: Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue-Based Products for Infection with *Treponema pallidum* (Syphilis),” dated September 2015; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM373311.pdf>.

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21 CFR 1271.75) and occurred in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement. If you, the distributing HCT/P establishment, have notified the contract facility that you have filed a deviation report, FDA does not intend to enforce any requirement for the contract facility to submit a second, duplicative HCT/P deviation report.

2. You are an establishment that performs all manufacturing steps for fresh skin. The HCT/P was cultured for microorganisms prior to distribution and distributed prior to the availability of the culture results. After distribution, a positive culture result was obtained that did not meet your release criteria designed to prevent the introduction, transmission, or spread of communicable disease.

Who must report: Under 21 CFR 1271.350(b)(1), you must investigate an HCT/P deviation related to a distributed HCT/P, and under 21 CFR 1271.350(b)(2), you must submit a report to FDA because the HCT/P deviation is related to a core CGTP requirement (specifically, 21 CFR 1271.265(c)(2)) and occurred in your facility.

3. You are an establishment that determined all release criteria have been met for an HCT/P and subsequently distributed the HCT/P to a hospital. The hospital stored the HCT/P in a cold room until needed for one of their patients. The cold room in the hospital lost power for a period of time. The surgeon voluntarily notified you that he had decided not to utilize the tissue.

Who must report: You are not responsible for submitting an HCT/P deviation report because the deviation was not related to a manufacturing step you performed. The hospital is not responsible for reporting because they meet the exception under 21 CFR 1271.15(d), which states that you are not required to comply with the requirements of 21 CFR Part 1271 if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

4. You are an establishment that has a contract, agreement, or other arrangement with another establishment to perform donor testing for you. After receiving negative results from the testing establishment, you determined the donor to be eligible and distributed the HCT/P. Subsequently, the testing establishment notifies you that during an internal audit, they discovered testing was performed using a diagnostic test kit for communicable disease testing instead of an FDA approved test kit for donor screening.

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Who must report: Under 21 CFR 1271.350(b)(1), you must investigate the HCT/P deviation related to a distributed HCT/P and under 21 CFR 1271.350(b)(2), you must submit a report to FDA because the HCT/P deviation is related to core CGTP requirements (specifically, 21 CFR 1271.80(c)) and occurred in a facility that performed a manufacturing step for you under a contract, agreement, or other arrangement. The HCT/P deviation report should include all distributed HCT/Ps for which donor testing was performed using a diagnostic test kit for communicable disease testing instead of an FDA approved test kit for donor screening.

The testing establishment is also required to investigate and document the HCT/P deviation under 21 CFR 1271.160(b)(6). Under 21 CFR 1271.160(b)(2)(ii), they are responsible for notifying you, and any other establishments for whom they performed testing with respect to the same HCT/P, of the event and providing details about the investigation. If you, the distributing HCT/P establishment, have notified the testing establishment that you have filed a deviation report, FDA does not intend to enforce any requirement for the testing establishment to submit a second, duplicative HCT/P deviation report to FDA.

5. You are an establishment that independently stores and distributes HCT/Ps, meaning you are not under a contract, agreement, or other arrangement with another establishment. You distributed an HCT/P that was stored at a higher temperature than your established acceptable temperature limits for storage (21 CFR 1271.260(e)), posing a potential risk for contamination.

Who must report: Under 21 CFR 1271.350(b)(1), you must investigate the HCT/P deviation related to a distributed HCT/P and under 21 CFR 1271.350(b)(2), you must submit a report to FDA because the HCT/P deviation is related to a core CGTP requirement (specifically, 21 CFR 1271.260(b)) and occurred in your facility. The HCT/P deviation report must include all distributed HCT/Ps that were stored at the unacceptable temperature.

D. When Am I Not Required to Submit a Report?

You are **not** required to submit a report when:

- The event does not meet the definition of an HCT/P deviation as defined in 21 CFR 1271.3(dd).
- The deviation is not related to a core CGTP requirement as defined in 21 CFR 1271.150(b).
- You detected a deviation, so you did not distribute the HCT/P.
- You detected a deviation and, prior to distribution, you made appropriate corrections following appropriate procedures.
- The deviation is related to an HCT/P not subject to HCT/P deviation reporting (e.g., reproductive tissue).

