Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Draft Guidance for Industry

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 assist you, establishments making donor eligibility determinations, in understanding the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps).[1]

This guidance includes general information on determining eligibility for donors of HCT/Ps. FDA also intends to issue separate guidance documents with recommendations regarding reducing the risk of transmission of specific communicable disease agents and diseases for donors of HCT/Ps as follows: human immunodeficiency virus, hepatitis B virus, hepatitis C virus, *Mycobacterium tuberculosis* (Mtb), sepsis, human transmissible spongiform encephalopathies, cytomegalovirus, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, human T-lymphotropic virus, *Treponema pallidum* (syphilis), vaccinia virus, West Nile virus, and communicable disease risks associated with xenotransplantation.

This guidance applies to human cells and tissues recovered on or after May 25, 2005, the effective date of the regulations contained in 21 CFR part 1271, subpart C (Ref. 1), and updates the August 2007 guidance, "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry." This guidance, along with the associated specific guidances, when finalized, will supersede the following guidance documents:

- "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry," dated August 2007;

[1] 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."

- "Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue-Based Products for Infection with *Treponema pallidum* (Syphilis), Guidance for Industry" dated September 2015;
- "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, Guidance for Industry" dated August 2016; and
- "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), Guidance for Industry" dated September 2016 and corrected May 2017.

Certain specific guidances also incorporate recommendations from the guidance titled "Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human-Derived Clotting Factor Concentrates, Guidance for Industry" dated November 2016.

This draft guidance, when finalized, will provide establishments, in an updated guidance format:

- updates on current recommendations to appropriately screen and test HCT/P donors for evidence of communicable disease risks;
- clarification of recommendations that have been the subject of recurrent inquiries from stakeholders; and
- corrections to outdated references, URLs, physical addresses, and FDA contact information.

When finalized, this guidance, along with the associated specific guidances, will supersede the aforementioned guidances and they will be withdrawn.

In general, FDA's guidance documents 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 purpose of this guidance?

This guidance will assist HCT/P establishments (establishments) in understanding the requirements under 21 CFR part 1271, subpart C, for donor eligibility determinations based on donor screening and testing for communicable disease risks. These requirements apply

to all donors of human cells or tissues used in HCT/Ps,[2] except as provided under 21 CFR 1271.90.

B. What is the scope of this guidance?

This guidance is intended for: (1) establishments responsible for performing any part of donor eligibility screening or testing, or for making donor eligibility determinations; and (2) establishments that determine that an HCT/P meets donor eligibility release criteria and make the HCT/P available for distribution.

Establishment, as defined under 21 CFR 1271.3(b), means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps. This includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of HCT/Ps and includes facilities that engage in contract manufacturing services. An establishment may engage another establishment under a contract, agreement, or other arrangement for screening and testing donors and for determining whether donors are eligible. Such allocations of responsibilities must comply with 21 CFR 1271.150(c).[3]

III. DONOR ELIGIBILITY: GENERAL (21 CFR part 1271, subpart C)

A. What is a donor eligibility determination?

A donor eligibility determination (21 CFR 1271.50) is a conclusion that a donor of cells or tissues to be used in HCT/Ps is either eligible or ineligible based on the results of donor screening (21 CFR 1271.75) and testing (21 CFR 1271.80 and 1271.85). Except in certain situations specified under 21 CFR 1271.60(d), 1271.65(b), and 1271.90, an HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been determined to be eligible (21 CFR 1271.45(c)).

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

- screening shows that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases (RCDADs),[4] and is free from communicable disease risks associated with xenotransplantation; and

[2] The recommendations in this guidance apply to HCT/Ps regulated solely under section 361 of the Public Health Service (PHS) Act (42 USC 264) and the regulations in 21 CFR part 1271, and HCT/Ps regulated as drugs, devices and/or biological products under section 351 of the PHS Act (42 USC 262) and/or the Federal Food, Drug, and Cosmetic Act, and applicable regulations.

[3] See Guidance for Industry, *Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements*, September 2006, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/compliance-21-cfr-part-1271150c1-manufacturing-arrangements.

[4] 21 CFR 1271.3(r).

- test results for relevant communicable disease agents are negative or nonreactive, except as provided in 21 CFR 1271.80(d)(1) for non-treponemal screening tests for syphilis.

If all required donor screening and testing are not performed, or not performed in accordance with the requirements under 21 CFR 1271.75, 1271.80, and 1271.85, then the donor eligibility determination is considered not complete and the donor cannot be determined eligible or ineligible. For example, if all required donor screening and testing are performed but the testing was performed without using appropriate FDA-licensed, cleared, or approved donor screening tests, then the donor eligibility determination is not complete. An HCT/P from a donor for whom donor eligibility has not been completed must not be implanted, transplanted, infused, or transferred, except as provided under 21 CFR 1271.60(d).

B. Who makes the donor eligibility determination?

In accordance with 21 CFR 1271.50(a), a responsible person must determine and document the eligibility of a cell or tissue donor. A responsible person is one who is authorized to perform designated functions for which he or she is trained and qualified (21 CFR 1271.3(t)).

A responsible person should have appropriate medical training and adequate knowledge of relevant Federal regulations and guidances.

C. What are "relevant communicable disease agents or diseases (RCDADs)"?

There are two groups of RCDADs. The first group consists of those communicable disease agents and diseases specifically listed in 21 CFR 1271.3(r)(1). The second group consists of communicable disease agents and diseases described under 21 CFR 1271.3(r)(2) that are not specifically listed in 21 CFR 1271.3(r)(1). These two groups are as follows:

1. RCDADs specifically listed in 21 CFR 1271.3(r)(1). A discussion of these RCDADs as well as additional information is provided in the specific guidance documents for these communicable disease agents and diseases.

   a. The following communicable disease agents and diseases are relevant for all types of HCT/Ps (21 CFR 1271.3(r)(1)(i)):

   - Human immunodeficiency virus (HIV), types 1 and 2;
   - Hepatitis B virus (HBV);
   - Hepatitis C virus (HCV);

- Human transmissible spongiform encephalopathies (TSEs); including Creutzfeldt-Jakob disease (CJD)[5]; and
- *Treponema pallidum* (syphilis).

b. The following cell-associated communicable disease agents or diseases are relevant for viable, leukocyte-rich cells and tissues, including reproductive cells or tissues if they are considered to be viable leukocyte rich (21 CFR 1271.3(r)(1)(ii)):

- Human T-lymphotropic virus (HTLV), types I and II.

c. The following communicable disease agents or diseases of the genitourinary tract are relevant for reproductive cells or tissues (21 CFR 1271.3(r)(1)(iii)):

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhoeae*.

2. A communicable disease agent or disease meeting the criteria described in 21 CFR 1271.3(r)(2), but not specifically listed in 21 CFR 1271.3(r)(1), is relevant if it is one:

a. For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with the HCT/P, such as medical personnel, because the disease agent or disease:

i. is potentially transmissible by an HCT/P; and
ii. either (1) has sufficient incidence and/or prevalence to affect the potential donor population (21 CFR 1271.3(r)(2)(i)(B)(*1*)), or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (21 CFR 1271.3(r)(2)(i)(B)(*2*));

b. That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (21 CFR 1271.3(r)(2)(ii)); and

c. For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available (21 CFR 1271.3(r)(2)(iii)).

In summary, FDA considers: (1) risk of transmission; (2) severity of effect; and (3) availability of appropriate screening measures or tests, in accordance with 21 CFR 1271.3(r)(2), as elements in determining whether a communicable disease agent or disease,

[5] Variant Creutzfeldt-Jakob disease (vCJD) is not specifically listed in 21 CFR 1271.3(r)(1)(i) but is an example of human transmissible spongiform encephalopathy.

not listed under 21 CFR 1271.3(r)(1), is relevant. The importance of these elements in determining relevance may be based on the clinical significance of the disease agent or disease. For example, *Ureaplasma urealyticum*, although highly prevalent and transmissible, is not considered a relevant communicable disease agent because its pathogenicity to reproductive cell and tissue recipients has low clinical significance. However, we require screening for TSEs and testing for HIV-2, although less prevalent, because they pose significant health risks.

D. May communicable disease agents or diseases, not listed in 21 CFR 1271.3(r)(1), be determined to be RCDADs?

Communicable disease agents and diseases, not specifically listed under 21 CFR 1271.3(r)(1), may be determined to be RCDADs under 21 CFR 1271.3(r)(2) based on the risk of transmission, severity of effect, and availability of appropriate screening measures or tests.

E. How will FDA handle other emerging communicable diseases in regard to HCT/P donor eligibility?

We intend to notify you through a guidance, if we determine that a disease meets the definition of an RCDAD under 21 CFR 1271.3(r)(2). The guidance would include our comments or recommendations for donor screening and testing. We also intend to notify you through a guidance, if we conclude that a disease identified as "relevant" under 21 CFR 1271.3(r)(2), no longer meets the criteria as a "relevant" disease for purposes of the donor eligibility regulations. In suitable situations, we will hold public meetings or consult with advisory committees to help us identify communicable disease agents or diseases for which donor testing (under 21 CFR 1271.80 and 1271.85) and/or donor screening (under 21 CFR 1271.75) must be performed.

F. What procedures must I establish and maintain?

You must establish and maintain procedures for all steps that you perform in testing, screening, determining donor eligibility, and complying with all other requirements of 21 CFR part 1271, subpart C (21 CFR 1271.47(a)). Establish and maintain means define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis (21 CFR 1271.3(cc)). A responsible person must review and approve all procedures before their implementation (21 CFR 1271.47(b)). These procedures must be readily available to personnel in the area where the procedures are performed, or if this is not practical, in a nearby area (21 CFR 1271.47(c)).

Under 21 CFR 1271.47(d), you must record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission. Before distributing an HCT/P manufactured under a departure from a procedure, a responsible person must determine that the departure did not increase the risk of communicable disease transmission.

We consider a departure to be an intended change from an established procedure, including a standard operating procedure (SOP), which occurs before the HCT/P is distributed, and is consistent with applicable regulations and standards. For example, a departure might include the use of a different manufacturer's reagents because the usual manufacturer's reagents were not available at the recovery site. In this example, although the use of the different manufacturer's reagent might represent a change from the established procedures, the change might be consistent with applicable regulations, standards, or established specifications. A departure is different from an HCT/P deviation, which under 21 CFR 1271.3(dd) is defined as an event that is inconsistent with applicable regulations, standards, or established specifications, or is unexpected or unforeseeable.

