Guidance for Industry

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

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

For questions on the content of this guidance, contact the Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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

I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility determinations, with complying with the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C) (Ref. 1). 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, and cellular and tissue-based products (HCT/Ps).

This guidance applies to cells and tissues procured on or after the effective date of the regulations contained in 21 CFR part 1271, subpart C (effective date May 25, 2005). This guidance replaces the guidance of the same title, dated February 27, 2007. This guidance does not replace the guidance concerning 21 CFR part 1270, entitled "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," (Ref. 2), which remains applicable to tissues recovered before May 25, 2005 and subject to 21 CFR part 1270.

We recognize that some HCT/Ps (e.g., hematopoietic stem cells), as well as Whole Blood and blood components, can be collected by venipuncture from living donors. We encourage you to contact the Center for Biologics Evaluation and Research (CBER) should you have any questions as to the applicable regulatory framework for collection and further processing of such products.

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

II. BACKGROUND

A. What is the purpose of this guidance?

This guidance will assist establishments (HCT/P establishments) in complying with the requirements under 21 CFR part 1271, subpart C, for donor-eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases. These requirements apply to all donors of cells or tissue used in HCT/Ps, except as provided under § 1271.90.

This guidance finalizes the draft guidance, "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated May 2004," (Ref. 3). This guidance also finalizes the draft guidance, "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated June 2002 (Ref. 4).

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 release criteria and make the HCT/P available for distribution.

Establishment, as defined under § 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. 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 § 1271.150(c)[1].

III. THE DONOR-ELIGIBILITY DETERMINATION (§ 1271.50)

A. What is a donor-eligibility determination?

A donor-eligibility determination is a conclusion that a donor is either eligible or ineligible to donate cells or tissues to be used in an HCT/P, based on the results of donor screening (§ 1271.75) and testing (§§ 1271.80 and 1271.85). Except in certain situations

[1] See Food and Drug Administration, Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements, dated September 2006. http://www.fda.gov/cber/guidelines.htm.

specified under §§ 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 (§ 1271.45(c)).

Under § 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, and is free from communicable disease risks associated with xenotransplantation; and
- Test results for relevant communicable disease agents are negative or nonreactive, except as provided in § 1271.80(d)(1) for non-treponemal screening tests for syphilis.

B. Who makes the donor-eligibility determination?

In accordance with § 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 (§ 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 relevant communicable disease agents and diseases. The first group consists of those communicable diseases and disease agents specifically listed in § 1271.3(r)(1). The second group consists of communicable diseases and disease agents described under § 1271.3(r)(2), that are not specifically listed in § 1271.3(r)(1). These two groups are as follows:

1. Relevant communicable disease and disease agents specifically listed in § 1271.3(r)(1).

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

   - Human immunodeficiency virus (HIV), types 1 and 2;
   - Hepatitis B virus (HBV);
   - Hepatitis C virus (HCV);
   - Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD)[2]; and
   - *Treponema pallidum* (syphilis).

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

b. The following cell-associated communicable disease or disease agents are relevant for viable, leukocyte-rich cells and tissues, including reproductive cells or tissues if they are considered to be viable leukocyte rich (see section VI.B.2. of this document) (§ 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 (§ 1271.3(r)(1)(iii)):

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

2. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 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 (§ 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 (§ 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 (§ 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 (§ 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 § 1271.3(r)(2), as factors in determining whether a communicable disease or disease agent, not listed under § 1271.3(r)(1), is relevant. The importance of these factors 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 screening or testing for HIV-2, although less prevalent, because they pose extremely significant health risks.

D. What communicable disease agents or diseases, not listed in § 1271.3(r)(1), have been determined to be relevant?

We have determined the following communicable disease agents and diseases, not specifically listed under § 1271.3(r)(1), to be relevant under § 1271.3(r)(2). This determination was based on the risk of transmission, severity of effect, and availability of appropriate screening measures or tests as described in section III.C. of this document. A brief discussion of these factors is provided under each relevant disease and agent listed. Additional background information is provided in the appendix, as indicated.

West Nile Virus (WNV)

Risk of Transmission: There is a risk of transmission of WNV by HCT/Ps. This is supported by observations of WNV transmission via organ transplantation, and via blood and blood product transfusion. Although it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5). (See Appendix 6).

Severity of Effect: WNV could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for WNV, such as the medical history interview and clinical evidence (see Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral). (Screening measures for WNV are discussed in sections IV.E. and IV.F. of this document.)
A donor screening test for WNV, using NAT technology, has been licensed for use in living and cadaveric HCT/P donors. IND studies are also ongoing for the development of other NAT screening tests for WNV (see section VI.A. and Appendix 6).

Sepsis

Risk of Transmission: There is a risk of transmission by HCT/Ps of any agent that could cause sepsis. The agents that cause sepsis include various bacterial, fungal, and viral agents. These agents have sufficient incidence and/or prevalence to

affect the potential HCT/P donor population and are potentially transmissible. For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock (see Appendix 6).

Severity of Effect: Sepsis could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Mortality from sepsis is substantial, as sepsis is now among the top ten leading causes of death in the United States (see Appendix 6).

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for detection of sepsis, such as the medical history interview, and clinical and physical evidence. (Screening measures for sepsis are discussed in sections IV.E., IV.F. and IV.G. of this document.)

Vaccinia

Risk of Transmission: There is a risk of transmission of vaccinia (the virus used in smallpox vaccine) by HCT/Ps. Vaccinia has sufficient incidence and/or prevalence to affect the potential donor population, especially in light of current small pox vaccination programs. Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, two different investigators reported that vaccinia virus could sometimes be isolated from a patient's blood 3 to10 days after vaccination (Ref. 8). These studies did not use the less virulent New York City Board of Health (NYCBOH) strain of vaccinia virus that comprises currently available vaccines in the United States. Other investigators using the NYCBOH strain of vaccinia virus were only able to detect virus in the blood of patients with disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination (see Appendix 6).

Severity of Effect: Vaccinia virus could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Historically, for every million people vaccinated in the past, up to 52 people have had a life-threatening reaction to smallpox vaccine and up to two people per million vaccinated have died (Refs. 10 and 11).

The potential consequences of vaccinia infection include severe complications (see Appendix 4). These consequences are more likely to occur in HCT/P recipients who are immunocompromised or who have burns or other serious skin conditions. Vaccinia virus infection rarely causes severe complications such as encephalitis and severe generalized vaccinia in otherwise healthy people. Also, the route of infection could influence the severity of the disease, so that it is possible that vaccinia infection transmitted via HCT/Ps could result in different or more severe infections than when acquired percutaneously (Ref. 12).

Availability of Appropriate Screening and/or Testing Measures: There are appropriate screening measures, such as the medical history interview, and clinical and physical evidence (see Ref. 12 for further information regarding the background and rationale for vaccinia deferral). (Screening measures for vaccinia are discussed in sections IV.E., IV.F. and IV.G. of this document.)

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

We intend to notify you through a guidance, if we determine that an infectious disease meets the definition of a relevant communicable disease under § 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 § 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 screening and testing must be performed under §§ 1271.75, 1271.80, and 1271.85.

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 part 1271, subpart C (§ 1271.47(a)). A responsible person must review and approve all procedures before their implementation (§ 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 (§ 1247(c)).

Under § 1271.47(d), at the time a departure occurs, you must record and justify that 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 § 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 §1271.47(e) to use appropriate standard procedures developed by another organization, provided that you have verified that the procedures are consistent with and at least as stringent as the requirements in part 1271. For example, you may use a current donor medical history questionnaire developed by a professional organization, provided that 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 § 1271.55(a) you must provide the following records with 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 1271.55(b), the summary of records in § 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 relevant communicable disease agents or diseases, and, if applicable, for CMV (§ 1271.85(b)(2))[3];

[3] 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 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 § 1271.65(b).

The records referenced in § 1271.55 must accompany an HCT/P when it is placed into distribution (as defined in § 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 § 1271.55(a), as long as they are in compliance with § 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 § 1271.55(d)(1), you must retain records of results and interpretation of all testing for relevant communicable disease agents and screening for communicable diseases, the name and address of the testing laboratory, 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 § 1271.55(d)(2), all records must be accurate, indelible, and legible.

Under § 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 (§§ 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 (§ 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 the testing was performed).

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

Before the completion of the donor-eligibility determination, you must keep an HCT/P in quarantine and clearly identify it as in quarantine (§ 1271.60(a) and (b)). The quarantined HCT/P must be easily distinguishable from HCT/Ps that are available for release and distribution (§ 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 (§ 1271.3(q)). An example of automated designation 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.

