

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

Guidance for Industry

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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

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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, FDA, are issuing this guidance to provide establishments¹ that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps) with recommendations for complying with the requirements under Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271) for investigating and reporting adverse reactions involving communicable disease in recipients of HCT/Ps that are regulated solely under section 361 of the Public Health Service Act (PHS Act) and 21 CFR Part 1271 (hereafter referred to throughout this guidance as “361 HCT/Ps”). In addition, this 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.

This guidance provides 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. This guidance does not apply to reproductive HCT/Ps or to tissues regulated under 21 CFR Part 1270 and recovered before May 25, 2005. Furthermore, this guidance does not apply to health professionals who implant,

¹ Establishment means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products. “Establishment” includes: (1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cells, tissues, and cellular and tissue-based products; and (2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products (21 CFR 1271.3(b)).

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transplant, infuse, or transfer HCT/Ps into recipients.² This guidance supplements section XXII of the FDA guidance document entitled “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, by providing additional recommendations specific to your responsibilities to investigate complaints of adverse reactions concerning 361 HCT/Ps under 21 CFR 1271.160(b)(2), 21 CFR 1271.320 and 21 CFR 1271.350(a). In addition, this guidance supersedes the FDA guidance entitled “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. This guidance also finalizes the draft guidance of the same title dated February 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

A. What is the Scope of this Guidance?

“HCT/Ps” are defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. FDA has implemented a risk-based approach to the regulation of HCT/Ps. Under the authority of section 361 of the PHS Act, FDA established regulations under 21 CFR Part 1271 for all HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases.

In 21 CFR 1271.10, the regulations identify the criteria for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the criteria under

² However, FDA notes that health professionals have an important role in identifying adverse reactions in recipients of HCT/Ps and reporting adverse reactions to manufacturers of HCT/Ps. Further, manufacturers may seek to obtain additional information from health 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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21 CFR 1271.10(a).³ As stated in section I. of this guidance, an HCT/P that falls into this category is referred to as a 361 HCT/P.

B. Who Should Read this Guidance?

This guidance is intended for any 361 HCT/P establishment that performs a manufacturing step and is responsible for complying with CGTP requirements⁴ pertaining to the review, evaluation, investigation, and reporting of complaints of adverse reactions under 21 CFR 1271.320 and 21 CFR 1271.350(a), with respect to 361 HCT/Ps. It is also intended for those 361 HCT/P establishments that share information pertaining to:

(1) the possible contamination of a 361 HCT/P; or (2) the potential for transmission of a communicable disease by a 361 HCT/P with other establishments (21 CFR 1271.160(b)(2)).

In this guidance, “you” means the establishment that made the HCT/P available for distribution. The term “available for distribution” means that the HCT/P has been determined to meet all release criteria (21 CFR 1271.3(z)).

III. REGULATORY REQUIREMENTS REGARDING INVESTIGATING AND REPORTING ADVERSE REACTIONS

A. What is an Adverse Reaction under 21 CFR Part 1271?

An “adverse reaction” for 361 HCT/Ps is defined as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response (21 CFR 1271.3(y)).

We recognize that whenever an HCT/P recipient experiences an unintended response, there may be multiple possible causes. Nevertheless, if one of the reasonable possibilities is that the HCT/P caused the response, then this would meet the definition of “adverse reaction.”

³ Under 21 CFR 1271.10(a), an HCT/P is regulated solely under section 361 of the PHS Act and the regulations in [21 CFR Part 1271] if it meets all of the following criteria: (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) 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.

⁴ The CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps. Establishments that manufacture HCT/Ps, including establishments that manufacture 361 HCT/Ps, must follow those CGTP requirements that pertain to the operations they perform to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (21 CFR 1271.150).

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B. Which HCT/Ps are Subject to Adverse Reaction Reporting Requirements under 21 CFR 1271.350(a)?