You are authorized under 21 CFR 1271.47(e) to use appropriate standard procedures developed by another organization, provided you have verified that the procedures are consistent with and at least as stringent as the requirements in 21 CFR part 1271. For example, you may use a donor medical history interview questionnaire developed by a professional organization, if you have reviewed the questionnaire and determined that it meets the requirements for donor screening.

G. What records must accompany the HCT/P after the donor eligibility determination has been completed?

Under 21 CFR 1271.55(a), the following records must accompany each HCT/P after the donor eligibility determination has been completed:

- A distinct identification code (such as an alphanumeric code) affixed to the HCT/P container, that relates the HCT/P to the donor and to all records pertaining to the HCT/P and, except in the case of autologous donations, directed reproductive donations, or donations made by first-degree or second-degree blood relatives, does not include an individual's name, social security number, or medical record number;
- A statement whether, based on the results of screening and testing, the donor is determined to be eligible or ineligible; and
- A summary of the records used to make the donor eligibility determination.

Under 21 CFR 1271.55(b), the summary of records described in 21 CFR 1271.55(a)(3) must include:

- A statement that the communicable disease testing was performed by a laboratory or laboratories: (1) certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493; or (2) meeting equivalent requirements, as determined by the Centers for Medicare and Medicaid Services (CMS);
- A listing and interpretation of the results of all tests performed for RCDADs,

and, if applicable, for cytomegalovirus (CMV) (21 CFR 1271.85(b)(2));[6]

- The name and address of the establishment that made the donor eligibility determination; and
- A statement noting the reason for the determination of ineligibility in the case of an HCT/P from a donor who is ineligible based on screening and released under 21 CFR 1271.65(b).

The records referenced in 21 CFR 1271.55 must accompany an HCT/P when it is placed into distribution (as defined in 21 CFR 1271.3(bb)), including distribution that occurs within the same facility (e.g., peripheral blood stem/progenitor cells are collected within a facility's cell processing laboratory and are then sent to a patient's floor in that same facility).

Once the consignee receives the accompanying records with the HCT/P, it is not necessary that those records physically accompany the HCT/P into the operating room or at the bedside (except for any information that is affixed to the HCT/P container). You should make accompanying records available for review by any medical personnel needing access to those records in order to provide patient care. Electronic access to accompanying records within a facility would satisfy the regulatory requirements under 21 CFR 1271.55(a), as long as they are in compliance with 21 CFR 1271.55(c) – deletion of personal information.

Records that must accompany an HCT/P shipped under quarantine are discussed in section III.J. of this document.

H. What records must I retain and for how long?

Under 21 CFR 1271.55(d)(1), you must retain records of: the results and interpretation of all testing for relevant communicable disease agents and screening for communicable diseases; the name and address of the testing laboratory(ies); and, the donor eligibility determination including the name of the responsible person who made the donor eligibility determination and the date of the determination.

Under 21 CFR 1271.55(d)(2), all records must be accurate, indelible, and legible.

Under 21 CFR 1271.55(d)(4), you must retain records pertaining to a particular HCT/P for at least 10 years after the date of its administration. This includes records created by laboratories performing donor eligibility testing (21 CFR 1271.55(d)). If the date of administration is not known, then you must retain records at least 10 years after the date of distribution, disposition, or expiration, whichever is latest (21 CFR 1271.55(d)(4)). Testing laboratories that are not aware of the date of administration, distribution, disposition or expiration, should retain records for at least 10 years after the record was created (i.e., after

[6] If a repeat anonymous semen donor has multiple tests for CMV and during this time he seroconverts (he initially tests CMV negative and subsequently tests CMV positive), then in the summary of records you should indicate the CMV positive result, or you may provide information about all CMV test results.

the testing was performed).

I. What do I do with the HCT/Ps before the donor eligibility determination has been completed?

The donor eligibility determination must be completed, and the donor found to be eligible, prior to use of an HCT/P (21 CFR 1271.45(c)) except as provided in 21 CFR 1271.60(d), 1271.65(b), and 1271.90.[7] Until the donor eligibility determination has been completed, you must keep an HCT/P in quarantine and clearly identify it as in quarantine (21 CFR 1271.60(a) and (b)). The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution (21 CFR 1271.60(b)).

Quarantine means the storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation (21 CFR 1271.3(q)). An example of automated designation for nonreproductive HCT/Ps is the use of a validated computer system to maintain information on bar-code-labeled HCT/Ps held in a freezer. When you release the HCT/P, the computer system is activated to assure identification and retrieval of the specific HCT/P for the intended recipient.

In accordance with 21 CFR 1271.47(a), you must describe in your SOPs the method you choose to store or identify the quarantined HCT/Ps.

J. May I ship an HCT/P that is in quarantine?

Yes, you may ship an HCT/P before completion of the donor eligibility determination (21 CFR 1271.60(c)). However, in accordance with 21 CFR 1271.60(c), during shipment the HCT/P must be kept in quarantine and must be accompanied by records that:

- Identify the donor (e.g., by a distinct identification code affixed to the HCT/P container);
- State that the donor eligibility determination is not complete; and
- State that the HCT/P must not be implanted, transplanted, infused, or transferred until the donor eligibility determination is complete, except in cases of urgent medical need under 21 CFR 1271.60(d) and described in section VII.F. and G. of this document.

[7] For HCT/Ps subject to the Current Good Tissue Practice regulations described in 21 CFR part 1271 subpart D, you must not make available for distribution an HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible, or for whom a donor eligibility determination has not been completed (except as provided under 21 CFR 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission (21 CFR 1271.265(c)(2)). Additional information about Current Good Tissue Practice is described in "Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry" dated December 2011 (Ref. 2).

K. How do I store HCT/Ps from a donor who has been determined to be ineligible?

Under 21 CFR 1271.65(a), if a donor is determined to be ineligible you must store or identify the HCT/Ps from the ineligible donor in a physically separate area clearly identified for such use or follow other procedures that are adequate to prevent improper release, until the HCT/Ps are destroyed or distributed for use in certain limited circumstances identified in 21 CFR 1271.65 (b) and (c) and described above. Examples of ways in which you may comply with this requirement, include employing separate refrigerators or freezers, using separate shelves in a single refrigerator or freezer, and using an automated designation system.

In accordance with 21 CFR 1271.47(a), you must describe in your SOPs the method you choose to store or identify the HCT/Ps from the ineligible donor.

IV. DONOR SCREENING: GENERAL (21 CFR 1271.75)

A. For what diseases or conditions must I screen cell and tissue donors?

Under 21 CFR 1271.75(a), unless an exception identified in 21 CFR 1271.90(a) applies, you must screen cell and tissue donors for: 1) RCDADs; and 2) communicable disease risks associated with xenotransplantation. For donors of viable, leukocyte-rich cells or tissue, you must also screen for HTLV (21 CFR 1275.75(b)) and, for donors of reproductive cells and tissue, you must also screen for additional diseases identified as relevant to those HCT/Ps (21 CFR 1271.75(c)).

See section III.C. of this document for discussion of RCDADs and see the associated specific guidance documents for recommendations for donor screening.

B. How do I screen a donor who is one month of age or younger?

Under 21 CFR 1271.75, you must screen all donors except as provided under 21 CFR 1271.90. For living donors, you must interview the donor if the donor is living and able to participate in the interview. If a donor is not able to participate in the interview, you must interview another individual "able to provide the information sought in the interview" (21 CFR 1271.3(n)(2)).

A birth mother may have a risk factor for an RCDAD that can be transmitted during pregnancy to the infant, including when the birth mother is asymptomatic. Because this may increase the risk of RCDAD transmission to the recipient through use of gestational cells or tissues, you should also screen the birth mother when an infant is one month of age or less.[8] Screening of the birth mother should involve a donor medical history interview

[8] For the purpose of determining donor eligibility, the infant is considered the donor of umbilical cord blood, umbilical cord tissue, amniotic membrane, and other gestational cells and tissues.

and review of available medical records; the physical examination or physical assessment of the birth mother is recommended when practical.

C. What sources of information do I review?

When you screen a potential cell or tissue donor, you must review "relevant medical records" for risk factors for and clinical evidence of the RCDADs listed in 21 CFR 1271.75(a)(1) and communicable disease risks associated with xenotransplantation (21 CFR 1271.75(a)(2)). Additionally, for a donor of viable, leukocyte-rich cells or tissue, you must review "relevant medical records" for clinical evidence of relevant cell-associated communicable disease agents and diseases, including Human T-lymphotropic virus (21 CFR 1271.75(b)). Under 21 CFR 1271.75(c) and as applicable, donors of reproductive cells or tissue must also be screened by reviewing the donor's "relevant medical records" for risk factors for and clinical evidence of infection due to relevant communicable diseases of the genitourinary tract.

Relevant medical records, as defined under 21 CFR 1271.3(s), means a collection of documents that includes: (1) a current donor medical history interview; (2) a current report of the physical assessment of a cadaveric (non-heart-beating) donor or the physical examination of a living donor; and, (3) other available records listed in 21 CFR 1271.3(s)(1) through (4). We describe these three elements as follows:

1. The donor medical history interview (21 CFR 1271.3(n)) is a documented dialogue concerning the donor's medical history and relevant social behavior:

    a. With a living donor; or

    b. If the donor is not living or is unable to participate in the interview, then with one or more individuals who can provide the information sought. These individuals might be:

    - The donor's next of kin;
    - The nearest available relative;
    - A member of the donor's household;
    - An individual with an affinity relationship with the donor (e.g., caretaker, friend, partner); or
    - The donor's primary treating physician.

The donor medical history interview must be current (21 CFR 1271.3(s)). Establishments should consider that some conditions or risks may be related to the current state of the donor or a specified timeframe. For cases where time, related to a risk factor, has elapsed between performing the donor medical history interview and recovery of cells or tissues, establishments should have a procedure in place to determine and document any changes in the donor's medical and behavioral history that occurred after the interview that would make the donor ineligible, including relevant travel, sexual, and social behavior.

Throughout this guidance, the term "sex" refers to vaginal, anal, and/or oral sex, regardless of whether or not a condom or other protection is used.

In accordance with 21 CFR 1271.47, you must establish and maintain SOPs to assure that receipt and review of relevant medical records are properly conducted. In addition, for medical records created for the purpose of assisting in determining donor eligibility, such as records of the donor medical history interview and the report of a physical assessment of a cadaveric (non-heart-beating) donor, you must establish and maintain SOPs to assure that such records are current, complete, and reliable. In addition, SOPs should describe how to handle situations in which the interviewee is uncertain about a response and whether another individual should be sought to assure that records are current, complete, and reliable.