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E. What Information Should I Include in an HCT/P Deviation Report?

Under 21 CFR 1271.350(b)(2), each HCT/P deviation report must contain a description of the HCT/P deviation, information relevant to the event and the manufacture of the HCT/P involved, and information on all follow-up actions that have been or will be taken in response to the HCT/P deviation (e.g., recalls).

We recommend that you complete a separate report for each event. However, if a single event involves more than one HCT/P, you only should complete one report listing all distributed HCT/Ps affected.

F. When Do I Report an HCT/P Deviation?

Under 21 CFR 1271.350(b)(3), you must report each HCT/P deviation that relates to a core CGTP requirement within 45 days of the discovery of the event. If the HCT/P deviation occurred in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement, the time period for reporting will start when that contract establishment learned about the event.

G. How and Where Do I Submit a Report for an HCT/P Deviation?

Under 21 CFR 1271.350(b)(3), you must report each HCT/P deviation on Form FDA 3486. We strongly encourage you to submit the report electronically through CBER's website (see instructions for using electronic biological product deviations reporting (eBPDR) system at <https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/ucm134535.htm>). The Form FDA 3486 and instructions for completing the form electronically or by mail may be found at <https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/default.htm>.

You may submit the completed report by mail to:

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002

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We also remind you that HCT/P establishments are required to report adverse reactions under 21 CFR 1271.350(a), and recommendations regarding adverse reaction reporting can be found in a separate guidance document.¹¹ If the adverse reaction occurs as a result of an HCT/P deviation, you must submit both an adverse reaction report and an HCT/P deviation report.

IV. EXAMPLES OF REPORTABLE HCT/P DEVIATIONS AND NON-REPORTABLE FINDINGS

This guidance provides examples of HCT/P deviations that have been most frequently reported to CBER.¹² These include deviations to the following core CGTP requirements:

- Donor-eligibility determinations, donor screening, and donor testing (21 CFR 1271.50, 1271.75, 1271.80, and 1271.85);
- Processing and process controls (21 CFR 1271.220); and
- Receipt, predistribution shipment, and distribution of an HCT/P (21 CFR 1271.265(a) through (d)).

However, we remind you that you are required to report HCT/P deviations relating to all core CGTP requirements.

Because timely and accurate reporting of HCT/P deviations has been of considerable interest to industry stakeholders, we describe examples of both reportable and non-reportable events. The following examples are not all-inclusive and do not represent all variations that may occur. In all examples, the HCT/P was distributed.

A. Donor Eligibility (21 CFR 1271.50)

1. What are the core CGTP requirements for donor eligibility?

In accordance with 21 CFR 1271.50(a), “if you are the establishment responsible for making the donor-eligibility determination, you must determine whether a donor is eligible based upon the results of donor screening in accordance with 21 CFR 1271.75 and donor testing in accordance with 21 CFR 1271.80 and 1271.85. A responsible person, as defined in 21 CFR 1271.3(t), must determine and document the eligibility of a cell or tissue donor.”

¹¹ See FDA’s “Guidance for Industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps),” dated November 2005; available at

<https://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/ucm153082.htm>.

¹² See FDA’s Annual Report Summaries available at

<https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/ucm129757.htm>.

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Under 21 CFR 1271.50(b), a donor is eligible only if:

- a. Donor screening in accordance with 21 CFR 1271.75 shows that the donor is free from risk factors for, and clinical evidence of, infection due to RCDADs, and is free from communicable disease risks associated with xenotransplantation; and
 - b. Test results for RCDADs in accordance with 21 CFR 1271.80 and 1271.85 are negative or nonreactive, except as provided in 21 CFR 1271.80(d)(1).
2. What are some examples of reportable HCT/P deviations related to donor-eligibility determination?

The following are examples of reportable HCT/P deviations which you discovered after you had already distributed an HCT/P that was obtained from a donor who was initially, but incorrectly, determined to be eligible. In each example, the donor information was overlooked and the donor was erroneously determined to be eligible.

