

Guidance for Industry

Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donors Who Were Tested For Communicable Diseases Using Pooled Specimens or Diagnostic Tests

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) and (3) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate. FDA has concluded that donor retesting, in certain cases, needs to be conducted in a timely manner in order to be feasible, and that there is a public health need to make certain HCT/Ps available for use, where appropriate.

FDA invites comments on this guidance. Submit written comments at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance when appropriate.

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 Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies at 301-827-6176.

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Table of Contents

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. INVESTIGATION AND CORRECTIVE ACTIONS..... 3

IV. HCT/P DEVIATION REPORTS FOR DISTRIBUTED HCT/PS..... 3

A. Are These Testing Deficiencies Considered HCT/P Deviations and Do They Relate to Core Current Good Tissue Practice Requirements?..... 3

B. Am I Required to Report an HCT/P Deviation for the HCT/Ps I Distributed? 4

C. How Should I Report an HCT/P Deviation? 5

D. Which Establishment Should Submit the HCT/P Deviation Report? 5

V. MITIGATION OF RISK OF HCT/PS IN INVENTORY..... 5

A. What Should I Do after Quarantining HCT/Ps in Inventory? 5

B. Which Donors Should be Retested and May I Distribute These HCT/Ps? 6

C. How Should I Label the HCT/P When I Distribute Them Without Retesting? 7

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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

This guidance provides you, an establishment¹ that makes donor eligibility determinations for certain human cells, tissues, and cellular and tissue-based products (HCT/Ps), with recommendations concerning the donor eligibility and additional requirements under Title 21 Code of Federal Regulations, Part 1271, Subpart C (21 CFR Part 1271). This guidance addresses certain HCT/Ps that were tested for communicable diseases using pooled specimens or diagnostic tests. For the purpose of this guidance, certain HCT/Ps mean hematopoietic stem cells, and reproductive cells and tissues.²

This guidance applies only to certain HCT/Ps recovered from donors beginning on or after the effective date of the regulations contained in 21 CFR Part 1271, Subpart C³ (effective date May 25, 2005), and within 30 days of publication of the *Federal Register* notice announcing the availability of this guidance.

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

¹ Under 21 CFR 1271.3(b)(2), an establishment includes facilities that engage in contract manufacturing services for a manufacturer of HCT/Ps (e.g., laboratories that perform donor eligibility testing under contract, agreement, or other arrangement with an establishment).

² FDA does not include tissues previously subject to regulation under 21 CFR Part 1270 within the category of "certain HCT/Ps" addressed in this guidance. Instead, we limit the application of this document to certain HCT/Ps not previously regulated as HCT/Ps.

³ 69 *Federal Register* 29785, May 25, 2004; correction 71 *Federal Register* 14798, March 24, 2006.

Contains Nonbinding Recommendations

II. BACKGROUND

FDA's new donor screening and testing regulations became effective on May 25, 2005 (21 CFR Part 1271, Subpart C). Section 1271.80(c) (21 CFR 1271.80(c)) of those regulations requires testing establishments to use appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases. FDA has since learned that some testing laboratories that perform communicable disease testing on donors of certain HCT/Ps have failed to comply with this provision. This guidance addresses two categories of compliance problems. Some laboratories, apparently familiar with pooling instructions for blood and plasma donor specimens, performed Nucleic Acid Testing (NAT) for human immunodeficiency virus, type 1 (HIV-1) and hepatitis C virus (HCV) on pooled HCT/P donor specimens, even though the manufacturer's instructions (package inserts) for the NAT tests specified that testing be performed on individual HCT/P donor specimens. Also, some test laboratories used diagnostic tests to test HCT/P donor specimens rather than the FDA-licensed donor screening tests required by 21 CFR 1271.80(c). Thus, in these two situations, establishments failed to perform donor testing in accordance with the regulations. FDA has received inquiries from establishments and professional associations regarding certain HCT/Ps affected by these testing deficiencies that were distributed or are currently in inventory.