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 (§ 1271.60(c)). However, in accordance with § 1271.60(c), 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 § 1271.60(d), and described in section VIII.C. of this document.

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

Under § 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 § 1271.65 (b) and (c), and described in section VIII.D. of this document. 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 § 1271.47(a), you must describe in your standard operating procedures (SOPs) the method you choose to store or identify the HCT/Ps from the ineligible donor.

IV. DONOR SCREENING (§ 1271.75)

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

Under § 1271.75(a), you must screen a cell and tissue donor by reviewing relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases; and communicable disease risks associated with xenotransplantation, unless an exception identified in § 1271.90(a) applies. For donors of viable, leukocyte-rich cells or tissue, you must also screen for HTLV (§ 1275.75(b)). You must also screen donors of reproductive cells and tissue for the additional diseases identified as relevant to those HCT/Ps in § 1271.75(c). (See section III.C. of this document for discussion of relevant communicable disease agents and diseases.)

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

Under § 1271.75, you must screen all donors, including infant donors one month of age or less, except as provided under § 1271.90. Since a donor who is one month of age or younger cannot participate in the donor medical history interview, you must interview another individual able to provide the information sought in the interview (§ 1271.3(n)(2)).

You should also screen the birth mother when an infant is one month of age or less. Donor screening of the birth mother should involve a donor medical history interview 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 relevant communicable diseases listed in § 1271.75(a)(1). Risk factors are described in section IV.E., clinical evidence in section IV.F., and physical evidence in section IV.G.

Relevant medical records, as defined under § 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 donor or the physical examination of a living donor; and (3) other available records listed in § 1271.3(s)(1) through (4). We describe these three elements as follows:

1. The donor medical history interview (§ 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.

In accordance with § 1271.47, you must establish and maintain standard operating procedures 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 donor, you must establish and maintain SOPs to assure that such records are current, complete, and reliable.

The medical history interview may take place in person or by telephone.

Since a donor medical history interview is a documented dialog (§ 1271.3(n)), if a donor medical history questionnaire is self-administered, the interviewer should review and verify the answers with the individual who has filled out the questionnaire form.

2. The purpose of the physical assessment of a cadaveric 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 donor, the physical assessment means a limited autopsy, or a recent antemortem or postmortem physical examination (§ 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 (see section IV.G. of this document for discussion about physical evidence). Because this is a step in determining donor eligibility, you must establish and maintain standard operating procedures (SOPs) for the conduct of the physical assessment or physical examination (§ 1271.47).

3. If they are available, the following other records also meet the definition of relevant medical records (§ 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 potential 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 define "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 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 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. Also, you should 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 submit to FDA an HCT/P deviation report within 45 days, if applicable.

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:

- 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.
- We do not require that this information be presented 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 (§ 1271.75(e)).

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

For all donors, you must review the relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for relevant communicable disease agents and diseases, and communicable disease risks associated with xenotransplantation (§ 1271.75(a)).

Following is a list of conditions and behaviors that increase the donor's relevant communicable disease risk. Except as noted in this section, and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following conditions or behaviors.

1. Men who have had sex with another man in the preceding 5 years (Refs. 17 through 46) (risk factor for HIV and Hepatitis B).

2. Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections (Refs. 18, 21, 22, 25, 27, 29, 33, 34, 36, 38, 42, and 45 through 59) (risk factor HIV, Hepatitis B and Hepatitis C).

3. Persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates in the preceding 5 years (Refs. 18 and 60) (risk factor for HIV, Hepatitis B and Hepatitis C). A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate.

4. Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years (Refs. 18, 21, 22, 24, 25, 27, 29, 33, 34, 38, 40, 44, 45, 46, 61, 62, and 63) (risk factor for HIV, Hepatitis B and Hepatitis C).

5. Persons who have had sex in the preceding 12 months with any person described in criteria 1 through 4 of this section or with any person who has HIV infection, including a positive or reactive test for HIV virus (Refs. 17 and 18), hepatitis B infection (Ref. 64), or clinically active (symptomatic) hepatitis C infection (Refs. 65 and 66).

6. Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV, and/or HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 18 and 64).

7. Children born to mothers with or at risk for HIV infection:

- If 18 months of age or younger, or
- If breast-fed within the preceding 12 months.

Note: We do not recommend deferral of a donor who is a child born to a mother with or at risk for HIV infection if the child is over 18 months of age and has not been breast-fed within the preceding 12 months, provided that the child's HIV antibody tests, physical examination, and medical records do not indicate evidence of HIV infection (Ref. 18).

8. Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months (Refs. 29, 67, and 68) (risk factor for HIV, Hepatitis B and Hepatitis C).

9. Persons who have lived with (resided in the same dwelling) another person who has hepatitis B or clinically active (symptomatic) hepatitis C infection in the preceding 12 months (Ref. 69).

10. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used (Ref. 69).

11. Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday (Refs. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as being caused by hepatitis A virus, Epstein-Barr Virus (EBV), or cytomegalovirus (CMV).

12. Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death. For example, if a statement such as "rule-out sepsis" is noted in the medical records, and subsequent notations indicate a diagnosis other than sepsis, a potential donor might still be eligible.

13. Persons who have had smallpox vaccination (vaccinia virus) in the preceding 8 weeks (Ref. 12) should be evaluated as follows:

a. For persons who had no vaccinia complications (see Appendix 4 for definition of vaccinia complication):

- You should defer the donor until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date, and until the physical examination or physical assessment includes a confirmation that there is no scab at the vaccination site.
- In cases where a scab was removed before separating spontaneously, you should defer the donor for two months after vaccination.

Note: We do not recommend deferral of a cadaveric donor who was vaccinated at least 21 days ago and who has no visible scab, if you are unable to obtain a history of how the scab separated.

b. For persons who have experienced vaccinia complications (see Appendix 4), you should defer the donor until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had vaccinia complications but who currently has no visible signs of vaccinia complications, if you are unable to obtain a history of the exact date of resolution of the vaccinia complications.

14. Persons who acquired a clinically recognizable vaccinia virus infection by contact with someone who received the smallpox vaccine (i.e., touching the vaccination area or the scab, including the covering bandages, or touching clothing, towels, or bedding that might have come into contact with an unbandaged vaccination area or scab) (Ref. 12).

- For living donors who developed skin lesions as a result of contact with someone who received the smallpox vaccine, you should question the donor regarding the loss of the scab, and you should examine the skin. For cadaveric donors, you should examine the skin.
- If no scab is present, we do not recommend deferral of:
    - a cadaveric donor;
    - a living donor if the scab spontaneously separated; or
    - after three months from the date of vaccination of the vaccine recipient, a living donor whose scab was otherwise removed.
- If a scab is present, you should consider:
    - a cadaveric donor to be ineligible; or
    - a living donor to be deferred until the scab spontaneously separates.

You should defer persons who developed other complications of vaccinia infection acquired through contact with a vaccine recipient until 14 days after all vaccinia complications have completely resolved.

Note: We do not recommend deferral of a cadaveric donor who previously had complications of vaccinia acquired through contact with a vaccine recipient, but has no visible signs of vaccine complications, if the date of resolution of the vaccinia complications is unknown.

We do not recommend deferral of contacts who never developed skin lesions or other complications of vaccinia infection.

15. Persons who have had a medical diagnosis or suspicion of WNV infection (based on symptoms and/or laboratory results, or confirmed WNV viremia) you should defer for 120 days following diagnosis or onset of illness, whichever is later (Refs. 5, 6, and 7).

16. Persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days (Refs. 5 and 7).

17. Persons who have been treated for or had syphilis within the preceding 12 months. We do not recommend deferral of donors if evidence is presented that the treatment occurred more than 12 months ago and was successful.

18. Reproductive HCT/P donors who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection in the preceding 12 months. We do not recommend deferral of persons who have been treated for or had *Chlamydia trachomatis* or *Neisseria gonorrhea* infection if evidence is presented that the treatment occurred more than 12 months ago and was successful.

Example: A potential donor has a medical record indicating that she was treated for Chlamydia 14 months ago. No follow-up testing was performed at the time of treatment. The medical record serves as evidence that she received treatment more than 12 months ago. Since the medical record does not include information that a follow-up test was performed after treatment and was negative, there is no evidence that the treatment was successful. However, a current negative test for Chlamydia (as part of the current donor testing) may serve as evidence that the treatment that occurred more than 12 months ago was successful.

