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)

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

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

For questions on the content of this guidance, contact CBER's Office of Biostatistics and Epidemiology, Division of Epidemiology, Therapeutics and Blood Safety Branch at 301-827-3974.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

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

I. INTRODUCTION

We, FDA, are supplementing the general instructions accompanying the MedWatch mandatory reporting form, Form FDA 3500A, with information about reporting adverse reactions related to human cells, tissues, and cellular and tissue-based products (HCT/Ps). These supplemental instructions are intended for manufacturers of HCT/Ps (you) who are required to report adverse reactions to FDA under Title 21 of the Code of Federal Regulations (CFR) 1271.350(a). The objective of this guidance is to standardize reporting requirements to improve the quality of the HCT/P reports submitted to the FDA Adverse Event Reporting System (AERS).

Section 1271.350(a) was finalized as part of the Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement - Final Rule, which published in the Federal Register on November 24, 2004 (69 FR 68612), and became effective on May 25, 2005 (www.fda.gov/cber/tissue/docs.htm).

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. DISCUSSION

We are providing the following information and recommendations to assist you in completing and forwarding to FDA, Form FDA 3500A. Specifically, we are providing instructions for reporting adverse reactions related to HCT/Ps described in 21 CFR 1271.10(a) and regulated solely under section 361 of the Public Health Service (PHS) Act.

A. What is an HCT/P?

- An HCT/P is defined as an article containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion, or transfer into a human recipient (21 CFR 1271.3(d)).
- An HCT/P is regulated solely under section 361 of the PHS Act and applicable regulations in 21 CFR Part 1271 if it meets all of the criteria described in 21 CFR 1271.10(a). HCT/Ps that fall into this category are referred to as "361" HCT/Ps.

If the HCT/P does not meet the criteria in 21 CFR 1271.10(a), then the HCT/P is regulated as a drug, medical device, or biological product under the Federal Food, Drug, and Cosmetic (FFD&C) Act and/or section 351 of the PHS Act and applicable regulations in Title 21 CFR, Chapter I, in addition to applicable regulations in 21 CFR Part 1271.

B. 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)).

C. What HCT/Ps are subject to adverse reaction reporting under 21 CFR 1271.350(a)?

Non-reproductive HCT/Ps as described in 21 CFR 1271.10 (i.e., "361" HCT/Ps) are subject to the adverse reaction reporting requirements under 21 CFR 1271.350(a). HCT/Ps that are considered "361" HCT/Ps must meet all of the criteria in 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 cell 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.

Some examples of HCT/Ps that are subject to adverse reaction reporting under 21 CFR 1271.350(a), provided that they meet all of the criteria in 21 CFR 1271.10(a), include:

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

Adverse reaction reporting is not required for reproductive tissues (oocytes, semen, and embryos) that are "361" HCT/Ps, or for "361" HCT/Ps regulated under 21 CFR Part 1270 and recovered before May 25, 2005. However, FDA would welcome voluntary reports, using MedWatch Form FDA 3500, of adverse reactions related to these HCT/Ps.

D. What adverse reactions related to "361" HCT/Ps do I investigate and/or report under 21 CFR 1271.350(a)?

Under 21 CFR 1271.350 (a), you must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. You must report to FDA an adverse reaction if it involves a communicable disease related to an HCT/P if it:

1. Is fatal
2. Is life-threatening
3. Results in permanent impairment of a body function or permanent damage to body structure or
4. Necessitates medical or surgical intervention, including hospitalization.

E. Who must report adverse reactions related to "361" HCT/Ps regulated under 21 CFR 1271.350(a)?

You must report to FDA adverse reactions related to HCT/Ps after you have investigated and determined that the adverse reaction should be reported and you are the establishment that made the HCT/P available for distribution (21 CFR 1271.350(a)). Available for distribution means an HCT/P that has been determined to meet all release criteria (21 CFR 1271.3(z)). Only adverse reactions involving a communicable disease, as described above (see Section D.), are required to be reported.

F. When do I report adverse reactions related to "361" HCT/Ps?

You must investigate an adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution, and submit adverse reaction reports to the Center for Biologics Evaluation and Research (CBER) (HFM-210) within 15 calendar days of the initial receipt of the information (21 CFR 1271.350(a)). You must also submit 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 to seek additional information and the reasons why it could not be obtained.

G. How do I report adverse reactions related to "361" HCT/Ps?

You must submit 2 copies of each report on a Form FDA 3500A (21 CFR 1271.350(a)(5)) to:

Center for Biologics Evaluation and Research (HFM-210)
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

You may obtain copies of Form FDA 3500A from CBER at this address or electronically at http://www.fda.gov/medwatch. General instructions for Form FDA 3500A are also available at the above website address. A fillable form may be used for both initial and follow-up reports and then mailed to CBER (http://www.fda.gov/medwatch/SAFETY/FDA3500A_fillable.pdf). For reports that require urgent attention, please contact the Office of Biostatistics and Epidemiology at 301-827-3974.