All non-reproductive 361 HCT/Ps are subject to the adverse reaction reporting requirements under 21 CFR 1271.350(a). At this time, FDA does not require adverse reaction reporting for reproductive 361 HCT/Ps (e.g., oocytes, semen, and embryos), or for tissues regulated under 21 CFR Part 1270 and recovered before May 25, 2005.

Provided that they meet all of the criteria listed in 21 CFR 1271.10(a), the following are examples of HCT/Ps that are subject to adverse reaction reporting under 21 CFR 1271.350(a) and fall within the scope of this guidance:

- Amniotic membrane
- Bone
- Cartilage
- Cornea
- Fascia
- Ligament
- Pericardium
- Hematopoietic stem/progenitor cells derived from peripheral blood⁵
- Hematopoietic stem/progenitor cells derived from cord blood⁶
- Sclera
- Skin
- Tendon
- Vascular graft
- Heart valve
- Dura mater

C. Which Adverse Reactions Related to 361 HCT/Ps Must I Investigate and Report under 21 CFR 1271.350(a)?

Under 21 CFR 1271.350(a)(1), you must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. Your investigation must begin as soon as practical (21 CFR 1271.350(a)(3)). In addition, under 21 CFR 1271.350(a)(1), you must report to FDA an adverse reaction involving a communicable disease if it:

- Is fatal;
- Is life-threatening;

⁵ Hematopoietic stem/progenitor cells derived from peripheral or cord blood may be regulated as a 361 HCT/P if the product meets the criteria under 21 CFR 1271.10(a) and either is for autologous use or is for allogeneic use in a first-degree or second-degree blood relative.

⁶ *Id.*

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- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention, including hospitalization.

D. Who Must Report Adverse Reactions Related to 361 HCT/Ps under 21 CFR 1271.350(a)?

Under 21 CFR 1271.350(a)(1), if you are the establishment that made the HCT/P available for distribution, you must report to FDA any adverse reaction involving a communicable disease related to the HCT/P that you have determined met the criteria for reporting under 21 CFR 1271.350(a) (see section III.C. of this guidance).

E. When Must I Submit Reports of Adverse Reactions Related to 361 HCT/Ps to FDA?

You must submit to FDA each report of an adverse reaction that you determine meets the criteria for reporting under 21 CFR 1271.350(a) within 15 calendar days of initial receipt of the information about the adverse reaction (see 21 CFR 1271.350(a)(2)). Under 21 CFR 1271.350(a)(3), you must, as soon as practical, investigate all adverse reactions that are the subject of these 15-day reports and must submit to FDA follow-up reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a follow-up report may be required that describes briefly the steps taken (e.g., phone call, email, registered mail) to seek additional information and the reasons why it could not be obtained (see 21 CFR 1271.350(a)(3)). This might include situations where you are unable to obtain the additional information you need to complete your investigation, such as clinical information about the recipient, in spite of repeated attempts.

F. How Must I Submit Reports of Adverse Reactions Related to 361 HCT/Ps to FDA?

You must submit two copies of each adverse reaction report on a Form FDA 3500A (21 CFR 1271.350(a)(5)).⁷ Send these copies to:

U.S. Food and Drug Administration,
Center for Biologics Evaluation and Research,
Document Control Center,
10903 New Hampshire Avenue,
WO71, G112,
Silver Spring, MD 20993-0002.

You may obtain copies of Form FDA 3500A from Center for Biologics Evaluation and Research (CBER) at the address listed above or electronically at:

⁷ We encourage manufacturers to use Form FDA 3500A whenever reporting adverse reactions to FDA, even if they are reporting voluntarily, to help ensure that FDA has sufficient information to evaluate the reported event or reaction.

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<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>.

General instructions for completing Form FDA 3500A are available at <http://www.fda.gov/Safety/MedWatch/HowToReport/>. However, section V. of this guidance gives you additional recommendations specific to HCT/Ps to help you complete Form FDA 3500A and to help ensure that you provide FDA with critical information.