The medical history interview may take place in person, by telephone, or through written or other forms of communication that allow the exchange of information between interviewer and interviewee. The interview method should allow the interviewer to ask follow-up questions to collect necessary information or to clarify responses. For living donors, a face-to-face or phone interview is generally the most effective way to conduct a dialog.[9, 10]

Since a donor medical history interview is a documented dialog (21 CFR 1271.3(n)), if a donor medical history questionnaire is self-administered, the interviewer should review the answers and follow-up with the individual who has filled out the questionnaire form. The follow-up interactive communication allows the interviewer to verify that the interviewee understood the questions, to clarify responses, answer the interviewee's questions, and, if necessary, collect additional information.

If the donor medical history interview is recorded (audio or video), and that recording is later used to complete the record that reflects the results of the interview, then the audio or video recording is considered a record that must be retained in accordance with 21 CFR 1271.55(d) and as described in section III.H. of this document. However, if the establishment creates a written record of the donor medical history interview as it's being conducted and concurrently records (audio or video) the interview itself, then the audio or video recording used for quality assurance purposes is not subject to the record provisions in 21 CFR 1271.55(d) provided that the recording is not used to alter or complete the written record. For example, an establishment conducts a donor medical history interview by telephone. The interviewer asks questions and records the answers in writing as the interviewee responds. The interviewer concurrently generates an audio recording of the interview. The audio recording is used as part of the establishment's quality program and is not reviewed for the purpose of determining donor eligibility. Only the written record

[9] See 69 FR 29786, comment 14.

[10] Interview methods used in the United States for screening blood donors (Refs. 3-5) and for screening organ and tissue donors (Ref. 6) have been evaluated by the American Red Cross and by the National Center for Health Statistics.

that was completed during the interview is used to determine donor eligibility. In this scenario, the audio record would not be subject to the retention requirements in 21 CFR 1271.55(d).

2. The purpose of the physical assessment of a cadaveric (non-heart-beating) donor or the physical examination of a living donor is to assess for physical signs of a relevant communicable disease and for signs suggestive of any risk factor for such a disease. For a cadaveric (non-heart-beating) donor, the physical assessment means "a limited autopsy, or a recent antemortem or postmortem physical examination" (21 CFR 1271.3(o)). For living donors, you may examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. You may rely on records of a recent report of a physical examination by other health care professionals. Because this is a step in determining donor eligibility, you must establish and maintain SOPs for the conduct of the physical assessment or physical examination (21 CFR 1271.47).

The physical examination of a living donor or physical assessment of a cadaveric (non-heart-beating) donor must be current (21 CFR 1271.3(s)). For living donors, if time has elapsed between performing the physical examination of the donor and recovery of cells or tissues, establishments should have a procedure in place to determine and document any changes in the donor medical history that could affect the physical examination.

3. If they are available, the following other records also meet the definition of relevant medical records (21 CFR 1271.3(s)).

- Laboratory test results (other than the results of testing required for the donor eligibility determination);
- Medical records;
- Coroner and autopsy reports; and
- Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease). Examples of these records include medical examiner reports, police records, and information from other tissue or medical establishments, if applicable.

You should make inquiries into these records and other information when the circumstances indicate that follow-up information might be relevant for screening a cell or tissue donor. For example, when reviewing the relevant medical records, including the medical/social history interview, the tissue bank might find information to suggest that the donor might have been incarcerated, pursued by the police, or been under police investigation, or that the cause of death resulted in a police report (e.g., fatal gunshot

wound). If that is the case, the tissue bank should make inquiries to obtain all relevant information regarding the eligibility of the donor, which is available from and disclosable by the police department.

We consider "available" to mean that a record or information exists, or is pending, and can be obtained through due diligence, within a reasonable amount of time. A "reasonable" amount of time is a period of time that would allow for the collection of important information without compromising the utility of the tissue. Examples of these terms are as follows:

> Example 1: A living donor brings his medical records with him to the screening site. These records are available and you would review them.
>
> Example 2: A cadaveric (non-heart-beating) donor dies as a result of an event that leads to the creation of a police report. If the police report was disclosable to you within a reasonable period of time, you would review it.
>
> Example 3: You know that an autopsy report will be prepared on a cadaveric (non-heart-beating) donor, but the report will not be complete for several weeks. If waiting several weeks to review the autopsy report would compromise the utility of the tissue, perhaps because your HCT/P (e.g., cornea) needs to be released within a limited timeframe, then the report could not be obtained in a reasonable time period. Under these circumstances, it might not be necessary to wait to review the final report of autopsy results before distribution of the HCT/P. If this is the case, you should use the available information when considering the donor's eligibility, including the presumed cause of death and other relevant preliminary autopsy findings and all other information obtained about the donor. You should also review the final autopsy report when it becomes available. If any new information in the final report indicates that the donor is ineligible, you should consider notifying the consignees of the distributed HCT/Ps and, if applicable, submit to FDA an HCT/P deviation report[11] within 45 days.

D. When may I perform an abbreviated donor screening procedure?

Section 1271.75(e) states, "If you have performed a complete donor screening procedure on a living donor within the previous 6 months, you may use an abbreviated donor screening procedure on repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior."

If you perform an abbreviated screening:

[11] For additional information, refer to the FDA Guidance for Industry, *Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271*, September 2017, https://www.fda.gov/media/107703/download.

- You do not need to conduct a new physical examination or a new review of relevant medical records.
- You should remind the donor about behaviors that could put him/her at risk of a relevant communicable disease. If any new behavioral risk has been identified in the interval since the last donation, you should also address that new behavioral risk.
- You do not need to present this information in any specific way. Possible methods include the use of a pamphlet or a wall chart, or other effective means of communication.
- You should then ask the donor if there have been any changes in donor history or risk factors since the previous donation.

If you wish to perform an abbreviated donor screening procedure, you must have conducted a complete donor screening procedure on the living donor (including donor history questionnaire, physical examination, and review of any new medical records, if applicable) within 6 months prior to the abbreviated procedure (21 CFR 1271.75(e)).

E. What risk factors or conditions do I look for when screening a donor?

For all donors, unless an exception identified in 21 CFR 1271.90(a) applies, you must review the relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for RCDADs, and communicable disease risks associated with xenotransplantation (21 CFR 1271.75(a)).

Refer to the associated specific guidance documents, when finalized, for recommendations regarding the conditions and behaviors that increase the donor's relevant communicable disease risk.

F. What clinical evidence do I look for when screening a donor?

You must review relevant medical records for clinical evidence of RCDADs (21 CFR 1271.75).

For cadaveric (non-heart beating) donors, you should:

- determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, or
- if an autopsy was performed, whether any special precautions were taken that would suggest there was special concern over the risk of transmission of a communicable disease from the donor.

For certain living donors of HCT/Ps, donor screening may be performed within the few weeks prior to recovery of the HCT/Ps. Establishments performing a donor eligibility determination for such donors may wish to screen the donor again at the time of recovery. This additional screening on the day of recovery is not required for determining donor eligibility, but may be useful for making informed decisions about the use of an HCT/P.

Similarly, establishments performing a donor eligibility determination for donors of cord blood may wish to request post-donation donor health information.

Refer to the associated specific guidance documents, when finalized, for recommendations regarding examples to look for when reviewing relevant medical records for clinical evidence of relevant communicable disease.

G. What physical evidence do I look for when screening a donor?

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric (non-heart-beating) donor (21 CFR 1271.3(o)) or the physical examination of a living donor. The physical assessment or physical examination of the donor should be appropriate to assess for signs of a relevant communicable disease and for signs suggestive of any risk factor for a relevant communicable disease.

Refer to the associated specific guidance documents, when finalized, for recommendations regarding examples of physical evidence of relevant communicable disease or high-risk behavior associated with these diseases.

V. DONOR TESTING: GENERAL (21 CFR 1271.80)

A. For what communicable diseases must I test all donors of HCT/Ps?

As required in 21 CFR 1271.85(a), you must test all donors of HCT/Ps for evidence of infection due to relevant communicable disease agents (including communicable disease agents or diseases that we have determined to be relevant under 21 CFR 1271.3(r)(2)) unless the donor is subject to an exemption in 21 CFR 1271.90(a).

B. What requirements apply to laboratories performing donor testing for relevant communicable disease agents?

1. Under 21 CFR 1271.1, you must be registered with FDA.

2. Under 21 CFR 1271.80(c):

   - You must use appropriate FDA-licensed, approved, or cleared donor screening tests, if such tests are available, in accordance with the manufacturers' instructions.
   - You must use a donor screening test specifically labeled for use with specimens from a cadaveric (non-heart-beating) donor instead of a more generally labeled donor screening test when applicable and when available.
   - You must be certified to perform such testing on human specimens either under the Clinical Laboratory Improvement Amendments (CLIA) or you must meet equivalent requirements as determined by CMS. Examples of the

latter include laboratories that have been accredited by accrediting organizations approved by CMS.[12] Certain states are exempt under CLIA because CMS has found their state programs to be in compliance with CLIA standards.[13]

3. Under 21 CFR 1271.55(d), you must maintain documentation of results and interpretation of all testing for at least 10 years after the date of administration of the HCT/P, "or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest."

C. What type of test must I use?

"You must test using an appropriate FDA-licensed, approved, or cleared donor screening test (if applicable to your HCT/P and available) in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of the RCDAD" (21 CFR 1271.80(c)).

- In the associated specific guidance documents, we list the types of tests that we currently consider to be adequate and appropriate to meet the requirements in 21 CFR 1271.80(c).[14]
- In some instances, you may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. For example, to test for HIV-1, it is appropriate to use a test that detects viral nucleic acid (e.g., a nucleic acid test) and a test that detects antibody to HIV-1 (e.g., an enzyme immunoassay). If HIV-1 infection is present, each test may be reactive at different times during the course of the disease.
- If you are testing a blood specimen collected from a living donor or from a donor while their heart is still beating, a screening test that is FDA-licensed, approved, or cleared for screening donors of blood or blood products is considered appropriate.
- If you are testing a specimen of cadaveric blood (i.e., taken from a non-heart-beating donor), you must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test, when such a test is applicable and available (21 CFR 1271.80(c)). A more generally labeled test includes screening tests that are FDA-licensed, approved, or cleared for screening donors of blood or blood products.

[12] CLIA certified laboratories are surveyed by either CMS or an accrediting organization authorized by CMS to survey laboratories ("deemed status") or they are located in a State approved for exemption under CLIA. CMS issues a certificate of compliance to laboratories surveyed by its inspectors and found to be "in compliance." Laboratories inspected by a CMS deemed status organization (e.g., College of American Pathologists, AABB, Joint Commission) for purposes of CLIA certification are awarded a Certificate of Accreditation by CMS.