19. Persons who have been diagnosed with vCJD or any other form of CJD (Refs. 3 and 75).

Note: Numbers 19 to 26 in this section are designed to screen for TSEs, including CJD and vCJD. If the living donor or the individual knowledgeable about the donor's medical and travel history is not familiar with the term "Creutzfeldt-Jakob Disease" or "variant Creutzfeldt-Jakob Disease," you may try to describe those in layman's terms. If the person being interviewed is still not familiar with those terms, you may consider the lack of familiarity with those terms as a negative response to questions using those terms.

20. Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or other neurological disease of unknown etiology (Refs. 3 and 75). Potential donors who have a diagnosis of delirium (e.g., delirium caused by toxic/metabolic diseases or recent head trauma) would not necessarily be considered to have a diagnosis of dementia and should be evaluated by the Medical Director. (HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident or brain tumor and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director).

21. Persons who are at increased risk for CJD (Refs. 3 and 75). Donors are considered to have an increased risk for CJD if they have received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD (see criterion 22 of this section).

22. Persons who have a history of CJD in a blood relative (Refs. 3 and 75) unless:

- The diagnosis of CJD was subsequently found to be an incorrect diagnosis;
- The CJD was iatrogenic; or
- Laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

23. Persons who spent three months or more cumulatively in the United Kingdom (U.K.) (see Appendix 5) from the beginning of 1980 through the end of 1996 (Refs. 3 and 75).

24. Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996 (Refs. 3 and 75).

25. Persons who spent 5 years or more cumulatively in Europe (see Appendix 5) from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996) (Refs. 3 and 75).

26. Persons who received any transfusion of blood or blood components in the U.K. or France between 1980 and the present (Refs. 3 and 75).

27. Persons or their sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

28. Persons who have received a blood transfusion or any medical treatment that involved blood in the countries listed in criterion 27, after 1977 (Refs. 66 and 76) (risk factor for HIV group O).

Note: Establishments utilizing an HIV-1/2 antibody donor screening test that has been licensed by FDA and is specifically labeled in the Intended Use Section of the package insert as sensitive for detection of HIV group O antibodies may delete items 27 and 28 from their screening procedures. If such establishments continue to ask items 27 and 28, the donor eligibility may be based on the results of the donor screening test regardless of the answers to items 27 and 28. Establishments that do not utilize an HIV antibody donor screening test that has been licensed by FDA for detection of HIV group O antibodies should continue to ask these items.

29. Persons who are xenotransplantation product recipients or intimate contacts of a xenotransplantation product recipient (Ref. 77).

a. For the purpose of this document, we define the following terms:

i. Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (1) live cells, tissues, or organs from a nonhuman animal source; or (2) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

ii. Xenotransplantation products include live cells, tissues, or organs used in xenotransplantation. Biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.

iii. Xenotransplantation product recipient means a person who undergoes xenotransplantation.

iv. Intimate contact of a xenotransplantation product recipient means a person who has engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with a xenotransplantation product recipient. Examples of intimate contacts include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. We do not consider sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, to be intimate contact.

b. To determine whether a potential HCT/P donor is a xenotransplantation product recipient, or is the intimate contact of a person who has received a xenotransplantation product, you should determine whether the potential donor, his/her sexual partner, or any member of his/her household has ever had a transplant or other medical procedure that involved being exposed to live cells, tissues, or organs from an animal. If the potential donor or his/her sexual partner is the recipient of a xenotransplantation product, you should defer the donor. If the potential donor is a member of the xenotransplantation product recipient's household, you should determine whether the potential donor has been exposed to blood, saliva, or other body fluids from the xenotransplantation product recipient. If the potential donor has been exposed to any of these fluids, you should defer the donor.

Note: There are circumstances in which it might not be necessary to defer a potential HCT/P donor who is an intimate contact of a recipient of certain xenotransplantation products. For example, an advisory

committee recommended and we concur that intimate contacts of persons who have received the product Epicel™ do not need to be deferred from blood donation, because the risk of zoonotic transmission from this product is minimal as the non-human animal cells used in the manufacture of this product originate from a well-characterized cell line. For this same reason, intimate contacts of Epicel™ recipients need not be deferred from tissue donation (Ref. 78) (Note: You should defer Epicel™ recipients from tissue donation).

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

You must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (§ 1271.75). For cadaveric 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.

You should look for the following examples of clinical evidence of relevant communicable disease. Except as noted in this section and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following examples of clinical evidence of relevant communicable disease.

1. HIV infection:

    - A prior positive or reactive screening test for HIV;
    - Unexplained weight loss;
    - Unexplained night sweats;
    - Blue or purple spots on or under the skin or mucous membranes typical of Kaposi's sarcoma;
    - Disseminated lymphadenopathy (swollen lymph nodes) for longer than one month;
    - Unexplained temperature of $> 100.5^{o}F$ ($38.06^{o}C$) for more than 10 days;
    - Unexplained persistent cough or shortness of breath;
    - Opportunistic infections;
    - Unexplained persistent diarrhea; and/or
    - Unexplained persistent white spots or unusual blemishes in the mouth (Ref. 79).

2. Hepatitis infection:

- A prior positive or reactive screening test for hepatitis B virus or hepatitis C virus;
- Unexplained jaundice;
- Unexplained hepatomegaly; and/or
- Past diagnosis of clinical, symptomatic viral hepatitis after the 11th birthday (Ref. 70 and 71), unless evidence from the time of illness documents that the hepatitis was identified as caused by hepatitis A virus, EBV, or CMV.

Note: Records of the following laboratory data might assist you in making the donor-eligibility determination in the face of an inconclusive history of hepatitis infection: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or prothrombin time (Ref. 71). If these tests are abnormal, but a cause other than viral hepatitis was established, we do not recommend that you defer the donor.

3. Syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* infection (Screening and donor deferral for *Chlamydia trachomatis* and *Neisseria gonorrhea* required only for reproductive donors):

- Persons who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* in the preceding 12 months (Ref. 79). We do not recommend deferral of donors who have had or have been treated for syphilis, *Chlamydia trachomatis*, or *Neisseria gonorrhea* more than 12 months ago, if evidence is presented that treatment occurred more than 12 months ago and was successful (Ref. 80).

4. Vaccinia infection (see IV. E., 13. and 14. for specific deferral criteria for recent smallpox vaccination or acquired vaccinia infection by contact with someone who received the smallpox vaccine):

- Recent smallpox vaccination;
- Eczema vaccinatum;
- Vesicular rash indicative of generalized vaccinia in a person who has had recent smallpox immunization or who is a contact of someone with recent smallpox immunization, as specified in IV. E. 14.;
- Progressive necrosis in an area of vaccination consistent with vaccinia necrosum;
- Postvaccinial encephalitis; and/or
- Vaccinial keratitis (Ref. 12).

5. WNV infection (Refs. 5, 6, and 7). Because signs and symptoms of WNV can be nonspecific, you should consider the following clinical evidence in light of other information obtained about the donor in making a donor eligibility determination.

- Mild symptoms might include fever, headache, body aches, or eye pain;
  - mild symptoms might also occasionally be accompanied by a skin rash on the trunk of the body; or
  - swollen lymph glands.
- Severe illness;
  - severe illness might include encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis;
  - signs and symptoms of severe illness might include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, and muscle weakness or paralysis.

6. Sepsis (includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) or septic shock):

In reference to deceased donors, if any of these conditions is specifically diagnosed in the medical records during a hospital stay immediately preceding death, you should determine the donor to be ineligible (see section IV.E. criterion 12 of this document). If a living donor appears healthy, the donor usually does not need to be evaluated for sepsis.

Sepsis may be described by the following clinical evidence (Ref. 84). You should consider these signs in light of other information obtained about the donor in making a donor eligibility determination.

- Clinical evidence of infection; and
- Two or more of the following systemic responses to infection if unexplained:
  - Temperature of >100.4º F (38º C);
  - Heart rate >90 beats/min;
  - Respiratory rate >20 breaths/min or PaCO2 <32; or
  - WBC >12,000 cells/mm^3, < 4,000 cells/mm^3, or >10% immature (band) forms.
- More severe signs of sepsis include unexplained hypoxemia, elevated lactate, oliguria, altered mentation, and hypotension.
- Positive (pre-mortem) blood cultures might be associated with the above signs.

7. HTLV infection (Screening and donor deferral for HTLV required only for viable, leukocyte-rich HCT/P donors):

- A prior positive or reactive screening test for HTLV;
- Unexplained paraparesis; and/or
- Adult T-cell leukemia (Refs. 85 and 86).