We, FDA, believe that the use of certain HCT/Ps recovered from donors tested in the situations described above may introduce some additional risk of communicable disease transmission. When NAT is performed on pooled donor specimens, the sensitivity of the test may not be comparable to the sensitivity of the test when performed according to the test kit manufacturer's instructions. For instance, the HIV-1 and HCV NAT tests have not been established as adequately sensitive when samples from certain HCT/P donors are tested in pools. Similarly, some tests cleared or approved by FDA for diagnostic use have not been demonstrated to be as sensitive as FDA-licensed, approved, or cleared donor screening tests.

FDA has also compared this incremental risk to the costs to patients if these products are unavailable. For example, patients may die if human leukocyte antigen (HLA) matched hematopoietic stem cells are unavailable. We think that, given the expected benefits of using such HCT/Ps, under these circumstances, patients may wish to accept the small increased risk presented by these testing deficiencies, provided the labeling is appropriate and accurately reflects the increased risk. Accordingly, in this guidance document, we describe ways to help mitigate the small increased risk presented by these two testing deficiencies. Ways to mitigate include retesting the donor or justifying why this is not possible, using special labeling for the HCT/P, and physician notification. With respect to these two categories of testing deficiencies, when the deficiency occurred soon after the effective date of 21 CFR 1271.80 (see next paragraph), and when the increased risk is appropriately mitigated (see Section V.), we intend to exercise enforcement discretion not to prevent distribution of these HCT/Ps.

The recommendations described in this guidance are limited to the two testing deficiencies described in this guidance; these recommendations do not apply to other failures to comply with 21 CFR 1271.80. Moreover, we intend to exercise our enforcement discretion as described in this guidance only with respect to certain HCT/Ps recovered from donors beginning on or after

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the effective date of the regulations contained in 21 CFR Part 1271, Subpart C (see footnote 3) and within 30 days of publication of the *Federal Register* notice announcing the availability of this guidance. After that time, the agency expects HCT/P establishments and testing laboratories to have corrected their procedures such that they are in full compliance with testing regulations in 21 CFR 1271.80.

III. INVESTIGATION AND CORRECTIVE ACTIONS

Any establishment that performed donor testing subject to one of the two deficiencies described in this guidance must investigate those deficiencies and ensure that appropriate corrective actions have been taken to prevent the events described above from occurring again (21 CFR 1271.160(b)(2) and (3)). If the establishment was a laboratory that performed such donor testing under a contract, agreement, or other arrangement with another HCT/P establishment(s), the laboratory must notify the affected HCT/P establishment(s) (21 CFR 1271.160(b)(2)(ii)). Whether it performed the testing in-house, or contracted with a laboratory to perform donor testing, the HCT/P establishment(s) must investigate and determine which distributed HCT/Ps are affected by these testing deficiencies. This includes identification of affected HCT/Ps that were distributed, and identification of affected HCT/Ps that are in inventory (21 CFR 1271.160(b)(3)(i)).

Establishments should identify, quarantine, and not distribute HCT/Ps currently in inventory that were obtained from donors tested using pooled specimens or diagnostic tests. To assure that all such HCT/P donors are identified:

- If donor testing was performed in-house by the HCT/P establishment, that establishment must investigate to determine which donors were so tested and determine which HCT/Ps currently in inventory are affected, and quarantine them (21 CFR 1271.160(a) and 1271.65); or
- If donor testing was performed by a laboratory under contract, agreement, or other arrangement, the laboratory must notify the HCT/P establishments affected (21 CFR 1271.160(b)(2)(ii)) and the HCT/P establishment must investigate and determine which donors were so tested and which HCT/Ps currently in inventory are affected and must quarantine affected HCT/Ps (21 CFR 1271.60(a) and 1271.65).

IV. HCT/P DEVIATION REPORTS FOR DISTRIBUTED HCT/PS

A. Are These Testing Deficiencies Considered HCT/P Deviations and Do They Relate to Core Current Good Tissue Practice Requirements?