IV. ADVERSE REACTION INVESTIGATION

A. What Information About the Recipient Should I Review as Part of the Investigation of an Adverse Reaction?

Your investigation should include the evaluation of pertinent information about the recipient's adverse reaction that might be informative about possible etiologies of the adverse reaction. Pertinent information may include:

- The time course, symptoms, and outcome of the reaction;
- The recipient's medical and social/behavioral history (including pre-existing medical conditions and travel history);
- Relevant test results; and
- History of transfusions, infusions, transplants, implants, and transfers that may have been a source for communicable disease transmission.

We recognize that you might not be able to obtain detailed clinical and behavioral risk factor information about the recipient; however, you should make diligent efforts (e.g., phone call, email, registered mail) to obtain relevant information in order to make an appropriate assessment of the possible etiologies of the adverse reaction.⁸

B. What Information Should I Review About the Donor Whose HCT/Ps are Involved in an Adverse Reaction?

You should review all information used to make the donor-eligibility determination (or any donor information that may have become available after the determination was made) and verify that screening and testing were performed in accordance with regulatory requirements. This would include review of information pertaining to whether the donor received transfusions or infusions that may have caused plasma dilution or may have been a source for communicable disease transmission if the complaint involves a disease that is potentially transmissible through transfusion. Part 1271, Subpart C and FDA's guidance document entitled "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)"

⁸ The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Information on HIPAA compliance for reporters to FDA MedWatch is available at: <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085589.htm>.

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dated August 2007, describe requirements and recommendations, respectively, for making a donor-eligibility determination.

C. What Recovery Information Should I Review in My Investigation of an Adverse Reaction?

You should review whether the facility where recovery of the HCT/P took place met the general requirements for HCT/P facilities under 21 CFR 1271.190. In addition, you should review:

- Whether the recovery was performed by a method appropriate to controlling contamination;
- Whether there were deviations from established procedures that may have increased the risk of contamination or cross-contamination;
- Whether the supplies and reagents used during recovery were in compliance with 21 CFR 1271.210; and
- Whether the recovery was performed within your established time and temperature limits for recovery.

D. What Processing Information Should I Review in My Investigation of an Adverse Reaction?

Under 21 CFR 1271.3(ff), “processing” means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as:

- Testing for microorganisms;
- Preparation;
- Sterilization;
- Steps to inactivate or remove adventitious agents;
- Preservation for storage; and
- Removal from storage.

Investigation of an adverse reaction related to a 361 HCT/P should include the review of processing records to determine whether there were any deviations or departures from your established procedures that may have resulted in contamination or cross-contamination of the HCT/P involved in the adverse reaction. The investigation should specifically include the following, as applicable:

- The review of records related to the evaluation of the incoming bioburden, such as the results of recovery or procurement cultures, or findings on inspection of the HCT/P packaging or container for damage and contamination.
- The review of pre- and post-processing culture results, if applicable, and the determination as to whether any microorganisms present on those cultures were also present on recipient cultures. Although some microbiology laboratories do not routinely identify the species of certain microorganisms, speciation is desirable as it aids in the investigation of adverse reactions.

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- The determination as to whether multiple cellular products were collected at different times from the same donor and combined to attain a certain therapeutic dose, and a review of the results of cultures performed on each separate product, if available.
- A verification that the process used for removal or inactivation of microorganisms was validated and performed as established in standard operating procedures. This verification should include a comparison of the list of representative challenge microorganisms that were used in your process validation to the type of microorganism(s) involved in the adverse reaction.
- The review of records of sterilization and/or disinfection process failures (i.e., positive microbiological testing results following sterilization or disinfection of an HCT/P) within the timeframe spanning an appropriate period before and after the suspect HCT/P was manufactured and a determination as to whether your establishment has experienced sterilization or disinfection process failures involving the same microorganism as identified in the recipient adverse reaction. An appropriate period should be supported by a risk-based analysis that includes the volume of processing cultures performed, but it should be no less than 7 days.
- A determination as to whether any HCT/Ps from the donor were discarded during or after processing because they did not meet your pre-established acceptance criteria related to communicable diseases (e.g., organism considered unacceptable, sterilization or disinfection process failures, contamination).