- a. A donor tested positive for an RCDAD. This information was provided by the testing laboratory and recorded in the relevant medical records.
 - b. A donor engaged in behavior related to risk factors for RCDADs (e.g., sex in exchange for drugs) in the preceding five years.
 - c. A donor's final autopsy report documented that death was due to sepsis and the donor's medical records documented a medical diagnosis of sepsis.
3. What are some examples of non-reportable findings related to donor-eligibility?
- a. A donor had a localized infection or positive blood culture, but no documented clinical evidence or diagnosis of sepsis.
 - b. A donor had a history of a disease not considered an RCDAD. (e.g., Chagas, malaria, Lyme disease, or lymphoma).
 - c. The autopsy report stated that the cause of death was unknown or undetermined.
 - d. A donor of an HCT/P intended for allogeneic use in a first-degree or second-degree blood relative was determined ineligible due to behavior related to risk factors for RCDADs. Limited uses of the product are not prohibited (21 CFR 1271.65(b)(1)).
 - e. A donor was determined ineligible due to behavior related to risk factors for RCDADs; however, there was a documented urgent medical need (as defined in 21 CFR 1271.3(u)) for the use of the HCT/P. Limited uses of the product are not prohibited (21 CFR 1271.65(b)(1)).

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B. Donor Screening (21 CFR 1271.75)

1. What are the core CGTP requirements for donor screening?

Under 21 CFR 1271.75(a), you must screen a cell or tissue donor by reviewing relevant medical records for risk factors for, and clinical evidence of, RCDADs; and communicable disease risks associated with xenotransplantation, unless an exception identified in 21 CFR 1271.90(a) applies. For donors of viable, leukocyte-rich cells or tissue, you must also screen for HTLV (21 CFR 1271.75(b)).

2. What are some examples of reportable HCT/P deviations related to donor screening?

The following are examples of reportable HCT/P deviations which you discovered after you had already distributed an HCT/P that was obtained from a donor who was initially, but incorrectly, determined to be eligible. In each example, the donor information was overlooked and the donor was erroneously determined to be eligible.

- a. Donor screening for evidence of RCDADs was not performed or documented, or the screening was incomplete. Relevant medical records were not reviewed.
 - b. During an audit (or review) of the electronically recorded donor medical/social history interview, you discover that responses to questions related to a risk factor for RCDADs were incorrectly reflected on the written donor medical/social history questionnaire.
 - c. New information was discovered during a quality audit of the relevant medical records, and a re-evaluation indicated there was a risk associated with human TSE, which is an RCDAD.
3. What are some examples of non-reportable findings related to donor screening?
 - a. Donor medical/social history questionnaire was missing responses or had discrepant responses (e.g., yes and no) to questions that were not related to the prevention or spread of communicable disease transmission or HCT/P contamination (e.g., donor had history of heart disease).
 - b. Donor screening was not performed for an autologous HCT/P donor which was required by your establishment's standard operating procedures (SOPs) but not required by FDA according to 21 CFR 1271.90.

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C. Donor Testing (21 CFR 1271.80 and 21 CFR 1271.85)

1. What are the core CGTP requirements for donor testing for RCDADs?

Under 21 CFR 1271.80:

- a. You must test a donor specimen for evidence of infection due to RCDADs and other required communicable disease agents (e.g., cytomegalovirus (CMV)) as specified in 21 CFR 1271.85.^{13, 14, 15}
- b. You must collect the donor specimen for testing at the time of recovery of cells or tissue from the donor; or up to 7 days before or after recovery, with specific exceptions.¹⁶
- c. You must use appropriate FDA-licensed, approved or cleared donor screening tests, in accordance with the manufacturer's instructions, if such tests are available.^{17,18}
 - i. You must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available.
 - ii. Testing must be performed by a lab either certified to perform such testing under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or the equivalent as determined by the Centers for Medicare and Medicaid Services.¹⁹
- d. You must determine certain donors to be ineligible, as specified in 21 CFR 1271.80(d).

¹³ See 21 CFR 1271.85 for specific requirements pertaining to what donor testing is required for different types of cells and tissues.

¹⁴ A listing of the recommended tests for RCDADs and other required communicable disease agents (e.g., CMV) can also be found in FDA's "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 2007; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/TissueSafety/ucm091345.pdf>.

¹⁵ See footnote 10.

¹⁶ See 21 CFR 1271.80(b) for specific exceptions.