FDA defines an HCT/P deviation 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

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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.

The testing deficiencies described in this guidance meet the definition of an HCT/P deviation. Requirements related to donor eligibility determinations, donor screening and donor testing are core current good tissue practices (CGTPs) (21 CFR 1271.150(b)(10)).

B. Am I Required to Report an HCT/P Deviation for the HCT/Ps I Distributed?

Under 21 CFR 1271.350(b)(1), you must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step. Therefore, the establishment that performed donor testing must investigate the HCT/P deviations described in this guidance.

Under 21 CFR 1271.350(b)(2), you must report any such HCT/P deviation relating to a core CGTP requirement, 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. Since donor testing is a core CGTP, the establishment that distributed the HCT/P related to a donor testing deficiency, must report these HCT/P deviations, as follows.

1. Report an HCT/P deviation for the following distributed HCT/Ps:
 - Hematopoietic stem cells derived from peripheral or cord blood:
 - For use in first-degree or second-degree blood relatives (related allogeneic). These HCT/Ps are regulated solely under section 361 of the Public Health Service Act (PHS Act).
2. Do not report an HCT/P deviation for the following distributed HCT/Ps:
 - Hematopoietic stem cells derived from peripheral or cord blood:
 - For use in unrelated allogeneic recipients. These HCT/Ps are regulated as biological products under section 351 of the PHS Act (21 CFR 1271.20). Section 1271.350 (21 CFR 1271.350) does not apply to HCT/Ps regulated as biological products. (21 CFR 1271.330)
 - If under an Investigational New Drug Application (IND), an information amendment should be submitted directly to the IND file, as appropriate (21 CFR 312.31).
 - For autologous use. No HCT/P deviation report is required because testing of autologous donors is not required for HCT/Ps regulated under section 361 of the PHS Act (21 CFR 1271.10).
 - Reproductive HCT/Ps, because the HCT/P deviation reporting requirements in 21 CFR 1271.350(b) do not apply to reproductive HCT/Ps.

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C. How Should I Report an HCT/P Deviation?

If an HCT/P deviation report is required for certain distributed HCT/Ps affected by one of the two testing deficiencies described in this guidance document, you may submit one HCT/P deviation report for all affected HCT/Ps. HCT/P deviation reports must be submitted using Form FDA 3486 (Biological Product Deviation Reports) either electronically as directed on the web at <http://www.fda.gov/cber/biodev.biodev.htm> or by mail to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448 (21 CFR 1271.350(b)(3)). Each 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 (21 CFR 1271.350(b)(2)).

D. Which Establishment Should Submit the HCT/P Deviation Report?

An establishment must report any HCT/P deviation relating to a core CGTP requirement for distributed HCT/Ps, if the HCT/P deviation occurred in its facility or in a facility that performed a manufacturing step (e.g., the testing laboratory) for it under contract, agreement, or other arrangement. Accordingly, the establishment that contracted for the testing, or that performed the testing in-house on the HCT/P it distributed, must report an HCT/P deviation (21 CFR 1271.350(b)(2)).

V. MITIGATION OF RISK OF HCT/Ps IN INVENTORY

A. What Should I Do after Quarantining HCT/Ps in Inventory?

If test kits cleared or approved by FDA for diagnostic use were utilized for the original donor testing, we recommend that when possible, donors should be retested for the communicable disease agent or disease by using the appropriate FDA-licensed, approved, or cleared donor screening tests following the manufacturer's instructions.

If pooled NAT testing was performed for the original donor testing, we recommend that when possible, donors should be retested utilizing the same NAT test, but using an individual specimen.

Whenever possible, donor specimens used in retesting should be collected within the time frame specified in 21 CFR 1271.80(b) (i.e., up to 7 days before or after recovery for a semen or cord blood stem cell donor, or up to 30 days before recovery for a peripheral blood stem cell or oocyte donor). If these time frames have already elapsed, you should still collect and retest a donor specimen from living donors.