G. What physical evidence do I look for?

Relevant medical records (§ 1271.3(s)) include the report of the physical assessment of a cadaveric donor (§ 1271.3(o)) or the physical examination of a living donor. 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 professionals. You should review the records of the physical assessment or physical examination for any of the following signs that may indicate high-risk behavior for or infection with a relevant communicable disease. Some of the following are not physical evidence of HIV, hepatitis, syphilis, or vaccinia but rather are indications of high-risk behavior associated with these diseases and would increase the donor's relevant communicable disease risk. Except as noted in this section and in accordance with § 1271.75(d), you should determine to be ineligible any potential donor who exhibits one or more of the following examples of physical evidence of relevant communicable disease or high-risk behavior associated with these diseases (see Refs. 12 and 87).

1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, chancroid (you should consider these signs in light of other information obtained about the donor in making a donor eligibility determination) (seen in HIV, Hepatitis B virus, *Chlamydia trachomatis*, and *Neisseria gornorrheae*).

2. Physical evidence for risk of, or evidence of syphilis.

3. For a male donor, physical evidence of anal intercourse including perianal condyloma (seen in HIV and Hepatitis B).

4. Physical evidence of nonmedical percutaneous drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (seen in HIV, Hepatitis B and Hepatitis C).

5. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 12 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used (seen in HIV, Hepatitis B and Hepatitis C).

6. Disseminated lymphadenopathy (seen in HIV).

7. Unexplained oral thrush (seen in HIV).

8. Blue or purple spots consistent with Kaposi's sarcoma (seen in HIV).

9. Unexplained jaundice, hepatomegaly, or icterus (seen in Hepatitis B and Hepatitis C).

Note: Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed.

10. Physical evidence of sepsis, such as unexplained generalized rash or fever.

11. Large scab consistent with recent history of smallpox immunization.

12. Eczema vaccinatum (seen in vaccinia).

13. Generalized vesicular rash (generalized vaccinia).

14. Severely necrotic lesion consistent with vaccinia necrosum.

15. Corneal scarring consistent with vaccinial keratitis.

V. DONOR TESTING: GENERAL (§ 1271.80)

A. What requirements apply to laboratories performing donor testing for relevant communicable disease agents or diseases?

1. Under § 1271.1, you must be registered with FDA.

2. Under § 1271.80(c):

   - You must use appropriate FDA licensed, approved or cleared donor screening tests, if such tests are available, in accordance with the manufacturer's instructions.
   - You must use a donor screening test specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available.
   - 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 the Centers for Medicare and Medicaid Services. Examples of the latter include laboratories that have been accredited by accrediting organizations approved by CMS. Certain states are exempt under CLIA because CMS

has found their state programs to be in compliance with CLIA standards.[4] Information about the CLIA program is available at the website: http://www.cms.hhs.gov/clia/.

3. Under §§ 1271.55(d), you must maintain documentation of results and interpretation of all testing for at least 10 years.

B. 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 relevant communicable disease agent or disease (§ 1271.80(c)).

- You should choose a test that is adequate, appropriate and available for detecting the relevant communicable disease agent or disease. We list tests that we currently consider to meet the requirements in § 1271.80(c) in section VI. of this document.
- 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 specimen of cadaveric blood (i.e., taken from a donor whose heartbeat has ceased), 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 (§ 1271.80(c)). You can find a list of donor screening tests that have been licensed for use with cadaveric specimens on CBER's website: http://www.fda.gov/cber/tissue/prod.htm. We intend to update the website periodically as additional tests are licensed, cleared or approved for this use and become available.

C. 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 (§ 1271.80(c)). The manufacturer's instructions also provide information about interpretation of test results.

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[4] CMS has approved the following accrediting organizations: AABB, the American Osteopathic Association, the American Society for Histocompatibility and Immunogenics, the College of American Pathologists, COLA, and the Joint Commission on Accreditation of Healthcare Organizations. CMS has determined two states to be exempt: New York and Washington. Since these lists are subject to change, we recommend that you consult CMS for the most current information. http://www.cms.hhs.gov/clia/.

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 §§ 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 triplicate (Ref. 18). The manufacturer's instructions for use of HCT/P donor screening tests currently do not provide instructions for initial triplicate testing, interpretation of test results of such testing, or for retesting after an initially reactive test when the tests are initially run in triplicate. Therefore, if initial tests are run in 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 triplicate, then under §§ 1271.50 and 1271.150 you must obtain and review the results of all three tests performed by that OPO. If any of those initial tests is reactive or positive, then the donor would not be eligible to donate.

D. 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 donor (§ 1271.80(a)). The specimen for testing from the birth mother must be collected within seven days of donation by the infant (§ 1271.80(b)), unless the donation consists of peripheral blood stem/progenitor cells or bone marrow according to 1271.80(b)(1). If a specimen from the birth mother of a donor one month of age or younger is unavailable, the donor is ineligible. 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.

E. 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 seven days before or after the recovery of cells and tissue (§ 1271.80(b)), with some exceptions as described in this section. As you are permitted under § 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 donor, as long as the specimen is collected within that timeframe.

In the case of donation of hematopoietic stem/progenitor cells (HPCs) obtained from peripheral blood or bone marrow (if not excepted under § 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 donation (§ 1271.80(b)(1)).

In the case of donation of oocytes that do not undergo a period of cryopreservation prior to implantation, an oocyte donor might need to be qualified before the 7 days prior to donation due to the time necessary for receiving hormonal stimulation. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (§ 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 the test kit.

F. May I test a specimen from a donor who has undergone transfusion or infusion?

Transfusion or infusion might dilute plasma, making test results unreliable (Refs. 18 and 88). 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 (§ 1271.80(d)(2)).

For adult donors who have suffered blood loss sufficient to require fluid replacement, certain volumes of transfusions and/or infusions (described in section V.F.1. of this document) 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 same surgical procedure would not need to be included in plasma dilution calculations.

1. Adult Donor (§ 1271.80(d)(2)(ii)(A))

   In accordance with § 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. Pediatric Donor (§ 1271.80(d)(2)(ii)(B))

In accordance with § 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 under, 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

We cannot provide guidance that anticipates every possible clinical situation where plasma dilution might affect test results. As the establishment that collects donor specimens for testing, you might be aware of additional circumstances in which plasma dilution might affect test results. Your SOPs should identify any additional circumstances where you believe plasma dilution might have occurred, and you should use a pre-transfusion/infusion specimen or apply an algorithm in those instances.

Examples: In the following situations, the donor has received a transfusion or infusion, but circumstances are not otherwise consistent with the examples set out in sections V.F.1. and 2. of this document. Nevertheless, you should consider test results on specimens collected at the time of donation to be potentially unreliable, triggering the need to test a pre-transfusion or pre-infusion sample, or to apply the algorithm, in the following circumstances:

- 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 medical director or designee believes may affect test results;
- 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 is still suspected, your SOPs should indicate how the situation would be handled (for example, by consulting the medical director).

4. Pre-Transfusion/Infusion Specimen

As part of establishing procedures for all steps in testing in accordance with § 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 infectious 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 (§ 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 (§ 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.

  (See Appendices 1, 2, and 3)

G. What are some useful definitions related to hemodilution?

1. *Blood component* means a product containing a part of human blood separated by physical or mechanical means (§ 1271.3(i)).

2. *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 (§ 1271.3(j)).

3. *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 (§ 1271.3(k)), or total parenteral nutrition (TPN) (Ref. 89).

4. *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 (§ 1271.3(p)).

VI. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85)

A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

You must test all donors of HCT/Ps, unless subject to an exemption in § 1271.90(a), for the diseases listed in section VI.A.1. through 5., as required in § 1271.85(a). You must use an FDA-licensed, approved, or cleared screening test, as described in section V. (§ 1271.80(c)). Current FDA-licensed donor screening tests for HIV, Hepatitis B, Hepatitis C, and HTLV are listed at the website: www.fda.gov/cber/products/testkits.htm. You may also check this website: http://www.fda.gov/cber/tissue/prod.htm for links to HCT/P-related, FDA-licensed, approved or cleared donor screening tests. The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable disease. Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. HIV, type 1 (FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2 (Refs. 79 and 90); and FDA-licensed screening NAT test for HIV-1, or combination NAT); (establishments

not utilizing an FDA-licensed screening test that tests for group O antibodies must evaluate donors for risk associated with HIV group O infection as described in section IV.E.27. and 28. (Refs. 66 and 76))

2. HIV, type 2 (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2) (Refs. 79 and 90);

3. HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) (Ref. 72) and for total antibody to Hepatitis B core antigen (anti-HBc)(IgG and IgM) (Refs. 91 through 98);

4. HCV (FDA-licensed screening test for anti-HCV[5]; and FDA-licensed screening NAT test for HCV, or combination NAT) (Refs. 2, 69, 90, 91, and 99); and

5. *Treponema pallidum* (FDA-cleared screening test for syphilis or FDA-cleared diagnostic serologic test for syphilis[6]) (Refs. 80 and 100).