[13] Information about the CLIA program, list of exempt states, and accreditation organizations with deemed status are available at the website: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index?redirect=/clia.

[14] The following CBER website includes a list of FDA-licensed, approved, or cleared donor screening tests (including manufacturers and tradenames): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

D. How do I perform the test and interpret test results?

You must perform the test according to the manufacturer's instructions in the test kit's package insert (21 CFR 1271.80(c)). The manufacturer's instructions also provide information about interpretation of test results.

Some HCT/P establishments routinely rely solely on the test results obtained by an organ procurement organization (OPO), while other establishments routinely perform their own donor testing with the awareness that OPOs are performing donor testing on the same donors. The use of an appropriate screening test, performed in accordance with the manufacturer's instructions for use, would satisfy the requirements of 21 CFR 1271.80 and 1271.85. However, because of testing practices related to organ donor screening as described by the Centers for Disease Control and Prevention (CDC), some OPOs may run an enzyme immunoassay donor screening test initially in duplicate or triplicate. The manufacturer's instructions for use of HCT/P donor screening tests currently do not provide instructions for initial duplicate or triplicate testing, interpretation of test results of such testing, or for retesting after an initially reactive test when the tests are initially run in duplicate or triplicate. Therefore, if initial tests are run in duplicate or triplicate and one or more reactive results are obtained, manufacturers do not provide instructions on determining whether the sample is actually (repeatedly) reactive. Accordingly, if you engage an OPO to perform testing for you or if you routinely perform your own tests but are aware that an OPO is also performing tests on that donor, and that OPO performs initial testing in duplicate or triplicate, then under 21 CFR 1271.50 and 1271.150 you must obtain and review the results of all duplicate or triplicate tests performed by that OPO. If any of those initial tests is reactive or positive, then the donor would not be eligible to donate HCT/Ps.

Additional Testing: If you or someone else perform donor testing for relevant communicable diseases using tests in addition to those required, as applicable, or if you are aware that other establishments are performing such tests and the test results are available, such test results must be included in the donor's relevant medical record (21 CFR 1271.3(s)).

Because these test results are part of the medical record, you must consider any results from those tests when you make a donor eligibility determination (21 CFR 1271.75(a)). For example, an eye bank is aware that a tissue bank performs an investigational nucleic acid testing (NAT) assay on a shared donor. The eye bank will not be informed of the test results until after the corneas need to be released in order to maintain their utility. The eye bank does not have to wait for the investigational NAT result before releasing the corneas but they should inform the consignee that the investigational NAT results are pending, and subsequently report the result to the consignee.

Confirmatory tests: You should consider performing confirmatory tests when a positive or reactive screening test result is received for such purposes as donor medical follow-up and counseling or investigating discordant test results. However, if you perform a confirmatory test, negative or nonreactive results on a confirmatory test would not override a positive or

reactive screening test (except for syphilis tests as described in the specific guidance for syphilis). For example, a potential donor's specimen tests reactive for antibody to HCV. However, a confirmatory test (e.g., radioimmunoblot assay) is negative. The donor would be considered ineligible despite the negative confirmatory test.

Hepatitis B surface antibody (anti-HBs) test: If you obtain a positive or reactive anti-HBs test and other markers for Hepatitis B infection are negative or non-reactive, the donor may be eligible. For example, your contract laboratory routinely performs four different tests for HBV: Hepatitis B virus nucleic acid test (HBV NAT), Hepatitis B surface antigen (HBsAg) test, Hepatitis B core antibody (anti-HBc) test, and anti-HBs test. You have a potential donor who is negative or nonreactive for HBV NAT, HBsAg and anti-HBc, but positive or reactive for anti-HBs. The presence of anti-HBs alone would not disqualify the donor, because it may be an indication of vaccination against Hepatitis B. However, in this situation, if the anti-HBc test was also positive or reactive, the donor is ineligible. Data suggests that such results can be associated with infectivity (Refs. 7-13).

E. If a donor is one month of age or younger, from whom must I collect a specimen?

If a donor is one month of age or younger, you must collect and test a specimen from the birth mother instead of the infant donor (21 CFR 1271.80(a)). The specimen for testing from the birth mother must be collected within seven days of recovery of the HCT/Ps (21 CFR 1271.80(b)). If a specimen from the birth mother of a donor one month of age or younger is unavailable, or a specimen was not collected within seven days of recovery, donor testing is not complete, and a donor eligibility determination cannot be made. Specimens collected for any infant donor more than one month of age, including adopted infants, should be collected from the donor rather than the birth mother.

F. When do I collect a specimen for testing?

You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or within 7 days before or after the recovery of cells and tissue (21 CFR 1271.80(b)), with some exceptions as described below. As you are permitted under 21 CFR 1271.80(b) to collect the donor specimen up to seven days before recovery of cells or tissues, you may use a premortem specimen to test a cadaveric (non-heart-beating) donor as long as the specimen is collected within that timeframe.

In the case of recovery (collection) of hematopoietic stem/progenitor cells (HPCs) sourced from peripheral blood or bone marrow (if not excepted under 21 CFR 1271.3(d)(4)), we realize that the recipient may begin myeloablative chemotherapy more than 7 days before the transplant. Therefore, the identified allogeneic donor might need to be qualified before this time, including screening and testing of the donor for relevant communicable diseases. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before recovery of HCT/Ps (21 CFR 1271.80(b)(1)).

In the case of donation of oocytes, because hormonal stimulation generally occurs more than 7 days before recovery of the oocytes, "you may collect the donor specimen used for communicable disease testing up to 30 days before recovery" (21 CFR 1271.80(b)(1)).

Although there is no requirement that specifies when to test the collected specimen, you should perform testing as soon as possible after collection and in accordance with the time limits stated in the manufacturer's instructions for use of each test kit.

G. May I use a specimen for testing from a donor who has undergone transfusion or infusion?

Transfusion or infusion might dilute plasma from a donor blood specimen, making test results unreliable (Refs. 11-13). You may test a specimen taken before the transfusion or infusion and up to seven days before recovery of cells or tissue, or if an adequate pre-transfusion/infusion specimen is not available, you may use an appropriate algorithm to determine whether plasma dilution is or is not sufficient to affect test results. In the absence of an appropriate specimen to test under either of these options, you must determine the donor to be ineligible (21 CFR 1271.80(d)(2)).

For donors over 12 years of age who have suffered blood loss sufficient to require fluid replacement, certain volumes of transfusions and/or infusions (described below) should be suspected of affecting test results. Blood loss might occur internally or externally. For donors 12 years of age or younger, you should suspect that any transfusion or infusion might affect test results regardless of blood loss. There might be other clinical situations involving transfusion or infusion that should also be suspected of affecting test results. Autologous blood removed pre-operatively or peri-operatively and reinfused during the surgical procedure would not need to be included in plasma dilution calculations. However, if a donor's autologous blood has undergone washing through a cell salvage procedure or equivalent, the fluid used for resuspension of the red cells may need to be considered in the evaluation for plasma dilution.

1. Donors over 12 years of age (21 CFR 1271.80(d)(2)(ii)(A))

In accordance with 21 CFR 1271.80(d)(2)(ii)(A), you must suspect plasma dilution sufficient to affect the results of communicable disease agent testing where blood loss is known or suspected in a donor over 12 years of age in any of the following situations:

a. The donor received a transfusion or infusion of more than 2000 milliliters of blood (e.g., whole blood or red blood cells) or colloids either: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen for testing is collected post-mortem, whichever occurred earlier.
b. The donor received more than 2000 milliliters of crystalloids within either: (i) the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if

the specimen for testing is collected post-mortem, whichever occurred earlier.
c. The donor received more than 2000 milliliters of any combination of whole blood, red blood cells, colloids, and/or crystalloids within the applicable time frames set out in paragraphs (a) and (b) in this section.

2. Donors 12 years of age or younger (21 CFR 1271.80(d)(2)(ii)(B))

In accordance with 21 CFR 1271.80(d)(2)(ii)(B), you must suspect plasma dilution sufficient to affect the results of communicable disease agent testing, regardless of the presence or absence of blood loss, in a donor 12 years of age or younger, in any of the following situations.

a. Any transfusion of blood or colloids: (i) within the 48 hours immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the 48 hours immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.
b. Any crystalloids: (i) within the one hour immediately preceding the collection of a pre-mortem specimen for testing; or (ii) within the one hour immediately preceding death, if the specimen is collected post-mortem, whichever occurred earlier.

3. Other Clinical Situations

Your SOPs should identify any additional circumstances where you believe plasma dilution might occur and, in these instances, you should use a pre-transfusion/infusion specimen or apply an algorithm to evaluate whether plasma dilution may have affected the results of communicable disease testing. For example, if the donor has received a transfusion or infusion, but circumstances are not otherwise consistent with the examples set out in section V.G.1. and 2. above, you should consider test results on specimens collected at the time of recovery to be potentially unreliable, triggering the need to test a pre-transfusion or pre-infusion sample, or to apply the algorithm, in the following situations:

- a donor who has previously had blood loss, stabilizes, then expires, but has received fluids in the 48 hours before specimen collection;
- a donor who is obese;
- a donor who in the absence of bleeding may have received large amounts of infusions which the responsible person or designee believes may affect test results;
- the birth mother of a donor who is 1 month of age or younger; and,
- a donor who weighs less than 45 kilograms or more than 100 kilograms.

For situations falling outside those described in your SOPs, but where plasma dilution remains suspect, your SOPs should describe how the situation would be handled (for example, by consulting the responsible person).

4. Pre-Transfusion/Infusion Specimen

As part of establishing procedures for all steps in testing in accordance with 21 CFR 1271.47(a), establishments making donor eligibility determinations must have SOPs that define those elements necessary to determine whether a pre-transfusion/infusion blood specimen is adequate for communicable disease testing (e.g., the amount of hemolysis, storage conditions, and age of the specimen). Testing laboratories must perform tests in accordance with the manufacturer's instructions (21 CFR 1271.80(c)), including any instructions concerning factors that might affect specimen stability.

5. Algorithms

An appropriate algorithm must evaluate the fluid volumes administered in the 48 hours before collecting the specimen from the donor and show that plasma dilution sufficient to affect test results has not occurred (21 CFR 1271.80(d)(2)(i)(B)). A plasma dilution of greater than 50% (1:2 dilution) could make test results unreliable. Therefore, you should use a method that compares the actual fluid volumes administered with both the donor's plasma and blood volumes to assess whether a greater than 50% dilution has occurred.