H. Which sections of Form FDA 3500A should I complete?

If you are a manufacturer of a "361" HCT/P that makes the HCT/P available for distribution, you should complete Sections A, B, C, E, and G. Do not complete Section D, F, and H, which relate to mandatory medical device reports. If there are sections that do not apply to you or the adverse reaction, indicate these as being not applicable (N/A). The following provides recommendations for completion of the applicable sections:

Section A: Patient Information

Provide information on the patient (**A1-A4**). Use patient's initials or some other identifier, which will facilitate follow-up if requested. Any identifiable patient or reporter information is protected and confidential, and will be excluded from any reports generated in response to Freedom of Information (FOI) Act requests. Complete a separate form for each patient.

Section B: Adverse Event or Product Problem

Provide information on the adverse reaction (**B1**). The term "adverse event" as used on the form is applicable to HCT/P adverse reactions. Check off all that apply for outcomes

attributed to the adverse reaction (**B2**). Please use **B5-B7** to provide all relevant information. This includes any information on the HCT/P that you are not able to provide in Section C. Such information may include donor screening tests, pre- and post-processing culture results.

Section C: Suspect Product(s)

Information on the suspect "361" HCT/P should be provided in Section C which is titled "Suspect Product(s)." In box **C1** "Name," provide the common name of the HCT/P, followed by "Tissue" or "Cell" in parenthesis. You can also indicate if the HCT/P has a proprietary or trade name, for example:

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

C2 is applicable for cells. Please provide information on the dose, frequency and route used.
C3 "Therapy Dates": Provide date of implantation (Line #1) and date of explanation (Line #2), if applicable.
C4 "Diagnosis for Use": Provide the diagnostic reason for HCT/P implantation, transplantation, or infusion.
C5 Mark "Doesn't Apply".
C6 "Lot #": Provide the lot number here. If more than two lines are needed please provide information on an additional page.
C7 "Exp. Date": Provide the date of expiration on the HCT/P label, if any.
C8 Mark "Doesn't Apply".
C9 "NDC# or Unique ID": Please provide the unique identification number for the HCT/P to facilitate tracking.
C10 "Concomitant Medical Products and Therapy Dates": Provide information on drugs, biological products, or devices that the patient received.

Section E: Initial Reporter

Indicate the person who initially reported the adverse reaction to the manufacturer. Provide the name, mailing address, and phone number of the individual who can be contacted if follow-up is necessary (**E1**). We recommend that you also provide the e-mail address and fax number, if known. Indicate if the reporter is a health professional, his/her occupation, and if the reporter sent a report to the FDA (**E2-E4**).

Section G: All Manufacturers

G1 and **G2** are for the manufacturer's contact information, including phone number.
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 MedWatch instructions for more detailed definitions of report sources: (http://www.fda.gov/medwatch/REPORT/instruc.htm).
G4 "Date Received by Manufacturer": Date you received information that the adverse reaction occurred, or date you received follow-up information (for follow-up reports).

G5 Does not apply.
G6 Does not apply.
G7 "Type of Report": Check off "15-day" for initial reports on 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 November 18, 2004, at http://www.ich.org/MediaServer.jser?@_ID=1714&@_MODE=GLB.
G9 "Manufacturer Report Number": If you are an HCT/P manufacturer, we recommend that the report number 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.

I. 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 FDA Form 3500A should be completed. The FDA Form 3500A should list the names of all HCT/Ps.

Adverse reactions may involve multiple HCT/Ps recovered from the same donor. If multiple recipients experience adverse reactions related to HCT/Ps from the same donor, there should be a MedWatch report for each recipient.

J. How do I report adverse reactions/events for other HCT/Ps (those regulated as drug, medical device, or biological products)?

If your HCT/P does not meet the criteria specified in 21 CFR 1271.10(a) for a "361" HCT/P, then adverse reaction report requirements in 21 CFR 1271.350 are not applicable. Such HCT/Ps are subject to the reporting requirements for drugs, medical devices, and/or biological products under the FFD&C Act and/or section 351 of the PHS Act and applicable regulations, in Title 21 CFR, Chapter I. The relevant regulations for reporting

pre- and post-marketing adverse reactions for HCT/Ps that are regulated as drugs, medical devices, or biological products are:

Medical Devices:

21 CFR Part 803 (2005)
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr803_05.html

Medical Device Reporting - General Information
http://www.fda.gov/cdrh/mdr/mdr-general.html

21 CFR Part 812 (2005)
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr812_05.html

Investigational Drugs and Biological Drugs:

21 CFR 312.32 (IND Safety Reports) and 21 CFR 312.64 (Investigators Reports) (2005)
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr312_05.html

Post-Market Drugs

21 CFR 314.80 (2005)
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr314_05.html

Post-Market Biological Drug Products

21 CFR 600.80 (2005)
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr600_05.html

K. Who can I contact if I have additional questions concerning reporting an adverse reaction related to an HCT/P?

You may address questions concerning reporting adverse reactions to an email address set up to handle such inquiries at TST@cber.fda.gov.

L. What happens to MedWatch Form FDA 3500A reports after I submit them?

CBER has established Standard Operating Procedures and Policies (SOPP) 8508 for handling adverse reaction reports related to "361" HCT/Ps (http://www.fda.gov/cber/regsopp/8508.htm). The reports are received in CBER's Office of Biostatistics and Epidemiology. They are reviewed by safety evaluators and then forwarded to an internal Tissue Safety Team (TST) if additional follow-up is deemed necessary. The TST conducts any further information gathering or intervention. The report information is entered into FDA's Adverse Event Reporting System (AERS) database.