As an exception for syphilis test results under § 1271.80(d)(1), you may determine to be eligible a donor whose specimen tests positive or reactive on a non-treponemal screening test for syphilis and negative or nonreactive on a specific treponemal confirmatory test (e.g., fluorescent treponemal antibody with absorption test (FTA-ABS), so long as all other required testing and screening are negative or nonreactive. A donor whose specimen tests positive or reactive on either a specific treponemal confirmatory test for syphilis or on a treponemal screening test is not eligible. If a cadaveric specimen is too hemolyzed to interpret the Rapid Plasma Reagin (RPR) test result, you should use another test, such as the FTA-ABS test result.

Discussion of Syphilis Assays

a. Nontreponemal assays, such as the Venereal Disease Research Laboratory (VDRL) test, the RPR test, and the Automated Reagin Test (ART), detect nonspecific antibodies (Reagin) to an antigen called cardiolipin present in host tissues as well as in treponemes. These assays are useful in monitoring the progression of disease and response to therapy. However, positive or reactive tests might be due to diseases other than syphilis (i.e., biological false positives). Samples that give positive or reactive results using nontreponemal assays may be retested using a treponemal-based assay as a confirmatory assay, such as the FTA-ABS. Nontreponemal test results usually become nonreactive within a year or two after successful treatment of syphilis.

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[5] On July 22, 2004, FDA approved the Abbott Laboratories Supplement to their Biological License Application for Hepatitis C Virus Encoded Antigen to modify the intended use of the Abbott HCV EIA 2.0 to include the testing of cadaveric specimens. This specifically labeled test kit is now available for commercial use.

[6] For purposes of this guidance, we consider FDA-cleared diagnostic serological tests to be adequate for use in donor screening for syphilis.

b. Treponemal assays incorporate specific treponemal antigens into the testing system and detect specific antibodies to these antigens. With a few exceptions, unlike nontreponemal assays, results of tests for treponemal antigens remain positive or reactive for specific antibodies throughout an individual's life, even after successful treatment for syphilis. Treponemal assays include the FTA-ABS, the *Treponema pallidum* immobilization test (TPI) and the *T. pallidum* hemagglutination assay (TPHA). Since both types of assays detect antibodies, they might not identify some very early syphilis infections before antibodies to either cardiolipin or specific treponemal antigens have appeared (Ref. 100).

c. Serological tests for syphilis may be either non-treponemal or treponemal-based assays. Because of the potential for false-positive results in non-treponemal assays, § 1271.80(d)(1) provides that a specific treponemal confirmatory test, such as FTA-ABS, may be used to determine the syphilis status of an HCT/P donor when a positive result on a non-treponemal assay is obtained. If the confirmatory test is positive or reactive, the donor is ineligible.

6. p24 Antigen Tests: We are aware that HIV-1 p24 antigen tests are not readily available because they are not currently being manufactured. Therefore, you are not required to use the HIV-1 p24 antigen test for HCT/P donors. There are currently more sensitive tests available (Refs. 90 and 101).

Discussion About Additional Testing

You or someone else might perform additional testing not listed in section VI.A. If you perform donor testing for relevant communicable diseases using tests in addition to those listed in section VI.A.1. through 5., VI.B., and VI.C., 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 (see § 1271.3). 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 (§ 1271.75(a)). By "available" we mean that the test result exists or is obtainable within a reasonable amount of time. A "reasonable" amount of time is a period of time that would not compromise the utility of the tissue.

Example: An eye bank is aware that a tissue bank performs an investigational NAT assay on a shared donor. The eye bank is not 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 results before releasing the corneas. The eye bank should inform the consignee that the investigational NAT results are pending, and subsequently report the result.

Confirmatory tests: You should consider performing confirmatory tests when a positive or reactive screening test result is received for such purposes as donor 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 previously described in this section).

> 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.

> Example: Your contract laboratory routinely performs three different tests for HBV: 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 HBsAg and anti-HBc, but positive or reactive for anti-HBs. The presence of anti-HBs alone would not disqualify the donor, because it usually is an indication of vaccination against Hepatitis B. However, in this situation, if the anti-HBc were also positive or reactive, the donor is ineligible. Data suggests that such results can be associated with infectivity (Refs. 92 through 98).

B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use?

1. You must test donors of viable, leukocyte-rich cells or tissue for the following diseases, in addition to those listed in section VI.A. of this document (§ 1271.85(b)). You must use an FDA-licensed, cleared, or approved donor screening test where such a test is available (§ 1271.80(c)). A list of currently licensed donor screening tests for HCT/Ps can be found at the website: http://www.fda.gov/cber/tissue/prod.htm.

The tests listed in this section adequately and appropriately reduce the risk of transmission of relevant communicable diseases:

a. Human T-lymphotropic virus, types I and II (FDA-licensed screening test for anti-HTLV I/II) (Refs. 85 and 86).

b. Cytomegalovirus (FDA-cleared screening test for anti-CMV) (total IgG and IgM).

Special note on CMV: CMV is not a relevant communicable disease agent or disease. However, establishments are required to test donors of viable, leukocyte-rich cells or tissues for CMV. A donor who tests positive or reactive for CMV (total antibody) is not necessarily ineligible to donate HCT/Ps. You must

establish and maintain an SOP regarding donors whose specimens test positive or reactive for CMV (§ 1271.85(b)(2)). This latter requirement only applies to establishments that make available for distribution HCT/Ps for which CMV testing is required.

Establishments should include procedures in their SOPs for communicating test results of donors who are positive or reactive for CMV antibody (total). The SOP should at least specify how the CMV test results should be communicated to the physician responsible for accepting the HCT/P. For example, the SOP should require that this information appear in materials accompanying the HCT/P, so that physicians may rely on this information to make informed decisions about the use of an HCT/P in a particular recipient's situation. An establishment's SOPs may also clarify that repeated testing of donors who are positive or reactive for CMV antibody (total) is unnecessary once it is established that a particular donor is positive or reactive, so long as this information is contained in the summary of records.

2. Examples of viable, leukocyte-rich cells or tissue include, but are not limited to:

- Hematopoietic stem/progenitor cells
- Semen

You should consider cells and tissues to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing might remove leukocytes.

3. Examples of cells or tissue that are not considered viable, leukocyte-rich cells or tissues include, but are not limited to:

- Corneas
- Sclera
- Skin
- Heart valves
- Dura mater
- Bone
- Tendons
- Ligaments
- Cartilage
- Oocytes

Under § 1271.45(b), in the case of embryos or cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor. Therefore, although an embryo might not be considered leukocyte-rich, when an embryo is transferred to an individual who is not a sexually intimate partner, the semen donor should be tested for HTLV types I and II and for CMV.

C. How do I assess a donor of dura mater for TSE?

You must perform an adequate assessment for donors of dura mater to detect evidence of TSE (§ 1271.85(e)). After the dura mater has been removed, you should have a qualified pathologist perform an examination of the donor's brain. Following fresh examination, the brain should be fixed and sliced, gross examination of the entire brain should be conducted (including multiple cross sections), and multiple specimens of tissue should be obtained (from different parts of the brain) for histological examination. Exclude potential donors when any possible evidence of TSE-related changes is observed on histological examination. There are currently no FDA-licensed, approved, or cleared donor screening tests for prions.

VII. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 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 § 1271.90, you must screen and test all directed reproductive donors (as defined in § 1271.3(l)) and anonymous donors of reproductive cells and tissues (§§ 1271.75, 1271.80, and 1271.85) (Refs. 102 through 138).

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 (§ 1271.75(c)). These include:

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

Specific donor screening recommendations are described in section IV. of this document.

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 (§ 1271.85(c)). These include:

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

Special note on *Chlamydia trachomatis* and *Neisseria gonorrhea* testing: Although there are diagnostic tests available, there are currently no FDA-licensed, approved, or cleared tests for donor screening. In the absence of such screening tests, you must use an FDA-licensed, approved, or cleared diagnostic test labeled for the detection of these organisms in an asymptomatic, low-prevalence population (§ 1271.80(c)). FDA recommends *Chlamydia trachomatis* and *Neisseria gonorrhea* test kits utilizing NAT technology to adequately and appropriately reduce the risk of infectious disease transmission (Refs. 81, 139 through 148). You can find a listing of FDA-licensed or approved test kits for *Chlamydia trachomatis* and *Neisseria gonorrhea* at the following website: http://www.fda.gov/cber/tissue/prod.htm.