If the algorithm shows that greater than a 50% dilution has occurred, then you should not use the post-transfusion/infusion specimen for testing. You should not use further procedures that attempt to qualify the ineligible specimen.

When calculating blood and plasma volumes for donors in the 45-to-100-kilogram range, where there is blood loss with replacement, you should calculate and assess both blood volume and plasma volume as follows:

- Determine the blood volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.015, or alternatively by multiplying the body weight in kilograms by 70 mL/kg.

- Determine the plasma volume in milliliters (mL) by dividing the body weight in kilograms (kg) by 0.025, or alternatively by multiplying the body weight in kilograms by 40 mL/kg.

When calculating blood and plasma volumes for a donor of any weight, you may consider using an algorithm based upon body surface area.

See Appendix 1 for additional information.

6. What are some useful definitions related to plasma dilution?

- *Blood component* "means a product containing a part of human blood separated by physical or mechanical means" (21 CFR 1271.3(i)).

- *Colloid* means: "(1) a protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or (2) blood components such as plasma and platelets" (21 CFR 1271.3(j)).
- *Crystalloid* "means an isotonic salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer's lactate solution, 5 percent dextrose in water" (21 CFR 1271.3(k)), or total parenteral nutrition (TPN) (Ref. 17).
- *Plasma dilution* "means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids" (21 CFR 1271.3(p)).

H. Are there additional considerations regarding specimens for donor testing?

Test kit manufacturers' instructions provide specific specimen procedures (i.e., collection, preparation, and storage) that were used in test validation. A donor's medical condition and treatment and/or collection or handling of a donor specimen can affect the reliability of testing and cause false negative test results thereby increasing the risk of donor-related transmission of communicable diseases. Such considerations are applicable to collection of specimens from living donors and cadaveric (non-heart-beating) donors.

In addition to evaluation of plasma dilution described in 21 CFR 1271.80(d)(2), the following factors can affect the donor specimen and the reliability of communicable disease test results: 1) donor medical conditions and treatment; and 2) collection and handling of donor specimens.

1. Donor medical conditions and treatment

Detection of antibodies against viral agents can be impaired if the donor is immunocompromised either due to an immunodeficiency disorder (Refs. 18-22) or if they have received immunosuppressive therapy (Refs. 23-25). These conditions can affect the reliability of test results due to the person's inability to produce an immune response. Therefore, it is important to consider the potential impact on communicable disease testing when a donor has an immunodeficiency disorder or has a recent history of treatment with immunosuppressive agents. Such therapies vary (i.e., type and duration of therapy) and should be evaluated on a case-by-case basis.

The donor's medical condition(s) and treatment(s) should be evaluated when reviewing available relevant medical records (21 CFR 1271.3(s)).

2. Collection and handling of donor specimens

Donor screening tests must be performed in accordance with the manufacturers'

instructions (21 CFR 1271.80(c)). Further considerations include:

- using blood collection tubes or specimen collection kits that are within the date of expiration;
- using the appropriate type of collection tube or collection kit for the test (e.g., for a blood specimen, no anticoagulant or a specific anticoagulant);
- understanding expectations for specimen stability such as storage and transport conditions post-collection, which can be reflected in instructions to refrigerate or freeze specimens, or to centrifuge blood tubes and/or separate plasma from red blood cells within time limits; and
- performing required testing within a specified timeframe post-collection.

A donor blood specimen can be diluted if the specimen is drawn in close proximity to a vascular access device (i.e., an infusion catheter or port). This can occur even though, after reviewing records of infusions and transfusions and applying an algorithm, you do not suspect plasma dilution sufficient to affect the results of communicable disease testing. Whenever possible, blood should be collected from the opposite arm where an IV fluid (including transfused blood products) is, or was recently, administered (Ref. 26).

VI. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (21 CFR 1271.75, 1271.80, AND 1271.85)

A. Do I need to screen and test all donors of reproductive cells and tissue?

Except as provided in 21 CFR 1271.90, you must screen and test all directed reproductive donors (as defined in 21 CFR 1271.3(l)) and anonymous donors of reproductive cells and tissues (21 CFR 1271.75, 1271.80, and 1271.85) (Refs. 27-46).

B. What additional screening must I do for donors of reproductive cells and tissue?

In addition to the screening required for all cell and tissue donors and, if applicable, the screening requirements for viable, leukocyte-rich cell and tissue donors, you must review the relevant medical records of donors of reproductive HCT/Ps (who are not sexually intimate partners) for risk factors for and clinical evidence of infection due to relevant sexually transmitted and genitourinary diseases that can be transmitted with the recovery of the reproductive cells or tissue (21 CFR 1271.75(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhoeae*.

For specific donor screening recommendations, refer to the specific guidance, when

finalized, for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

C. What additional testing must I perform on donors of reproductive cells and tissue?

In addition to the testing required for all cell and tissue donors, and, if applicable, the testing required for donors of viable, leukocyte-rich cells and tissues, you must test donors of reproductive HCT/Ps (who are not sexually intimate partners) for evidence of infection due to relevant genitourinary disease agents (21 CFR 1271.85(c)). These include:

- *Chlamydia trachomatis*; and
- *Neisseria gonorrhoeae*.

D. After the initial donor eligibility determination is performed, and the donor is determined to be eligible, what follow-up testing is required to qualify donations by an anonymous semen donor?

For an initial donation, even though the donor eligibility determination is performed and the donor is determined eligible, you must quarantine that initial donation and any subsequent donations for at least 6 months (21 CFR 1271.60(a)). At least 6 months after the [initial] donation, you must collect a new specimen from the anonymous semen donor and repeat testing required under 21 CFR 1271.85(a) through (c) (21 CFR 1271.85(d)). The results from the requisite retesting serve as the test of record to qualify the donation(s) for release that have been held in quarantine for at least 6 months. Also see section IV.D. of this document for a discussion of when you may use an abbreviated donor screening procedure to screen repeat donors.

Examples:

- *Initial anonymous semen donation:* An anonymous semen donor begins a donation program. Complete donor screening (21 CFR 1271.75) is performed on February 2, 2020; donor specimens for testing[15] (21 CFR 1271.80 and 1271.85) are collected on February 3, 2020. Screening finds no evidence of risk factors for, or clinical evidence of, RCDADs and testing is negative or non-reactive for evidence of infection due to RCDADs. The donor is determined to be eligible on February 5, 2020; however, the initial semen donation, as well as all subsequent semen donations must each be quarantined for at least six months in accordance with 21 CFR 1271.60(a).
- *Subsequent anonymous semen donations during a 6-month period:* The donor continues to donate semen multiple times through August 8, 2020. Prior to each donation, abbreviated donor screening is completed (21 CFR 1271.75(e)), as required. The semen donations must be quarantined until you have results of retesting of the donor performed at least six months after the date of semen

[15] See FDA's webpage on "Testing HCT/P Donors for Relevant Communicable Disease Agents and Diseases", available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

collection (see 21 CFR 1271.60(a)).

- *Retesting the anonymous semen donor at least 6 months after the date of initial donation (21 CFR 1271.85(d)):* New specimens are collected from the donor on August 8, 2020, and are re-tested for evidence of infection due to RCDADs for which testing is required under 21 CFR 1271.85 (a) through (c). The results from all required retesting are negative or non-reactive.[16] These results now serve as the test of record to qualify semen donations collected on or before February 9, 2020. Donations collected on or before February 9, 2020, may now be released from quarantine for distribution.

Complete donor screening, donor testing for RCDADs, and a donor eligibility determination are required every six months for repeat anonymous semen donors who choose to continue donating (see 21 CFR 1271.45, 1271.50, 1271.60, 1271.75, and 1271.85). The 6-month semen quarantine and donor re-testing requirements also apply to these subsequent donations.

If a repeat anonymous semen donor discontinues donations, you should wait at least 6 months from the final donation and re-test the donor for all RCDADs in order to qualify the final donation.

E. Is follow-up testing required for directed donors of semen?

No, we do not require follow-up testing when semen is donated for directed use. Specimens collected for use in donor eligibility testing must be collected within 7 days of each collection (21 CFR 1271.80(b)). You may alternately elect to perform quarantine of semen and retesting of the directed donor as described for anonymous semen donors in section VI.D. of this document (21 CFR 1271.85(d)), rather than performing donor testing within 7 days of each collection.

F. Is a donor eligibility determination required for gestational carriers or surrogate carriers?

No. Gestational or surrogate carriers are considered HCT/P *recipients*. A donor eligibility determination is not required for a recipient of HCT/Ps.

[16] If the results from any of the required retesting are positive or reactive, you must not release any semen donation(s) held in quarantine since the previous negative or non-reactive test results for relevant communicable disease agents. In some instances, the retesting specimens may also serve as the testing to complete a new donor eligibility determination that is required at least every 6 months.

G. Is a donor eligibility determination required for donors of reproductive cells and tissues used to form embryos that will be transferred to a gestational or surrogate carrier?

21 CFR 1271.45(b) states that "in the case of an embryo or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor." In complying with screening and testing requirements when embryos are involved, you should consider the relationship between the gestational carrier and the oocyte and semen donors separately in order to determine which donor eligibility requirements apply.

In the following examples the embryos are intended for transfer to a gestational carrier.

Example 1: A gestational carrier known to a couple will carry embryos formed using oocytes from the female member of the couple and a mixture of semen from the male member of the couple and an anonymous donor. The embryos have not been formed.

- A donor eligibility determination is not required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so both members of the couple are considered directed donors (21 CFR 1271.3(l)).
- A donor eligibility determination must be made for both members of that couple (21 CFR 1271.45(b)), but the use of reproductive cells or tissue from an ineligible directed donor is not prohibited (with proper labeling) (21 CFR 1271.65 (b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (21 CFR 1271.60(a) and 1271.85(d)).
- The other semen donor is not known to the gestational carrier, so that donor is considered an anonymous donor and must have a donor eligibility determination. If the anonymous semen donor is ineligible or the donor eligibility determination is not complete, the semen must not be used because none of the exceptions for use under 21 CFR 1271.60(d), 1271.65(b), or 1271.90 are met.
- Quarantine of the anonymous donor's semen and retesting of the anonymous semen donor is required (21 CFR 1271.60(a) and 1271.85(d)).

Example 2: A gestational carrier known to a couple will carry embryos formed from oocytes donated by a donor who is known to the couple, but not to the gestational carrier, and semen from a member of that couple. The embryos have not been formed.

- A donor eligibility determination is not required for the gestational carrier.
- The couple is known to the recipient (the gestational carrier) so the semen donor in this situation would be a directed donor (21 CFR 1271.3(l)).