E. What Environmental Control and Monitoring Information Should I Review in My Investigation of an Adverse Reaction?

Under 21 CFR 1271.195(a), where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, you must adequately control environmental conditions and provide proper conditions for operations.

Under 21 CFR 1271.195(c), you must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, and you also must provide environmental monitoring for microorganisms, where appropriate.

As part of your investigation, you should review environmental control and monitoring records from all areas where the involved HCT/Ps were processed, including records pertaining to:

- Temperature and humidity controls;
- Ventilation and air filtration;
- Air samples;
- Work surfaces;
- Sinks and drains;
- Personnel;

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- Maintenance of equipment; and
- Cleaning and disinfection of rooms and equipment.

You also should determine:

- What types of microorganisms have been detected;
- Whether the same microorganism responsible for the recipient infection has been cultured during routine environmental monitoring; and
- Whether results reached or exceeded your established action levels in the general timeframe surrounding the processing of the implicated HCT/P.

Even if the microorganisms cultured from the environment and from the recipient are not the same, the recurrence or persistence of microorganisms in the environment near or above established action levels may indicate a general problem within your establishment.

F. What Storage and Distribution Information Should I Review in My Investigation of an Adverse Reaction?

You should review storage and distribution records to determine whether the HCT/P was stored under appropriate conditions (e.g., stored within defined temperature limits); whether there was a possibility of mix-up, contamination, or cross-contamination; whether the HCT/P was properly made available for distribution (e.g., met release criteria); and whether the HCT/P was shipped under established conditions (21 CFR 1271.260 and 1271.265).

G. What Tracking Information Should I Review in My Investigation of an Adverse Reaction?

You should review tracking information to identify the following pertaining to the donor of the HCT/P involved in an adverse reaction:

- Number of HCT/Ps produced and distributed;
- Number of HCT/Ps reported as implanted;
- Number of HCT/Ps that remain in inventory; and
- Number or types of HCT/Ps you sent to other establishments for further manufacture.

Such tracking information facilitates timely corrective actions, including notification of consignees as appropriate (21 CFR 1271.160(b)(2)(iii)).

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H. What Labeling Information Should I Review in My Investigation of an Adverse Reaction?

You should review records pertaining to the information in the product label to determine whether it was labeled appropriately, including warnings and instructions for use related to prevention of the introduction, transmission, or spread of communicable diseases (see 21 CFR 1271.250, and 1271.370(b) and (c)).

I. What Complaint File Information Should I Review in My Investigation of an Adverse Reaction?

Under 21 CFR 1271.320(b), you must maintain a record of complaints that you receive in a file designated for complaints. As part of every investigation, you should review this file to determine if other relevant complaints of adverse reactions have been reported to your establishment. This may include other complaints involving the same donor, complaints involving the same infectious agent or microorganism, or complaints involving the same reporting facility or surgeon. Should you find other relevant complaints, you should review the relevant documentation from the investigation(s) of these complaints, including any results or findings, to determine if there are any correlations with the current complaint under investigation.

J. What Information Pertaining to Adverse Reactions Concerning 361 HCT/Ps Should I Share with Other Establishments?

If you are an establishment that performs any step in the manufacture of HCT/Ps, under 21 CFR 1271.160(a), you must maintain a quality program intended to prevent the introduction, transmission, or spread of communicable diseases through the manufacture and use of HCT/Ps. Among other things, one of the functions your quality program must perform is the establishment and maintenance of procedures for sharing with other establishments information pertaining to the possible contamination of the HCT/P or pertaining to the potential transmission of communicable disease by the HCT/P with other establishments that are known to have recovered HCT/Ps from the same donor, and with other establishments that are known to have performed manufacturing steps with respect to the same HCT/P (21 CFR 1271.160(b)(2)(i) and (ii)). We recommend that the shared information include any pertinent information that you have collected from your investigation of an adverse reaction and note that these procedures can be designed so that patient confidentiality is not compromised. Sharing this information should assist other establishments in taking appropriate action(s). We also recommend that you seek information regarding any complaints that the other establishments who have recovered or performed manufacturing steps on HCT/Ps from the same donor may have received related to the HCT/Ps.⁹

⁹ We refer you to the FDA guidance entitled “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, for further recommendations pertaining to sharing information with, and receiving information from, other establishments.