Exception from testing requirement:

If the reproductive cells or tissue are recovered by a method that ensures freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract, then tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* are not required (§ 1271.85(c)). However, if these tests are performed and one or both results are reactive, the donor must be determined ineligible, regardless of the recovery method used (§ 1271.80(d)(1)).

D. What follow-up testing is required for anonymous semen donors?

At least 6 months after the donation, you must collect a new specimen from the anonymous semen donor and repeat testing required under § 1271.85(a) through (c) (§ 1271.85(d)). You must quarantine the donated semen until the retesting is complete and the donor is determined to be eligible (§ 1271.60(a)). See IV. D. for a discussion of screening of repeat donors.

Note: 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, except that you may use the results of tests for *Chlamydia trachomatis* and *Neisseria gonorrhea* obtained at the final donation, or any time later than that, as the test of record to qualify that final donation.

Example: A donor tests negative or nonreactive for HBsAg and Hepatitis B core antibody. He is retested 6 months later, and is still negative or nonreactive for HBsAg, but is positive or reactive for Hepatitis B core antibody. The donor is ineligible. The semen in quarantine should not be transferred to an anonymous recipient.

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 (§ 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 VII.D. of this document (§ 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 not considered to be donors according to the FDA definition of a donor (§ 1271.3(m)). Gestational or surrogate carriers are considered to be HCT/P recipients.

G. Is a donor eligibility determination required for donors of reproductive cells and tissues that are transferred to gestational or surrogate carriers?

Section 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.

The following examples assume that when the embryos were formed, they were intended for transfer to a gestational carrier.

Example: A gestational carrier known to a couple will carry an embryo formed from the woman's oocyte and a mixture of semen from the man and an anonymous donor. The embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is 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 (§ 1271.3(l)).
- A donor eligibility determination must be made for both members of that couple (§ 1271.45(b)), but the use of reproductive cells or tissue from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65 (b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 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 (§ 1271.3(l)). If the semen donor is ineligible, the semen may not be used (§ 1271.45(b)).
- Quarantine of the anonymous donor's semen and retesting of the anonymous semen donor is required (§§ 1271.60(a) and 1271.85(d)).

Example: A gestational carrier known to a couple will carry an embryo formed from an oocyte 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 embryo(s) were formed to be carried for the couple by the gestational carrier.

- No donor eligibility determination is 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 (§ 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) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 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 (§ 1271.3(l)).
- The oocyte donor must have a donor eligibility determination (§ 1271.45(b)). If the oocyte donor is ineligible, the oocytes may not be used (§ 1271.45(c)).

Example: A surrogate carrier is known to a couple. The surrogate's oocyte(s) and semen from a member of that couple will be used to form embryo(s) that will be carried for the couple by the surrogate.

- No donor eligibility determination is required for the surrogate.
- The couple is known to the surrogate, so the semen donor would be a directed donor (§ 1271.3(l)).
- A donor eligibility determination is required for the semen donor each time he donates semen (§ 1271.45(b)), but the use of semen from an ineligible directed donor is not prohibited (with proper labeling) (§ 1271.65(b)).
- Neither quarantine of the directed donor's semen nor retesting of the directed donor is required (§§ 1271.60(a) and 1271.85(d)).

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

This section describes: (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 §§ 1271.60(d), 1271.65(b), and 1271.90(b), 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 sections VIII.B.3., 5., and 6. of this document may accompany the HCT/P.

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

There are five situations in which you are not required to make a determination of donor eligibility or to perform donor screening and testing (§ 1271.90(a) and § 1271.15(a)). You must apply special label requirements if you do not screen and test (§ 1271.90(b)).

Donor eligibility determinations are not required (§ 1271.90(a) (1) through (4)) for:

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

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

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 of suitable cells and tissues are unavailable due to the infertility or health condition of a donor of the cryopreserved reproductive cells or tissue; and

   b. appropriate measures (see note after section VIII.A.4. of this document) are taken to screen and test the donor(s) before transfer to the recipient (§ 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 at least six months after recovery of the cryopreserved HCT/Ps and before the donation is made. 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 (section VIII.D.2. of this document).

4. A cryopreserved embryo, originally excepted under § 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 note after section VIII.A.4. of this document) to screen and test the semen and oocyte donors before transfer of the embryo to the recipient (§ 1271.90(a)(4)).

This exception addresses the situation where sexually intimate partners were not screened and tested at the time of cyropreservation of their embryos, and later wish to make a directed or anonymous donation of their cryopreserved embryo(s). Under these circumstances, you should cryopreserve the embryos for at least 6 months and when the decision is made to donate the embryo(s) to an individual or a gestational carrier, you should screen and test the semen and oocyte donors when possible. In such cases, as in other cases involving directed donations of reproductive tissue (section VIII.D.2. of this document), the use of embryos from an ineligible directed donor is not prohibited. In addition, although FDA requires appropriate screening and testing when possible, if appropriate screening and testing are not possible (e.g., because one of the donors is unavailable), you may still transfer the embryo into a recipient. Labeling requirements apply, regardless of whether the semen and oocyte donors were screened and tested (those labeling requirements are described in section VIII.B. of this document).

Because one of the gamete donors would already have been found eligible, FDA also intends to apply this policy 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.

Note: 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 be made, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea*. The reason is that testing for *Chlamydia trachomatis* or *Neisseria gonorrhea* at the time of donation of the reproductive cells or tissue would not provide information about the status of the donor(s) for these agents at the time of the earlier cryopreservation.

To meet the donor testing requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., 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 the appropriate testing.

To meet the donor screening requirements described in section VIII.A.3. or recommendations described in section VIII.A.4., 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 § 1271.3(n), and section IV.C. of this document.

5. In accordance with § 1271.15(a), you are not required to make a determination of donor eligibility or to perform donor screening and testing if you are an establishment that uses HCT/Ps solely for nonclinical scientific or educational purposes (see section VIII.E. for those labeling requirements). The § 1271.90 labeling requirements do not apply.

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

Note: More than one of the following label requirements may apply to a particular HCT/P.

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

2. For HCT/Ps excepted under § 1271.90(a)(1 through 4), if you do not test and screen a donor, then under § 1271.90(b)(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 §§ 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 § 1271.90(b)(6).

Example 1: You must label an HCT/P from an autologous donor who has not been screened and tested under the exception in § 1271.90(a)(1), "FOR AUTOLOGOUS USE ONLY" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

Example 2: A man wishes to donate his stored semen to his sexually intimate partner. You test the man for HIV-1 and HIV-2 before he donates the semen to his sexually intimate partner, but under the § 1271.90 (a)(2) exception you are not required to test for any of the other relevant communicable diseases for which anonymous or directed sperm donors would be required to be tested. If you do not perform all of the additional testing, you must label the stored semen "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

3. For HCT/Ps excepted under § 1271.90(a)(2 through 4), (excluding HCT/Ps for autologous use), you must under § 1271.90(b)(3) 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 relevant communicable disease agents or diseases.

4. For HCT/Ps excepted under § 1271.90(a), if donor screening or testing indicates the presence of relevant communicable disease agents or diseases and/or risk factors for or clinical evidence of relevant communicable disease agents or diseases, then under 1271.90(b)(4) you must label the HCT/P with the Biohazard legend shown in § 1271.3(h).

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

6. If reproductive tissue will be donated to a directed recipient under § 1271.90(a)(3) or a directed or anonymous recipient under § 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 § 1271.90(b)(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 §§ 1271.75, 1271.80, and 1271.85, then § 1271.90(b)(2) would apply.

Example: HCT/Ps from a sexually intimate couple are used to form embryos. The partners were not required to be screened and tested (§ 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.

- No donor eligibility determination is required for the gestational carrier.
- The couple agrees to be screened and tested now, in accordance with §§ 1271.75, 1271.80, and 1271.85, except that the donor(s) do not have to be tested for *Chlamydia trachomatis* or *Neisseria gonorrhea* (See note in section VIII. A. of this document). They are both determined to be eligible.
- Under § 1271.90(b)(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.

- Note that 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" (§ 1271.90(b)(2)) and "Warning: Advise recipient of communicable disease risk" (§ 1271.90(b)(3)).

The records required under section § 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 § 1271.90(a). The reason is that § 1271.55 applies only after a donor eligibility determination is complete, and this does not occur in the situations in § 1271.90. However, you should include this information, if known.

C. Can cells or tissue from a donor be used before the donor eligibility determination under § 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 § 1271.60(d) if there is a documented urgent medical need. However, you must comply with the following requirements under § 1271.60(d)(2) through (4).

1. 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. 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.

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. 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.