Contains Nonbinding Recommendations

B. Which Donors Should be Retested and May I Distribute These HCT/Ps?

1. Hematopoietic stem cell donors (other than autologous)

- If retesting of the retained donor specimen utilizing a licensed donor screening test is performed in accordance with the manufacturer's instructions and found negative or nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these HCT/Ps. Note that in the case of cord blood stem cells, the donor to be tested is the birth mother.
- If a new specimen is obtained and testing of the donor is performed in accordance with the manufacturer's instructions and found negative or nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these HCT/Ps.
- If retesting of the donor is not feasible (e.g., where a retained specimen is not available and the donor cannot be located or refuses to be retested), FDA intends to exercise enforcement discretion regarding the distribution of these HCT/Ps provided that:
 - The establishment includes in the accompanying records the reason retesting could not be performed and maintains this information in its files;
 - The establishment documents that the recipient's physician was notified of the results of testing and screening, including the labeling provisions described in section IV.C., below; and
 - The HCT/Ps are labeled in accordance with section IV.C., below.

When these inventoried HCT/Ps described above are distributed under this guidance, we intend to exercise enforcement discretion and do not expect you to submit an HCT/P deviation report to FDA.

2. Reproductive HCT/P donors

Sexually intimate partners who donate gametes for use by the intimate couple are not required to have donor eligibility determinations (21 CFR 1271.90(a)(2)). However, directed and anonymous donors of reproductive HCT/Ps are required to be tested (21 CFR 1271.85(c)).

- a. Cryopreserved embryos created for sexually intimate partners using a third party gamete donor
 - If retesting of the retained donor specimen is performed in accordance with the manufacturer's instructions and found to be negative or nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these cryopreserved HCT/Ps.
 - If a new specimen is obtained and testing of the donor is performed in accordance with the manufacturer's instructions and found negative or

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nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these HCT/Ps.

- If retesting of the donor is not feasible (e.g., where a retained specimen is not available and the donor cannot be located or refuses to be retested), FDA intends to exercise enforcement discretion regarding the distribution of these HCT/Ps provided that:
 - The establishment includes in the accompanying records the reason retesting could not be performed and maintains in its files this information;
 - The establishment documents that the recipient's physician was notified of the results of testing and screening, including the labeling provisions described in section IV.C., below; and
 - The HCT/Ps are labeled in accordance with section IV.C., below.

b. Cryopreserved semen or oocytes from anonymous and directed donors

- If retesting of the retained donor specimen is performed in accordance with the manufacturer's instructions and found to be negative or nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these cryopreserved HCT/Ps.
- If a new specimen is obtained and testing of the donor is performed in accordance with the manufacturer's instructions and found negative or nonreactive, FDA intends to exercise enforcement discretion regarding distribution of these HCT/Ps.
- If retesting is not feasible, FDA does not intend to exercise enforcement discretion. These HCT/Ps must not be distributed (21 CFR 1271.45(c) and 1271.50).

When these inventoried HCT/Ps described above, are distributed under this guidance, you do not have to submit an HCT/P deviation report to FDA. Reproductive HCT/P establishments are not currently subject to 21 CFR 1271.350(b) and are not required to submit HCT/P deviation reports.

C. How Should I Label the HCT/P When I Distribute Them Without Retesting?

HCT/Ps from donors that are distributed without retesting should be labeled with the statement: "WARNING: Advise patient of communicable disease risks."

If NAT testing was performed on pooled samples, not individual samples as specified in the manufacturer's instructions, you should list the NAT test and result in the summary of records and add a qualifier that it was "not performed according to the manufacturer's instructions."

Contains Nonbinding Recommendations

If HCT/P donors were tested using tests cleared or approved by FDA for diagnostic use rather than FDA licensed donor screening tests, you should list the diagnostic tests performed and the result in the summary of records, identifying the tests as “diagnostic tests used, instead of donor screening tests.”