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V. ADVERSE REACTION REPORTING

A. What Information Should I Report on Form FDA 3500A?

If you are an establishment that makes the 361 HCT/P available for distribution, you should use the information that you collected from your investigation of the adverse reaction to complete Sections A, B, C, E, and G, as well as the “Other Remarks” section of Form FDA 3500A. If any items in those sections do not apply to you or the adverse reaction, indicate these as being not applicable (N/A). The following recommendations are specific to the information you should provide to complete the sections applicable to 361 HCT/Ps; you also may need to refer to the general instructions for completing Form FDA 3500A available at

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf>.

Section A: Patient Information

Information in this section pertains to the recipient of the HCT/P.

A1: Patient Identifier. Use recipient’s initials or some other identifier that will facilitate follow-up if requested. Complete a separate form for each recipient.

A2: Age or Date of Birth. Provide the most precise information available. For age, indicate time units used (e.g., years, months, and days).

A3: Sex. Enter the recipient’s gender.

A4: Weight. Provide the weight if it is relevant to the adverse reaction. Indicate the weight units used (e.g., pounds, kilograms).

A5a: Ethnicity. Choose only one response.

A5b: Race. Choose all that apply.

Section B: Adverse Event or Product Problem

B1: Adverse Event *and/or* Product Problem. The term “adverse event” as used on the form is applicable to HCT/P adverse reactions; check this box to report an adverse reaction. FDA does not require reporting of 361 HCT/P problems that did not result in or contribute to an adverse reaction.

B2: Outcomes Attributed to Adverse Event. Check off all that apply for outcomes attributed to the adverse reaction. Refer to the general instructions that accompany the Form FDA 3500A for descriptions of the outcome categories.

B3: Date of Event. Provide the actual or best estimate of the date of first onset of the adverse reaction, such as the approximate date of onset of symptoms or the date the health professional identified the infection.

B4: Date of this Report. Provide the date the report is filled out.

B5: Describe Event or Problem. Describe the adverse reaction in detail using the words of the individual who reported the adverse reaction to the manufacturer. Include a description of what happened and a summary of all clinical information relevant to the event (e.g., recipient’s medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome). If available and if relevant, include synopses of any office

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visit notes or the hospital discharge summary. To save time and space (and if permitted by the institution), you may attach copies of these records and simply refer to them in your response. Include information about any environmental exposures that may have influenced the event (e.g., for an adverse reaction involving West Nile Virus (WNV), note whether the recipient lives in or has traveled to an area with high WNV activity). Include the Manufacturer Report Number(s) in this field to identify other MedWatch reports filed regarding the same donor.

B6: Relevant Tests/Laboratory Data, Including Dates. Provide results of the recipient's relevant tests and laboratory data, including relevant negative tests and laboratory findings, and dates performed. This includes recipient cultures or serology performed before or after receipt of the product, or tests performed to evaluate the reaction. Copies of any reports may be submitted as attachments. In cases where cultures were not obtained from the recipient, make note of that in this field.

B7: Other Relevant History, Including Preexisting Medical Conditions.

This item should include information about the recipient and the donor.

- Provide any relevant information about the recipient's history that has not already been requested in Section B, including preexisting medical conditions, behavioral risk factors, and history of transfusion of blood and/or blood products.
- Provide any relevant information about the donor. Such information may include relevant donor medical and social history, donor screening test results, and pre- and post-processing culture results. Include a statement about whether the donor record review revealed any problems with donor screening, testing, or eligibility determination, and whether the donor received blood or blood products.