D. Can cells or tissue from an ineligible donor ever be used for implantation, transplantation, infusion, or transfer? (§ 1271.65(b))

Yes. Under § 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, or transfer in the following three circumstances.

1. The HCT/P is for allogeneic use in a first-degree or second-degree blood relative. (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. (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 (§ 1271.3(l)); or

3. There is an urgent medical need for the HCT/P based upon a physician's request documented by the establishment. (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 (§ 1271.3(u)).

An HCT/P made available under these provisions from an otherwise ineligible donor must be labeled prominently with the Biohazard legend (§ 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)" (§ 1271.65(b)(2)). The records required under § 1271.55 must accompany the HCT/Ps used under § 1271.65(b). The records required under § 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 (§ 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 (§ 1271.65(b)(3)).

Note: 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.

E. 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" (§ 1271.65(c)).

IX. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than 6 months after the original issuance date of this guidance (February 27, 2007).

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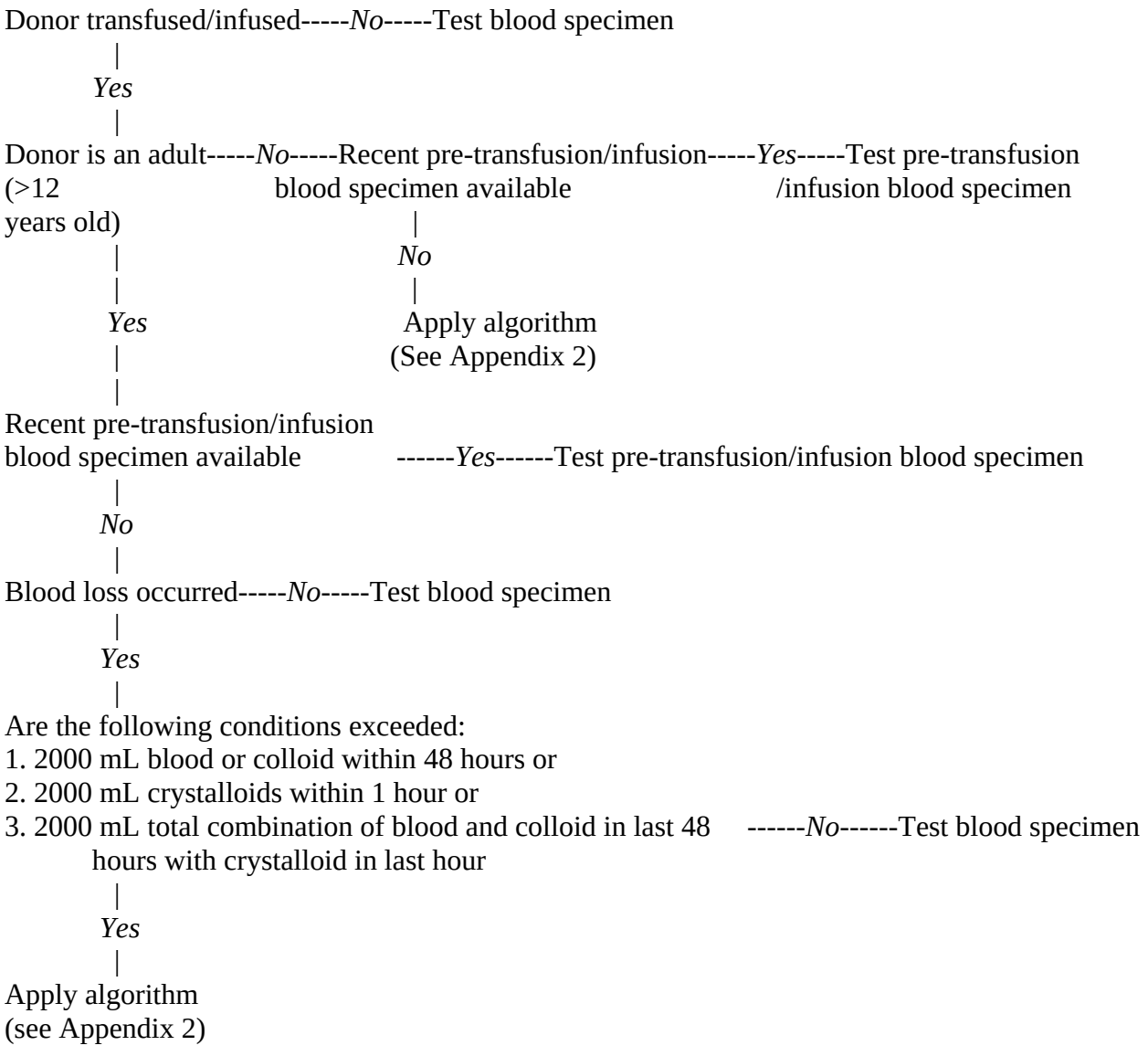
APPENDIX 1

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



ACCOMPANYING QUESTIONS FOR FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS ADEQUATE FOR INFECTIOUS 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 the donor an adult?

- If the answer to question #2 is no, then ask question #2a
- If the answer to question #2 is yes, then ask question #3

Question #2a – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is twelve years of age or younger?

- If the answer to question # 2a is no, then apply the algorithm (see appendix 2)
- If the answer to question #2a is yes, then test the pre-transfusion/infusion blood specimen that is available

Question #3 – Is there a recent pre-transfusion/infusion blood specimen available for the donor who is more than twelve years of age?

- If the answer to Question #3 is yes, then test the pre-transfusion/infusion blood specimen
- If the answer to Question #3 is no, 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 number 4 is yes, then ask Question #5

Question #5 – Are any of the following conditions exceeded?

- 2000 mL of blood or colloid given to the donor within the past 48 hours;
- 2000 mL of crystalloids within the last hour; or
- 2000 mL total of any combination of blood and colloid within past 48 hours, and crystalloid within the past hour
- If the answer to Question #5 is no, then test the blood specimen
- If the answer to Question #6 is yes, then apply algorithm (see Appendix 2)

APPENDIX 2

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 sample collection, whichever comes first

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

C = Total volume of crystalloid infused in the 1 hour before death or sample 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 Sample Acceptability for Infectious Disease Tests</u>:

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

If the answer to <u>either</u> 1 <u>or</u> 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

APPENDIX 3

Example of a Plasma Dilution Worksheet (Using Appendix 2 Algorithm)

Donor ID # _____

Date and Time of Sampling……. _____ am/pm

Donor Weight in kg …… _____ kg

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

A. Total Volume of Blood Transfused/48 hours (before death or sample collection, whichever comes first)

Volume of: RBCs transfused/48 hours _____

\+ whole blood transfused/48 hours _____ A = _____ mL

B. Total Volume of Colloid Infused/48 hours (before death or sample collection, whichever comes first)

Volume of: dextran _____ mL

\+ plasma _____ mL

\+ platelets _____ mL

\+ albumin _____ mL

\+ hetastarch _____mL

\+ Other _____ mL _____

_____mL _____

B = _____ mL

C. Total Volume of Crystalloid Infused/1 hour (before death or sample collection, whichever comes first)

Volume of: saline _____ mL

\+ Dextrose in water _____ mL

\+ Ringer's lactate _____ mL

\+ Other _____ mL _____

_____ mL _____ C = _____ mL

Determination of Sample Acceptability for Infectious Disease Tests:

[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 <u>both</u> 1 and 2 are NO, the post-transfusion/infusion sample is acceptable

* If the answer to either 1 or 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

APPENDIX 4

MODERATE AND SEVERE COMPLICATIONS OF SMALLPOX VACCINATION AND INADVERTENT VACCINIA VIRUS INFECTION

Complications of smallpox vaccine or of inadvertent vaccinia virus infection, for the purpose of this guidance, are defined as the following, and are consistent with CDC definitions of moderate to severe adverse reactions to the smallpox vaccine, or to inadvertent vaccinia virus infection in contacts of vaccine recipients (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm).

Eczema vaccinatum
Generalized vaccinia
Progressive vaccinia
Postvaccinial encephalitis
Vaccinial keratitis

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in someone with eczema (atopic dermatitis) or a history thereof, or with other chronic or exfoliative skin conditions.

Generalized vaccinia is characterized by a vesicular rash of varying extent that can occur among persons without underlying illnesses. The rash is generally self-limited and requires minor or no therapy except in rare cases, when the vaccine recipient is systemically ill.

Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic vaccinia lesions. It has occurred almost exclusively among persons with cellular immunodeficiency.

Postvaccinial encephalitis is a rare but serious complication of vaccinia virus infection.