¹⁷ See complete list of current FDA-licensed donor screening tests for RCDADs available at <https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm>.

¹⁸ CLIA categorized FDA approved/cleared tests can be found on FDA's public CLIA database: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm>.

¹⁹ Information about the CLIA program is available at the website: <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/downloads/HowObtainCLIACertificate.pdf>.

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2. What are some examples of reportable HCT/P deviations related to donor testing?

The following are examples of reportable HCT/P deviations which you discovered after you had already distributed an HCT/P that was obtained from a donor who was initially, but incorrectly, determined to be eligible. In each example, the donor information was overlooked and the donor was erroneously determined to be eligible.

- a. Required donor testing was not performed for all RCDADs and other communicable disease agents (e.g., CMV).
 - b. Required donor testing for RCDADs was not performed in accordance with the manufacturer's test kit instructions.
 - c. Required donor testing for RCDADs was performed with an unacceptable donor specimen, in that the specimen was collected 10 days before the recovery of musculoskeletal HCT/Ps.
 - d. A donor specimen was incorrectly filtered or collected in an expired sample collection tube (containing anticoagulant) and, as such, did not meet the requirements according to the manufacturer's instructions.
 - e. A donor of viable, leukocyte-rich HCT/Ps was not tested for HTLV or CMV.
 - f. A donor specimen was tested using a diagnostic test kit instead of an FDA-licensed, approved, or cleared donor screening test.
 - g. A donor was either not evaluated for, incorrectly evaluated for, or the evaluation was not documented for plasma dilution.
3. What are some examples of non-reportable findings related to donor testing?
 - a. Required donor testing for RCDADs was performed by a facility that was not registered with FDA, but was CLIA certified, and licensed test kits were used for testing.²⁰
 - b. Donor testing for RCDADs was incorrectly performed on a specimen from an autologous donor. Donor eligibility determination, donor screening and donor testing of autologous donors is not required (21 CFR 1271.90(a)(1)).
 - c. Although the donor testing sample was collected within the required timeframe, an incorrect sample collection time was documented on an infectious disease testing result report.
 - d. A donor eligibility determination for a RCDAD was made according to existing recommendations, however subsequently the recommendations

²⁰ If you are a domestic or foreign establishment that manufactures an HCT/P described in 21 CFR 1271.10(a), you must register with FDA (see 21 CFR 1271.10(b)(1)). Section 1271.10(b)(1) is not a core CGTP requirement so the example does not meet the criteria to report the finding as an HCT/P deviation. However, failure to register with FDA would be in violation of 21 CFR 1271.10(b)(1).

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changed in a manner that the donor eligibility would now be inconsistent with the recommendation. For example, a donor-eligibility determination for an RCDAD that was tied to date of recovery and/or geographic location of recovery or travel of the donor such as the case described for WNV or Zika virus.

D. Processing and Process Controls (21 CFR 1271.220)

1. What are the core CGTP requirements for HCT/P processing?

If you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P (21 CFR 1271.220(a)).

Human cells or tissues from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing (21 CFR 1271.220(b)).

Furthermore, under 21 CFR 1271.220(c), you must ensure that specified requirements, consistent with the general requirements of 21 CFR 1271.220(a), for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or until necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated (21 CFR 1271.220(c)).

For dura mater, when there is a published validated process that reduces the risk of TSE, you must use this process (or an equivalent process that you have validated), unless following this process adversely affects the clinical utility of the dura mater (21 CFR 1271.220(d)(1)). When you use a published validated process, you must verify such a process in your establishment (21 CFR 1271.220(d)(2)).²¹

²¹ Additional guidance and recommendations for other HCT/Ps (e.g., musculoskeletal HCT/Ps) are provided in Section XIII. Processing and Process Controls (§ 1271.220) in FDA's "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; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>.

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2. What are some examples of reportable HCT/P deviations related to processing and process controls²²?
 - a. Musculoskeletal HCT/Ps from two or more donors were pooled during manufacturing.
 - b. In-process control procedures were not followed.
 - c. During in-process testing, the HCT/P was cultured for microorganisms; however the sample was not representative of the material being evaluated.
3. What are some examples of non-reportable findings related to processing and process controls?
 - a. During a processing step of freezing an HCT/P, a different concentration of dimethyl sulfoxide (DMSO) was used than was specified in the HCT/P establishment's SOP.
 - b. Processing steps were performed according to the HCT/P establishment's SOP, but were not documented concurrently with performance of each step (21 CFR 1271.270(a)).