- A donor eligibility determination must be made for the directed semen donor each time he donates semen, but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (21 CFR 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (21 CFR 1271.60(a) and 1271.85(d)).
- The oocyte donor is known to the couple but not known to the gestational carrier, so the donor is considered an anonymous donor.
- An anonymous donor must have a donor eligibility determination (21 CFR 1271.45(b)). If the oocyte donor is ineligible, or the donor eligibility determination cannot be made, the oocytes cannot be used because none of the exceptions for use under 21 CFR 1271.60(d), 1271.65(b), or 1271.90 are met.

Example 3: A surrogate is known to a couple. The surrogate's oocytes and semen from a member of the couple will be used to form embryos that will be carried for the couple by the surrogate. The embryos have not been formed.

- A donor eligibility determination is not required for the surrogate because the oocytes are for autologous use (21 CFR 1271.90(a)(1)).
- The couple is known to the surrogate, so the semen donor would be a directed donor (21 CFR 1271.3(l)).
- A donor eligibility determination is required for the semen donor at the time of each donation (21 CFR 1271.45(b)), however, to form embryos, the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (21 CFR 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (21 CFR 1271.60(a) and 1271.85(d)).

Example 4: A gestational carrier is known to the intended parent, but not to the gamete donors. Embryos have not been formed. The establishment did not ask any donor screening questions related to an RCDAD risk exposure for the semen donor. Because the donor eligibility determination was not complete, the establishment subsequently contacted the semen donor and appropriately screened him, relevant to the recovery date of semen, for the RCDAD risk factor that was initially missed. The screening and testing of the semen donor did not identify any other risk factors for RCDADs.

- A donor eligibility determination is not required for the gestational carrier.
- The gamete donors are not known to the gestational carrier, so the donors are considered anonymous donors and must each have a donor eligibility determination. If the gamete donors are determined ineligible or the donor eligibility determination is not completed for each donor, the oocytes and semen donors do not meet any exceptions for use under 21 CFR 1271.60(d), 1271.65(b), or 1271.90.
- Quarantine of the anonymous donor's semen and retesting of the anonymous semen donor is required (21 CFR 1271.60(a) and 1271.85(d)).

- Because the donor screening and testing were completed and the semen donor had no identified risk factors for RCDADs, the semen donor is determined to be eligible.

VII. EXCEPTIONS FROM THE REQUIREMENTS FOR DETERMINING DONOR ELIGIBILITY AND SPECIAL CIRCUMSTANCES (21 CFR 1271.90, 1271.60(d), 1271.65(b), AND 1271.65(c))

The regulations describe (1) situations when you are not required to perform a donor eligibility determination; (2) situations in which the donor eligibility determination is incomplete; and (3) situations in which the use of cells or tissue from a donor who has been determined to be ineligible is not prohibited. These situations require special labels. We define the term "label" when used in this guidance and in 21 CFR 1271.60(d), 1271.65(b), and 1271.90(c), to mean either (1) a printed label affixed to the HCT/P container, or (2) a printed label affixed as a tie-tag to the HCT/P container. However, if it is not physically possible to comply with (1) or (2), either because the container is too small to affix all of these labels to the container, or because the container is frozen, and therefore affixing the labels or attaching a tie-tag is not feasible, then the "Warning" statements in section VII.D. of this guidance may accompany the HCT/P.

A. When is a donor eligibility determination not required? (21 CFR 1271.90)

There are four exceptions to the requirement to make a determination of donor eligibility or to perform donor screening and testing (21 CFR 1271.90(a)):

1. Cells and tissue for autologous use (21 CFR 1271.90(a)(1));

2. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use (21 CFR 1271.90(a)(2));

This exception addresses the situation where the donor is a sexually intimate partner of the recipient. These examples provide scenarios that do and do not qualify for the exception.

Example 1: Sexually intimate partners want to form embryos using the male partner's semen (i.e., the semen donor) and oocytes from an anonymous donor. The resulting embryos will be implanted into the female partner (i.e., the recipient). A donor eligibility determination is not required for the semen donor because he is the sexually intimate partner of the recipient (21 CFR 1271.90(a)(2)). However, a donor eligibility determination must be completed for the anonymous oocyte donor, and the donor found to be eligible, in order for the couple to use oocytes from the anonymous donor..

Example 2: A female has been performing home inseminations using semen provided by a donor with whom she is friends, but they are not sexually intimate

partners. After several attempts at home insemination, the female decides to undergo in vitro fertilization using her oocytes and her friend's semen. A donor eligibility determination would not have to be performed for the female since the oocytes are for autologous use (21 CFR 1271.90(a)(1)). However, a donor eligibility determination must be completed for the semen donor because he is not a sexually intimate partner. Because the semen donor and recipient know each other, the semen donor is a directed reproductive donor (21 CFR 1271.3(l)). See section VII.F. of this document for additional discussion on use of HCT/Ps from an ineligible directed reproductive donor.

3. Cryopreserved cells or tissue for reproductive use, other than embryos, exempt at the time of donation as described in 1 and 2, above, that are subsequently intended for directed donation, provided that:

a. additional donations are unavailable, for example, due to the infertility or health condition of a donor of the cryopreserved reproductive cells or tissue; and
b. appropriate measures are taken to screen and test the donor(s) before transfer to the recipient (21 CFR 1271.90(a)(3)).

This exception addresses the situation where the donor was not screened and tested at the time of cryopreservation of the reproductive cells or tissue, and where the donor cannot make additional donations (e.g., the woman is post-menopausal or has had her ovaries or uterus removed, or because the man has undergone chemotherapy which renders him infertile). The donor wishes to make a directed donation of the cryopreserved semen or oocytes to someone the donor knows. Under these circumstances, you should screen and test the donor before transfer to the recipient. In such cases, as in other cases involving directed donations of reproductive tissue, we would not prohibit the use of an HCT/P from an ineligible directed donor (see section VII.F.2. of this document).

4. A cryopreserved embryo, originally excepted under 21 CFR 1271.90(a)(2) at the time of cryopreservation, that is subsequently intended for directed or anonymous donation. When possible, you should take appropriate measures (see below in this section of this document) to screen and test the semen and oocyte donors before transfer of the embryo to the recipient (21 CFR 1271.90(a)(4)).

This exception addresses the situation where sexually intimate partners were not screened and tested at the time of cryopreservation of their embryos, and later wish to make a directed or anonymous donation of their cryopreserved embryo(s). In such cases, the use of embryos from an ineligible directed donor is not prohibited (see 21 CFR 1271.90(b)). For cryopreserved embryos excepted under 21 CFR 1271.90(a)(4), although FDA requires appropriate screening and testing, when possible, you may still transfer the embryo if appropriate measures (i.e., donor screening and testing) are not possible (e.g., because one of the donors is unavailable). Labeling requirements apply, regardless of whether the semen and

oocyte donors were screened and tested (those labeling requirements are described in section VII.B. in this guidance).

Because one of the gamete donors would already have been found eligible, FDA also intends to apply the exception under 21 CFR 1271.90(a)(4) to a sexually intimate couple's cryopreserved embryos where one of the gametes is from a qualified (i.e., eligible) third party gamete donor, and the other gamete is from the sexually intimate partner of the intended recipient. In this circumstance, you should also screen and test the sexually intimate partner gamete donor when possible, and labeling requirements would apply.

By "appropriate measures", we mean that you screen and test the donor(s) for those communicable disease agents for which a donor of such reproductive cells or tissue would ordinarily be tested at the time of donation, and a donor eligibility determination would be made, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. The reason is that subsequent testing later for *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, which would occur at the time of donation of the reproductive cells or tissue to a recipient, would not provide information about the status of the donor(s) for these agents at the time of the earlier cryopreservation.

If the donor(s) cannot be tested due to death or inability to locate the donor, you should use the most recent available specimen from the donor(s) to perform appropriate testing.

If the donor(s) cannot be interviewed in person due to death or inability to locate the donor(s), then the donor medical history interview may be performed with another individual as described in 21 CFR 1271.3(n), and section IV.C. of this document.

B. What does the 21 CFR 1271.90(b) exception mean for establishments that form or use embryos?

The exception under 21 CFR 1271.90(b) allows the reproductive use of cryopreserved embryos that were formed for specific individuals or couples and subsequently donated for directed or anonymous reproductive use even when the applicable donor eligibility requirements under 21 CFR part 1271, subpart C, were not met. Cryopreserved embryos that were formed and cryopreserved on or after May 25, 2005, can be made available for reproductive use.

21 CFR 1271.90(b) does not create an exception for deficiencies that occurred in making the donor eligibility determination for gamete donors as required under 21 CFR 1271.45(b), or for deficiencies in performing donor screening or testing, as required under 21 CFR 1271.75, 1271.80, and 1271.85. Establishments remain responsible for making the appropriate donor eligibility determination in accordance with 21 CFR part 1271 regulations.

21 CFR 1271.90(c) requires appropriate labeling for embryos that clearly describes the donor screening, testing, and eligibility status of the individual donors whose gametes were used to form the embryo. The labeling is expected to provide specific and accurate information to ensure that recipients and their physicians are fully informed of potential risks of communicable diseases when the donor eligibility requirements under 21 CFR part 1271 subpart C are not met.

C. Will an exemption request be required for embryos, originally intended for reproductive use for a specific individual or couple, when regulatory requirements for donor eligibility were not met?

No. Under 21 CFR 1271.90(b), if an embryo was "originally intended for reproductive use for a specific individual or couple, its subsequent directed or anonymous donation for reproductive use would not be prohibited under (21 CFR 1271.45(c))". For such use, an exemption request is not required to be sent to FDA.

D. What special labeling is required for HCT/Ps that are excepted under the provision of 21 CFR 1271.90(a) from the donor eligibility determination (21 CFR 1271.90(c)(1) through (6))?

If an HCT/P meets any of the exceptions in 21 CFR 1271.90(a), special labeling will be required as described below. More than one of the following label requirements may apply to a particular HCT/P.

For HCT/Ps excepted under 21 CFR 1271.90(a)(1), if the HCT/Ps are stored for autologous use, then under 21 CFR 1271.90(c)(1) you must label the HCT/Ps "FOR AUTOLOGOUS USE ONLY."

For HCT/Ps excepted under 21 CFR 1271.90(a)(1 through 4), if you do not test and screen a donor, then under 21 CFR 1271.90(c)(2) you must label the HCT/Ps from that donor "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" unless you have performed all otherwise applicable screening and testing under 21 CFR 1271.75, 1271.80, and 1271.85. For instance, if you perform some but not all of the testing and screening that would otherwise be required in these sections, or if you do not use a registered, CLIA-certified laboratory, or FDA licensed, cleared, or approved donor screening tests, this label would apply. This label would not apply to reproductive cells and tissue labeled in accordance with 21 CFR 1271.90(c)(6).