Section C: Suspect Product(s)

Provide information about the 361 HCT/P that is suspected of causing the adverse reaction in this section. Up to two (2) suspect products may be reported on one form

C1: Name, Manufacturer/Compounder, Strength. Space provided to identify two products. Provide the common name of the HCT/P, followed by "Tissue" or "Cell" in parentheses, for example:

- Demineralized bone (Tissue)
- Cornea (Tissue)
- Hematopoietic stem/progenitor cells derived from peripheral blood (Cell)

You also can indicate if the HCT/P has a proprietary or trade name, in addition to the common name of the HCT/P. Provide the name of the manufacturer.

Lot #. Provide the lot number here.

NDC # or Unique ID. Provide the unique identification number for the HCT/P to facilitate tracking.

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C2: Concomitant Medical Products and Therapy Dates. List and provide therapy dates for any other medical products (drugs, biological products, medical devices, blood or blood products) that were administered to the recipient at the time of receipt of the HCT/P.

C3: Dose, Frequency & Route Used. This is applicable for cells. Please provide information on the dose, frequency and route used.

C4: Therapy Dates. Provide date of implantation, transplantation, or infusion (Line #1) and date of explantation (Line #2), if applicable.

C5: Diagnosis for Use. Provide the diagnostic reason for HCT/P implantation, transplantation, or infusion.

C6: Is the Product Compounded? Leave Blank

C7: Is the Product Over-the-Counter? Leave Blank

C8: Expiration Date. Provide the date of expiration on the HCT/P label, if any.

C9: Event Abated After Use Stopped or Dose Reduced? Check the box “Doesn't Apply.”

C10: Event Reappeared After Reintroduction? Check the box “Doesn't Apply.”

Section E: Initial Reporter

E1: Name and Address, Phone #. Provide the name, mailing address, and phone number of the individual who initially reported the adverse reaction to the manufacturer or distributor so that individual can be contacted if follow-up is necessary to obtain additional clinical information related to the recipient's adverse reaction. We recommend that you also provide the email address and fax number of the initial reporter, if known.

E2: Health Professional? Indicate whether the initial reporter is a health professional (check “Yes” or “No”).

E3: Occupation. Indicate the initial reporter's occupation (e.g., physician, nurse, dentist, etc.).

E4: Initial Reporter Also Sent Report to FDA. Indicate whether the initial reporter also notified or sent a report to FDA or check “Unk” if unknown.

Section G: All Manufacturers

G1: Contact Office – Name/Address/Email Address. Provide the full name and address of the manufacturer reporting site, including the name of the contact at that site. Include the email address of the contact.

G2: Phone Number. Provide the telephone number of the contact at the manufacturer reporting site who is knowledgeable about the report.

G3: Report Source. Check the box(es) that describe how the manufacturer became aware of the reported adverse reaction or where the information originated. See the MedWatch instructions for more detailed definitions of report sources:

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf>

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G4: Date Received by Manufacturer. Provide the date the manufacturer initially received information that the adverse reaction occurred, or the date the manufacturer received follow-up information (for follow-up reports).

G5: Does not apply (leave blank).

G6: Does not apply (leave blank).

G7: Type of Report. Check off “15-day” as well as “Initial” for initial reports of adverse reactions related to HCT/P’s. Check off “Follow-Up” if the report is a follow-up to a previously submitted report. You should provide additional or corrected information on the previously reported event. You should include information that was submitted in the original report if the information is still correct.

G8: Adverse Event Term(s). Include a list of adverse event terms that most accurately characterize the adverse event described in the narrative format in box B5. Terms should be listed with the most important term(s) first. The terminology may be an accepted standard (e.g., MedDRA or WHOART), a verbatim term, or the manufacturer’s own terminology. For more information on MedDRA coding, see the MedDRA Term Selection: Points to Consider dated October 1, 2012, at

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/MedDRA/MedDRA_Documents/MedDRA_Term_Selection/Release_4.4_based_on_v.15.1/TermSelection_PTC_R4.4_October.2012.pdf.