E. Receipt, Predistribution, Shipment, and Distribution (21 CFR 1271.265(a) through (d))

1. What are the core CGTP requirements for HCT/P receipt, predistribution, shipment, and distribution?

Under 21 CFR 1271.265(a), you must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. You also must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission.

Under 21 CFR 1271.265(b), if you ship an HCT/P within your establishment or between establishments (e.g., procurer to processor) and the HCT/P is not available for distribution as described in 21 CFR 1271.265(c) (known as "predistribution shipment"), you must first determine and document whether pre-established criteria designed to prevent communicable disease transmission have been met, and you must ship the HCT/P in quarantine.

Under 21 CFR 1271.265(c)(1), before making an HCT/P available for distribution, you must review manufacturing records (such as records from the donor-eligibility determination, recovery, processing, and storage) and tracking records pertaining to the HCT/P, and, on the basis of that record review, you must

²² If there is a deviation in a process control operation that you perform only periodically, you should report all potentially affected products distributed since the last successful operation.

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verify and document that the release criteria have been met. Also, a responsible person must document and date the determination that an HCT/P is available for distribution (21 CFR 1271.265(c)(1)). Moreover, under 21 CFR 1271.265(c)(2), you must not make available for distribution an HCT/P that is:

- in quarantine;
- contaminated;²³
- received from a donor who has been determined to be ineligible or a donor with an incomplete donor-eligibility determination (except as provided in 21 CFR 1271.60, 1271.65, and 1271.90); or
- otherwise does not meet release criteria designed to prevent communicable disease transmission.

Under 21 CFR 1271.265(c)(3), if you make a departure from a procedure that is relevant to preventing risks of communicable disease transmission, you must not make an HCT/P manufactured under the departure available for distribution, unless a responsible person has determined that the departure does not increase the risk of communicable disease through the use of the HCT/P. You must record and justify any departure from a procedure at the time of its occurrence.

For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit (21 CFR 1271.265(d)).

2. What are some examples of reportable HCT/P deviations related to receipt, predistribution, shipment, and distribution?
 - a. A responsible person did not review and verify tracking records, and did not document that the release criteria had been met for an HCT/P that was distributed.
 - b. A quarantined HCT/P that was not available for distribution because it was recovered from an ineligible donor was distributed.²⁴
 - c. A contaminated HCT/P was distributed (e.g., an HCT/P with a positive bacterial or fungal culture result was distributed).

²³ Note that skin cultures taken post-processing may be positive for non-pathogenic normal flora but this is not considered contamination. See section XVIII.E. of FDA's "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; available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>.

²⁴ In certain situations, there are limited uses of an HCT/P from an ineligible donor. See 21 CFR 1271.65(b) and (c).

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3. What are some examples of non-reportable findings related to receipt, predistribution, shipment, and distribution?
 - a. An incorrect HCT/P (e.g., the establishment distributed a properly labeled bone instead of tendon, which was ordered) was distributed, but the HCT/P had met all the release criteria and was acceptable for distribution.
 - b. A summary of records is missing the date and time of the release of the HCT/P.
 - c. An HCT/P was acceptable at the time of distribution. The consignee caused the sterility to be compromised by improperly opening or mishandling the product.

V. CONCLUSION

This guidance describes scenarios to illustrate who must investigate and report HCT/P deviations, what must be reported, and when such reports must be submitted to FDA under 21 CFR Part 1271. Because timely and accurate reporting of HCT/P deviations has been of considerable interest to industry stakeholders, we provide examples of both reportable and non-reportable events. The examples provided in this guidance have been chosen to illustrate the most frequently reported HCT/P deviations that have historically been submitted to CBER. They are not all-inclusive and do not represent all variations that may occur. For these reasons, FDA encourages communication and inquiries to ensure proper reporting of HCT/P deviations. If you have questions, you should contact CBER's Biological Product Deviation Reporting team in the Office of Compliance and Biologics Quality (OCBQ) via telephone at 240-402-9160 or email at hctp_deviations@fda.hhs.gov.