> Example 1: You must label an HCT/P from an autologous donor who has not been screened and tested under the exception in 21 CFR 1271.90(a)(1), "FOR AUTOLOGOUS USE ONLY" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."
>
> Example 2: A man wishes to donate semen for later use with a sexually intimate partner. You opt to test the man for HIV-1 and HIV-2 before he donates the semen for use with his sexually intimate partner, but under the 21

CFR 1271.90 (a)(2) exception you are not required to test for any of the relevant communicable diseases for which anonymous or directed sperm donors would be required to be tested. If you do not perform all of the testing as required under 21 CFR 1271.80, and 1271.85, you must label the stored semen "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

For HCT/Ps excepted under 21 CFR 1271.90(a)(2 through 4), (excluding HCT/Ps for autologous use), you must label the HCT/P with "WARNING: Advise recipient of communicable disease risks" when either the donor eligibility determination has not been completed or if screening or testing indicates the presence of relevant communicable disease agents and/or risk factors for or clinical evidence of RCDADs, 21 CFR 1271.90(c)(3).

For any HCT/Ps excepted under 21 CFR 1271.90(a), if donor screening or testing indicates the presence of an RCDAD or diseases and/or risk factors for or clinical evidence of an RCDAD, then under 21 CFR 1271.90(c)(4) you must label the HCT/P with the Biohazard legend shown in 21 CFR 1271.3(h).

If HCT/Ps are recovered under 21 CFR 1271.90(a) from donors who have positive or reactive test results for any relevant communicable disease agent, then under 21 CFR 1271.90(c)(5) you must label the HCT/P with "WARNING: Reactive test results for (name of disease agent or disease)."

If recovered reproductive cells or tissue are subsequently intended for a directed donation under 21 CFR 1271.90(a)(3) or directed or anonymous donation under 21 CFR 1271.90(a)(4), and the screening and testing is performed before transfer to the recipient rather than at the time of recovery, then under 21 CFR 1271.90(c)(6) you must label the HCT/P, "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently." Before transfer, if you have not performed all otherwise applicable screening and testing under 21 CFR 1271.75, 1271.80(a), 1271.80(c)[17], and 1271.85, then 21 CFR 1271.90(c)(2) would apply.

Example 1: HCT/Ps from a sexually intimate couple are used to form embryos. The partners were not required to be screened and tested (21 CFR 1271.90(a)(2)). Some embryos are transferred to the female partner and other embryos are cryopreserved. It is determined that the female partner cannot carry a fetus to term. The couple then decides to transfer the cryopreserved embryos to a gestational carrier who is known to the couple.

- A donor eligibility determination is not required for the gestational carrier.
- These cryopreserved embryos, originally excepted under 21 CFR 1271.90(a)(2), are subsequently intended for directed donation. In accordance with 21 CFR 1271.90(a)(4), appropriate measures should be

[17] Note that 21 CFR 1271.80(b) is excluded because the specimens for subsequent donor testing are not collected within the specified timeframe.

taken, when possible, to screen and test the semen and oocyte donors before transfer of the embryo to the recipient. The couple agrees to be screened and tested now, in accordance with 21 CFR 1271.75, 1271.80, and 1271.85 (see section VII.A. of this document).

- Under 21 CFR 1271.90(c)(6), you must prominently label the HCT/P with the statement: "Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive cells or tissue, but have been performed subsequently."
- The cryopreserved embryos are transferred to the gestational carrier.

If it was not possible to take appropriate measures to screen and test the donors (e.g., because one donor resides outside the United States and is unavailable) the embryos could nevertheless be transferred to the gestational carrier. In that case, the labeling would contain the statements: "Not evaluated for infectious substances" (21 CFR 1271.90(b)(2)) and "Warning: Advise recipient of communicable disease risk" (21 CFR 1271.90(c)(3)).

The records required under 21 CFR 1271.55 (see section III.G. of this document), including the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, based on the results of the screening and testing, and the summary of records are NOT required for HCT/Ps excepted under 21 CFR 1271.90(a). The reason is that 21 CFR 1271.55 applies only after a donor eligibility determination is complete, and this does not occur in the situations in 21 CFR 1271.90. However, you should include this information, if known.

Example 2: Embryos were formed using oocytes and semen from anonymous donors, who were determined eligible in accordance with 21 CFR part 1271 regulations. However, several weeks later the laboratory informed the reproductive establishment that the tests for anti-HCV and total anti-HBc (IgG and IgM) were not performed in accordance with manufacturer's instructions for use and are invalid. Subsequently, the oocyte and semen donors were tested for anti-HCV and total anti-HBc (IgG and IgM) in accordance with the manufacturer's instructions for use. The oocyte donor was found to be positive for anti-HCV, but negative for total anti-HBc (IgG and IgM). The semen donor was found to be negative for anti-HCV and negative for total anti-HBc (IgG and IgM).

- An exemption request is not required for use of these embryos.
- The oocyte donor would be considered ineligible for future donations of the oocytes because of the positive test result for anti-HCV.
- These embryos must be appropriately labeled with "WARNING: Advise recipient of communicable disease risks" (21 CFR 1271.90(c)(3)), biohazard legend shown in 21 CFR 1271.3(h) (21 CFR 1271.90(c)(4)), with "WARNING: Reactive test results for hepatitis C virus" (21 CFR 1271.90(c)(5)).

E. Can cells or tissue from a donor be used before the donor eligibility determination under 21 CFR 1271.50(a) is completed?

Yes. The use of cells or tissues from a donor before the donor eligibility determination is completed, is not prohibited under 21 CFR 1271.60(d) if there is a documented urgent medical need. An urgent medical need means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P (21 CFR 1271.3(u)). However, you must comply with the following requirements under 21 CFR 1271.60(d)(2) through (4).

1. Under 21 CFR 1271.60(d)(2), if an HCT/P is made available based on a physician's request for urgent medical need before completing the donor eligibility determination, you must document the urgent medical need and label the HCT/P prominently: "NOT EVALUATED FOR INFECTIOUS SUBSTANCES," and "WARNING: Advise patient of communicable disease risk."

2. Under 21 CFR 1271.60(d)(2)(i-iii), the HCT/P must be accompanied by a statement of: (a) the results of any required donor screening that has been completed; (b) the results of any required testing that has been completed; and (c) a list of any required screening and testing that has not yet been completed.

   For example, if a risk factor for an RCDAD is identified during donor screening or for any test result, the label could include a Biohazard legend and a list of disease agents or diseases for which a risk has been identified. This labeling is in addition to the labeling required under 21 CFR 1271.60(d)(2).

3. Under 21 CFR 1271.60(d)(3), the manufacturer of the HCT/P must document that the physician using the HCT/P was notified that the testing and screening were not complete.

4. Under 21 CFR 1271.60(d)(4), you must complete the donor eligibility determination during or after the emergency use of the HCT/P and inform the physician of the results of the determination.

5. If the donor eligibility determination under 21 CFR 1271.50(a) *cannot* be completed in accordance with the donor screening and testing requirements, the cells or tissues may be made available under limited circumstances if there is a documented urgent medical need (21 CFR 1271.60(d)). In limited circumstances involving certain lifesaving HCT/Ps (e.g., cryopreserved hematopoietic stem/progenitor cells derived from cord blood), it may not be possible to complete the donor eligibility determination in accordance with the donor screening and testing requirements under 21 CFR 1271.75, 1271.80, and 1271.85. For example, the donor testing may have been performed by a foreign establishment using a donor screening test that is not FDA-licensed, approved, or cleared, and an adequate or acceptable specimen is not available for retesting the donor within the required

specimen collection timeframe. In such limited circumstances, the establishment should have a process for documenting attempts to complete the donor eligibility determination and the outcome of such attempts. The HCT/P must be labeled in accordance with 21 CFR 1271.60(d)(2) and the establishment must notify the physician using the HCT/P that the testing and screening were not complete (21 CFR 1271.60(d)(3)).

F. Can cells or tissue from an ineligible donor ever be used for implantation, transplantation, infusion, or transfer (21 CFR 1271.65(b) and 1271.90(b))?

Yes. Under 21 CFR 1271.65(b), an HCT/P from an ineligible donor, based on required testing and/or screening results, is not prohibited from use for implantation, transplantation, infusion, or transfer in the following three circumstances.

1. The HCT/P is for allogeneic use in a first-degree or second-degree blood relative (21 CFR 1271.65(b)(1)(i)). (Parents, children, and siblings are considered first-degree relatives. Aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren are second-degree relatives. Relations by adoption or marriage are not included);

2. The HCT/P consists of reproductive cells or tissue from a 'directed reproductive donor' (21 CFR 1271.65(b)(1)(ii)). A directed reproductive donor means a donor of reproductive cells or tissue, including semen, oocytes, and embryos, to which the donor contributed the spermatozoa or oocyte, to a specific recipient, and who knows and is known by the recipient before donation. The term does not include a sexually intimate partner (21 CFR 1271.3(l)). The intent is to allow donation of gametes in situations where there is a prior established relationship between donor(s) and recipient.[18] FDA considers it the responsibility of the individual establishment to determine if a relationship between donor(s) and recipient meets the 21 CFR 1271.3(l) definition.

Example: A couple intends to form embryos using the male partner's semen and anonymous oocytes. Because the female partner is unable to carry the pregnancy, the couple decides to use a gestational carrier known to the couple. A complete donor eligibility determination is performed on both gamete donors. The anonymous oocyte donor is determined to be eligible. The semen donor (male partner) is determined to be ineligible because he resided in a country with transmissible spongiform encephalopathy (TSE) risk in the 1980s.

- A complete donor eligibility determination is required for both gamete donors.

[18] See 69 FR 29786, Comment 13 and Response: "We have distinguished between directed reproductive donors and anonymous donors to respect the existence of relationships between people who know each other and have made a joint decision for the recipient to conceive a child."

- The semen donor knows and is known by the recipient (the gestational carrier), so he is considered a directed reproductive donor. However, the oocyte donor is anonymous (i.e., she is not known to the recipient) and therefore is not a directed donor.
- The use of HCT/Ps from this ineligible directed semen donor is not prohibited under 21 CFR 1271.65(b)(1)(ii) with proper labeling (21 CFR 1271.65(b)(2-3)).