G9: Manufacturer Report Number. The report number should consist of three numbers separated by dashes. The first number will be the 10-digit FDA Establishment Identifier (FEI) number, which was assigned to you as part of the Human Cells and Tissue Establishment Registration System (HCTERS). The second number should be the year that you are submitting the report. The last number should be a consecutive 5-digit number for each report filed during the year by the manufacturer. Example: 1234567890-2005-00005.

- In the upper right corner of the front page in the field “Mfr Report #” enter the same manufacturer report number.
- For a follow-up report, the manufacturer report number should be identical to the number assigned to the initial report.

Section “Other Remarks” on page 3 of Form FDA 3500A

In this section, include statements summarizing the findings from review of manufacturing records, including information as to:

- Any problems with the donor eligibility determination;
- Any problems with the tissue recovery protocols;
- Any deviations or departures from established procedures;
- Any microorganisms present on donor tissue or in cell product pre- or post-processing culture results that are also present on recipient cultures;
- Any sterilization or disinfection process failures your establishment experienced within the timeframe spanning at least 7 days before and after the suspect HCT/P was manufactured involving the same microorganism as identified in the recipient adverse reaction;

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- Any problems with environmental monitoring; indicate what types of microorganisms have been detected, and whether results reached or exceeded action levels in a general timeframe surrounding the processing of the implicated HCT/P; and
- Any other complaints involving the same donor or complaints of the same microorganism involving tissues processed in the same general timeframe as those from the implicated donor.

B. How Do I Report Adverse Reactions Involving Multiple HCT/Ps?

If a reportable adverse reaction involves two or more 361 HCT/Ps transplanted in the same recipient, only one Form FDA 3500A should be completed. The Form FDA 3500A should list the names and lot numbers of all HCT/Ps.

If multiple recipients experience adverse reactions related to HCT/Ps from the same donor, you should submit a separate Form FDA 3500A for each recipient. Include the Manufacturer Report Number(s) in field B5 of Form FDA 3500A to identify the other Forms FDA 3500A you submitted regarding the same donor.

C. How Do I Report Adverse Reactions/Events for Other HCT/Ps that are not Regulated as 361 HCT/Ps, but are Regulated as Drugs, Medical Devices, or Biological Products?

If your establishment manufactures and makes available for distribution other HCT/Ps that do not meet the criteria specified in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act, then the adverse reaction report requirements in 21 CFR 1271.350 are not applicable. Those other HCT/Ps are regulated as either drugs, medical devices, or biological products and therefore are subject to the reporting requirements for drugs, medical devices, or biological products under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the PHS Act and the applicable regulations in Title 21 of the CFR. For those types of HCT/Ps, we refer you to the following, relevant sections of the CFR for reporting pre- and post-marketing adverse reactions to FDA:

Medical Devices:

21 CFR Part 803 (Medical Device Reporting)

Medical Device Reporting - General Information

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

21 CFR Part 812 (Investigational Device Exemptions)

Investigational Drugs (including Investigational Biological Drugs):

21 CFR 312.32 (IND safety reporting) and 21 CFR 312.64 (Investigator reports)

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Prescription Drugs:

21 CFR 314.80 (Postmarketing reporting of adverse drug experiences)

Licensed Biological Drugs (Postmarket Biological Drug Products):

21 CFR 600.80 (Postmarketing reporting of adverse experiences)

D. Who Can I Contact if I Have Additional Questions Concerning the Reporting of an Adverse Reaction Related to a 361 HCT/P?

You may send questions concerning reporting adverse reactions related to 361 HCT/Ps to FDA's Tissue Safety Team (TST) at the following email address: TST@cber.fda.gov.

E. What Happens to MedWatch Form FDA 3500A Reports After I Submit Them to FDA?

CBER has established Standard Operating Procedures and Policies (SOPP) 8508 for handling adverse reaction reports related to 361 HCT/Ps (see <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm073048.htm>). The reports are reviewed by FDA's TST which conducts further information gathering and recommends interventions, if necessary.

VI. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than six months after the issuance date of this guidance.

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VII. REFERENCES

1. Food and Drug Administration. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (August 2007). <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf>.
2. Food and Drug Administration. 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). <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>.