Vaccinial keratitis is an infection of the cornea, which can cause corneal scarring and visual impairment. This condition is usually caused by accidental self-inoculation of the eye from the vaccine site, or from self-inoculation after contact with another vaccine recipient, and is not believed to be due to hematogenous spread or associated with a secondary viremia.

APPENDIX 5

LIST OF BSE-AFFECTED COUNTRIES APPLICABLE TO DONOR DEFERRAL

European Countries to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

[1]For purposes of this guidance, the United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

APPENDIX 6

West Nile Virus (WNV)

WNV was first identified in the United States in 1999, in an epizootic outbreak among birds and horses and an epidemic of meningitis and encephalitis in humans in the New York City area. Throughout 2000 - 2001, avian mortality surveillance documented geographic spread to about half of the United States. In 2001, 66 human cases of WNV encephalitis or meningitis occurred in 10 states. In 2002, a major epizootic outbreak of WNV was detected in many parts of the United States combined with the largest human WNV meningoencephalitis outbreak ever documented, and the largest outbreak of meningoencephalitis from any cause in North America. In 2002, the number of human cases far surpassed those reported in 2001 with 4,161 cases of WNV illness and 277 deaths reported as of March 12, 2003. Ninety-nine percent of the human cases occurred between July 1 and October 31, 2002. Human cases were reported in 736 counties in 39 states and the District of Columbia. The 2002 WNV epidemic involved the first documented cases of WNV transmission through organ transplantation, blood transfusion, and possibly breastfeeding (Refs. 149 and 150). In addition, intrauterine infection was reported (Ref. 151). Surveillance reports published weekly in Morbidity and Mortality Weekly Report (MMWR) indicated that WNV was active in the United States in 2003 and had spread to additional areas of the country as compared to 2002. Blood establishments began using WNV nucleic acid amplification tests (NAT) under investigational drug exemptions (IND) beginning late June 2003. It is estimated that, through 2004, at least 1017 presumptively viremic donations were removed from the blood supply as a result of blood establishments' voluntary participation in WNV NAT screening studies (Ref. 5). In 2003, a total of 9,862 cases of human illness, including 2,775 neuroinvasive disease cases and 264 fatalities were reported to CDC (Refs. 5, 152, 153, and 154). In the 2004 WNV epidemic, CDC reported WNV activity in 47 continental states, with 2,470 reported human cases and 88 fatalities (Refs. 5, 154, 155, and 156).

WNV has the potential to be spread via HCT/Ps, as evidenced by its transmission via organ transplantation, and via blood and blood product transfusion. Though it is not possible to predict the incidence or severity of future WNV epidemics, our experience with the transmission pattern of WNV and the rapid geographic spread of the disease epidemic suggests that all or most of the United States would be at risk for exposure to the illness each year. WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year (Ref. 5).

Our current recommendation is only for donor screening. Some HCT/P donors are being tested under the IND previously mentioned, though testing with an investigational product is not a requirement. In WNV infection, 80% of persons are asymptomatic, 20% have mild symptoms, and only about 1/150 persons experience severe illness. Because symptoms occur in only approximately 20% of persons infected with WNV, donor exclusions based on donor health screening will have limited effectiveness. Laboratory screening tests to detect donor infections with WNV will be needed if the epidemic persists. We may recommend routine use of appropriate licensed donor screening test(s) to detect acute infections with WNV using NAT

technology once such tests are available. (See Refs. 5, 6, and 7 for further information regarding the background and rationale for WNV deferral.)

Sepsis

For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS), or septic shock. The causative agent in sepsis has been changing over the years. Fungal pathogens have become an increasingly important cause of sepsis. Gram-negative organisms were the most common organisms leading to sepsis between 1979 and 1987, but, by 2000, gram-positive organisms caused 52.1% of cases and gram-negative organisms were responsible for about 37.6% (Ref. 157). Various bacterial, fungal, and viral agents have been shown to be transmissible via HCT/Ps (Refs. 158 through 162) and bacterial infection potentially resulting in sepsis with associated morbidity and mortality is a widely recognized risk from transfused blood and blood products (Refs. 163 and 164).

A recent study in the New England Journal of Medicine (NEJM) reviewed the epidemiology of sepsis in the United States from 1979 through 2000 by looking at discharge data contained in the National Hospital Discharge Survey (Ref. 157). This study showed that the incidence of sepsis has been increasing over that time period and estimated the incidence as of 2000 to be 240.4 cases/100,000 population. The NEJM study also cited references stating that sepsis is now among the top ten leading causes of death in the United States. Another widely cited sepsis study by Angus, et al. reviewed all the 1995 discharge data from a sample of hospitals in 7 states that collectively served approximately 25% of the population of the United States (Ref. 165). The Angus study estimated the incidence of sepsis over that year to be about 3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges. The Angus study estimated that in 1995, about 9.3% of all deaths in the United States were a direct or indirect result of sepsis – similar to the number of deaths caused by myocardial infarction over the course of that year. The mortality rate of sepsis in these studies was estimated to be about 17.9% and 28.6%, respectively. These studies (Refs. 157 and 165), as well as others (Refs. 166, 167, and 168), agree that the risk of sepsis is increased with age (after one year old), male sex, comorbid illness, and in non-whites. The incidence and prevalence of sepsis is widely believed to be increasing (Refs. 157, 165, 166, 167, and 169). While the mortality rate of sepsis has been decreasing slightly with advances in medical care, the overall number of deaths due to sepsis has been increasing (Ref. 157).

Vaccinia

Although there are no documented cases of transmission of vaccinia virus through implantation, transplantation, infusion, or transfer of HCT/Ps into a human recipient, FDA believes that vaccinia virus is potentially transmissible via HCT/Ps. Two different investigators, in 1930 and 1953, reported that vaccinia virus could sometimes be isolated from a patient's blood 3-10 days after vaccination (Ref. 8). These studies did not use the less virulent NYCBOH strain of vaccinia virus that comprises currently available vaccines in the U.S. Using the NYCBOH strain of vaccinia virus, other investigators were only able to detect virus in the blood of patients with

disseminated infection, but not in patients who only had localized lesions (Refs. 9 and 10). These studies are of limited value, however, because of their small size. Studies are now underway to determine the presence and frequency of vaccinia virus in the blood after vaccination.

A frequent complication of smallpox vaccination is autoinoculation or inadvertent inoculation of a contact (Refs. 170, 171, and 172). Vaccinia virus is readily recovered from the vaccination site until the vaccination scab spontaneously separates from the skin. The scabs themselves contain infectious virus. Thus, although viremia is unlikely once an immune response is initiated, recipients of the vaccine could still inadvertently infect contacts that touch the vaccination site or dressing (Ref. 173). Vaccinia virus can be recovered from the skin at the vaccination site for a mean duration of 7.8 days, with a range of 0 to 18 days (Ref. 174). After an individual is vaccinated with the vaccinia virus, vaccinia can be accidentally spread to other parts of the body and to others since the virus is capable of contact transmission (Refs. 11, 172, and 175). Nosocomial spread of vaccinia has also been reported (Ref. 172). Recent literature describes the conjugal transfer of vaccinia from 2 different active-duty military personnel to their respective partners after smallpox vaccination (Ref. 176).

Smallpox vaccination was routinely performed in the U.S. until 1971. In recent years, smallpox vaccination has been recommended only for laboratory personnel working with certain orthopox viruses, including vaccinia and smallpox. On June 20, 2002, the Advisory Committee for Immunization Practices (ACIP) of the CDC recommended that smallpox vaccine also be given to persons pre-designated to conduct investigation and follow-up of initial smallpox cases and to personnel in facilities that are pre-designated to serve as referral centers to provide care for initial smallpox cases. On December 13, 2002, President Bush announced his decision to begin a smallpox vaccination campaign targeted to those military and civilian personnel who have an occupational risk of contracting smallpox. There is a policy in place to vaccinate Department of Defense (DoD) personnel who are deployed to areas designated as high-threat by the Secretary of Defense. In addition, DoD offers voluntary smallpox vaccination for military members and their families, civilian employees and their family members, and contract personnel serving at Department of State missions in Near East Asia, Israel, Turkey, North Africa, Lebanon, Syria, Jordan, Egypt, and Korea (Refs. 177 through 180). Implementation and review of these policies appear to be ongoing (Ref. 181). According to the DoD Smallpox Vaccination Program website (updated 4/14/05) (Ref. 182), more than 760,000 people have been vaccinated with smallpox vaccine since December 2002 through its vaccination program. Since the smallpox vaccination program affects a large number of people throughout the country, we believe the incidence of vaccinia in the donor population is sufficient to warrant its addition to the list of relevant communicable diseases.