3. There is an urgent medical need for the HCT/P based upon a physician's request documented by the establishment.

An HCT/P made available under these provisions from an otherwise ineligible donor must be labeled prominently with the Biohazard legend (21 CFR 1271.3(h)) and with the statement "WARNING: Advise patient of communicable disease risk," and, in the case of reactive or positive test results, "WARNING: Reactive test results for (name of disease agent or disease)" (21 CFR 1271.65(b)(2)). The records required under 21 CFR 1271.55 must accompany the HCT/Ps used under 21 CFR 1271.65(b). The records required under 21 CFR 1271.55 (section III.G. of this document) include the distinct identification code affixed to the HCT/P container, the statement of donor eligibility or ineligibility, and the summary of records. If the donor was determined to be ineligible based on screening, the summary of records must contain a statement noting the reason or reasons for the determination of ineligibility (21 CFR 1271.55(b)(4)).

Moreover, if you are the manufacturer of an HCT/P used in the previously described circumstances, you must document that you notified the physician using the HCT/P of the results of screening and testing (21 CFR 1271.65(b)(3)).

If testing and screening are not required under the regulations, such as when a donor donates reproductive tissue to a sexually intimate partner, then the reproductive tissue may be donated in accordance with that exception, even if you know that the donor is otherwise ineligible. In addition, under 21 CFR 1271.90(b), an embryo, in which one or both gametes were determined ineligible, is excepted from prohibition on use under 21 CFR 1271.45(c) even when the applicable donor eligibility requirements under subpart C are not met. Under this circumstance, the embryo must be appropriately labeled as described in 21 CFR 1271.90(c).

G. Are there any other uses for HCT/Ps from donors determined to be ineligible?

Yes. The use of HCT/Ps from a donor determined to be ineligible, is not prohibited for nonclinical uses, so long as they bear the Biohazard legend and are labeled "For Nonclinical Use Only" (21 CFR 1271.65(c)).

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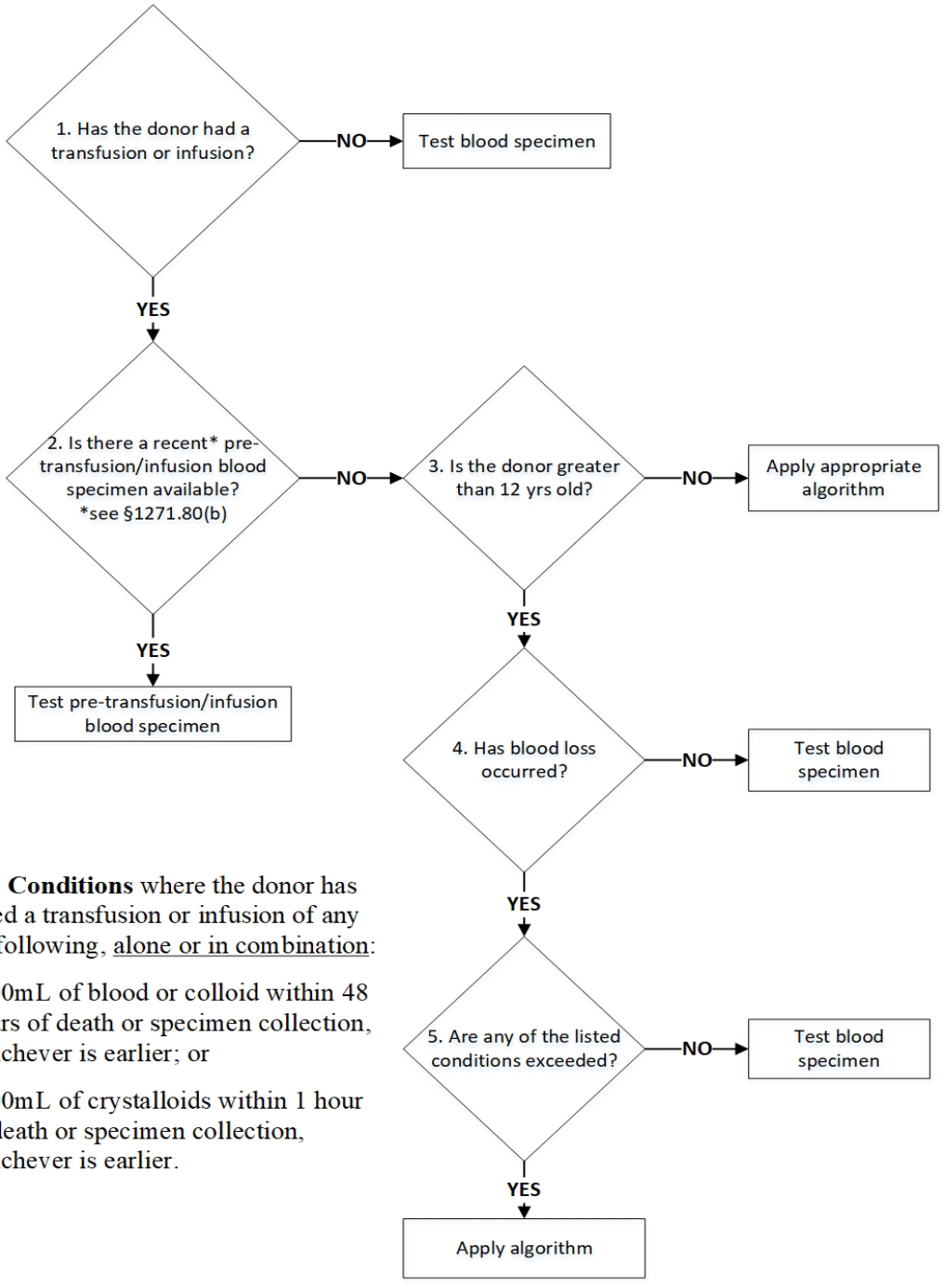
APPENDIX 1: PLASMA DILUTION

EXAMPLE OF A FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR COMMUNICABLE DISEASE TESTING



Step 5. **Conditions** where the donor has received a transfusion or infusion of any of the following, alone or in combination:

- 2000mL of blood or colloid within 48 hours of death or specimen collection, whichever is earlier; or
- 2000mL of crystalloids within 1 hour of death or specimen collection, whichever is earlier.

ACCOMPANYING QUESTIONS FOR FLOW CHART WHEN DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR COMMUNICABLE DISEASE TESTING

Question #1 – Has the donor had a transfusion or infusion?

- If the answer to question # 1 is no, then test the blood specimen
- If the answer to question #1 is yes, then ask question #2

Question #2 – Is there a recent (see 21 CFR 1271.80(b)) pre-transfusion/infusion blood specimen available?

- If the answer to Question #2 is no, then ask Question #3
- If the answer to Question #2 is yes, then test the pre-transfusion/infusion blood specimen that is available

Question #3 – Is the donor greater than 12 years old?

- If the answer to Question #3 is no, then apply an appropriate algorithm
- If the answer to Question #3 is yes, then ask Question #4

Question #4 – Has blood loss occurred?

- If the answer to Question #4 is no, then test the blood specimen
- If the answer to Question #4 is yes, then ask Question #5

Question #5 – Are any of the following conditions exceeded where the donor has received a transfusion or infusion of any of the following?

- 2000 mL of blood or colloid given to the donor within 48 hours before death or specimen collection, whichever occurred earlier;
- 2000 mL of crystalloids within the last hour before death or specimen collection, whichever occurred earlier; or
- 2000 mL total of any combination of blood and colloid within 48 hours, and crystalloid within the past hour, before death or specimen collection, whichever occurred earlier

    * If the answer to Question #5 is no, then test the blood specimen
    * If the answer to Question #5 is yes, then apply algorithm

Contains Nonbinding Recommendations

Draft – Not for Implementation

EXAMPLE OF AN ALGORITHM

DONOR ID # _____

Date and time of specimen collection _____
Donor's weight in kg _____

A = Total volume of blood transfused in the 48 hours before death or specimen collection, whichever comes first

B = Total volume of colloid infused in the 48 hours before death or specimen collection, whichever comes first

C = Total volume of crystalloid infused in the 1 hour before death or specimen collection, whichever comes first

BV = Donor's blood volume

Calculated blood volume = donor's weight (kg) ÷ 0.015 OR
donor's weight (kg) x 70 mL/kg

PV = Donor's plasma volume

Calculated plasma volume = donor's weight (kg) ÷ 0.025 OR
donor's weight (kg) x 40 mL/kg

Calculate <u>both</u>:

1. Is B + C > PV?
2. Is A + B + C > BV?

[Enter a zero if a category (A, B, or C) was not transfused/infused.]

<u>Determination of Donor Specimen Acceptability for Communicable Disease Tests</u>:

If the answers to <u>both</u> 1 and 2 are NO, the post-transfusion/infusion specimen is acceptable.

If the answer to <u>either</u> 1 <u>or</u> 2 is YES, the post-transfusion/infusion specimen is not acceptable; use a recent (see 21 CFR 1271.80(b)) pre-transfusion/infusion specimen or the donor is ineligible.

EXAMPLE OF A PLASMA DILUTION WORKSHEET

Donor ID # _____

Date and time of specimen collection …… _____am/pm

Donor weight in kg ……. _____kg

A. Total volume of blood transfused in the 48 hours before death or specimen collection, whichever comes first

A		RBCs	mL
		Whole blood	mL
	TOTAL		**mL**

B. Total volume of colloid fluids infused in the 48 hours before death or specimen collection, whichever comes first

B		Dextran	mL
		Plasma	mL
		Platelets	mL
		Albumin	mL
		Hetastarch	mL
	Other		mL
	TOTAL		**mL**

C. Total volume of crystalloid fluids infused in the 1 hour before death or specimen collection, whichever comes first

C		Saline	mL
		Dextrose in water	mL
		Ringer's lactate	mL
	Other		mL
	TOTAL		**mL**

Blood Volume (BV) = donor's weight (kg)_____÷ 0.015 ……

OR (BV) = donor's weight (kg)_____x 70 mL/kg…….. _____mL

Plasma Volume (PV) = donor's weight (kg)_____÷ 0.025 ……

OR (PV) = donor's weight (kg)_____x 40 mL/kg…….. _____mL

Determination of Donor Specimen Acceptability for Communicable Disease Testing:
[Calculate both 1. and 2. Enter a zero if a category (A, B, or C) was not transfused/infused]

1. Is B + C > PV? Y N
2. Is A + B + C > BV? Y N

If the answers to both 1 and 2 are NO, the post-transfusion/infusion specimen is acceptable.

□ Specimen is acceptable

OR

If the answer to either 1 or 2 is YES, the post-transfusion/infusion specimen is not acceptable.

□ Specimen is not acceptable; use a recent (see 21 CFR 1271.80(b)) pre-transfusion/infusion specimen, or a different qualified specimen, or the donor eligibility determination cannot be made.