Guidance for Industry

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

DRAFT GUIDANCE

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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.

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Contains Nonbinding Recommendations

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I. INTRODUCTION

A. What is the purpose of this guidance?

We, FDA, are providing recommendations for complying with the requirements contained in the donor-eligibility regulations for human cells, tissues, and cellular and tissue-based products (HCT/Ps) (21 CFR part 1271, subpart C) (Ref. 1). The regulations in part 1271, subpart C, require you (described in section I.B.) to perform an eligibility determination for most cell and tissue donors, based on testing and screening for relevant communicable diseases.

Part 1271 also contains other requirements applicable to HCT/Ps (e.g., registration and listing), which are not addressed in this guidance.

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

This guidance does *not* replace earlier guidance on 21 CFR part 1270 (Ref. 2). This guidance only applies to cells and tissues procured on or after the effective date of the final regulations contained in 21 CFR part 1271, subpart C. [Effective date is May 25, 2005.]

We have previously issued a separate draft "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. 3). We intend to issue a single final guidance document that incorporates the guidance on CJD and vCJD and the subject of this guidance into a final guidance on donor eligibility determination.

B. Who should read this guidance?

Establishments may allocate in several ways the responsibilities for screening and testing donors and for determining whether donors are eligible, including by contracting or otherwise arranging with other establishments to perform one or more of these activities. This guidance is intended to help the following entities: (1) any party responsible for performing donor eligibility screening and testing and for making donor eligibility determinations; and (2) the establishment that determines that an HCT/P meets release criteria and makes the HCT/P available for distribution.
In this guidance, "***you***" means

- The establishment or person that screens the donor;
- The establishment or person that tests the donor;
- The establishment or person that makes the donor-eligibility determination; or
- The establishment or person that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution.

II. THE DONOR-ELIGIBILITY DETERMINATION

A. What is a donor-eligibility determination?

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

Under the rule (§ 1271.50(b)), a donor is eligible only if:

- screening shows that the donor is free from risk factors for, and clinical and physical 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 and diseases are negative or nonreactive.

B. Who makes the donor-eligibility determination?

A "responsible person" must make the donor-eligibility determination (§ 1271.50(a)). A responsible person is one who is authorized to perform designated functions for which he

or she is trained and qualified (§ 1271.3(t)). You are permitted to make the donor-eligibility determination only if you are trained, qualified, and authorized to do so. The donor eligibility determination must be documented (§ 1271.50(a)).

C. What is a "relevant communicable disease agent or disease"?

1. Under the rule, 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); and
- *Treponema pallidum* (syphilis)

In addition, for viable, leukocyte-rich cells and tissues, including reproductive cells or tissues if they are considered to be viable leukocyte rich (see section V.B.2), the following cell-associated communicable disease agents or diseases are identified in the rule as relevant (§ 1271.2(r)(1)(ii)):

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

For reproductive cells or tissues, the following communicable disease agents or diseases of the genitourinary tract are identified as relevant (§ 1271.3(r)(1)(iii)):

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

2. In addition, the rule states that a communicable disease agent or disease not named in the rule is relevant under this rule if the communicable disease agent or disease is one (§ 1271.3(r)(2)):

   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, 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. 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)).

These factors are considered **together**. For instance, a highly prevalent but relatively harmless disease agent might not be considered to be a relevant communicable disease. An example is *Ureaplasma urealyticum*, which may cause a disease of the genitourinary tract. *Ureaplasma urealyticum* is a prevalent organism, but its pathogenicity to reproductive cell and tissue recipients is of questionable clinical significance. For this reason, we do not currently consider *Ureaplasma urealyticum* to be a relevant communicable disease agent. On the other hand, testing or screening might be required for a less prevalent but particularly virulent agent. Examples of communicable diseases that are less prevalent, yet pose extremely significant health risks, are TSEs and HIV-2.

FDA believes that the following communicable disease agents and diseases meet these standards for identification of relevant communicable disease agent or disease not specifically identified in the regulations:

West Nile Virus (WNV)

Risk of Transmission: FDA believes that there is a risk of transmission of WNV through HCT/Ps because it is potentially transmissible by HCT/Ps and that WNV has sufficient incidence and/or prevalence to affect the potential donor population, as follows:

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 (Ref. 4). In addition, intrauterine infection was reported (Ref. 5). Surveillance reports published weekly in Morbidity and Mortality Weekly Report (MMWR) indicate that WNV has been active in the United States in 2003 and has spread to additional areas of the country as compared to 2002. Blood establishments have begun using WNV nucleic acid amplification tests (NAT) under investigational drug exemptions (IND), beginning late June 2003. As of September 16, 2003, 601 blood donations out of approximately 2.5 million total blood donations have tested reactive for WNV by investigational NAT screening (Refs. 6, 7).

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.

Severity of Effect: As described in the previous paragraphs, WNV can be fatal or life threatening, can result in permanent impairment to a body function or permanent damage to a body structure, and can necessitate medical or surgical intervention to preclude permanent impairment or permanent damage to a body structure.

Availability of Screening and/or Testing Measures: FDA believes that appropriate screening measures have been developed for WNV.

Our current recommendation is only for donor screening, given that no appropriate donor screening test for WNV has been licensed, approved, or cleared for such use by FDA. However, some HCT/P donors are being tested under the IND previously mentioned. 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. Our current thinking is that we would recommend routine use of appropriate licensed donor screening tests to detect acute infections with WNV once such tests are available. Symptoms of WNV are discussed in Section III.F.5. of this document.

Screening measures for WNV are discussed in Sections III.E. and III.G. of this document. (See Ref. 8 for further information regarding the background and rationale for WNV deferral.)

Sepsis

Risk of Transmission: FDA believes that there is a risk of transmission of any agent causing sepsis through HCT/Ps because it is potentially transmissible by HCT/Ps and it has sufficient incidence and/or prevalence to affect the potential donor population, as follows:

For the purpose of this document, sepsis includes, but is not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection 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. 9). Various bacterial, fungal, and viral agents have been shown to be transmissible via HCT/Ps (Refs. 10-14).

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. 9). 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. 15). 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. 9, 15), as well as others (Refs. 16, 17), 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. 9, 15, 16, 18). 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. 9).

Severity of Effect: Sepsis can be fatal or life threatening, can result in permanent impairment to a body function or permanent damage to a body structure, and can necessitate medical or surgical intervention to preclude permanent impairment or permanent damage to a body structure. As discussed in the previously cited studies, mortality from sepsis is substantial.

Availability of Screening and/or Testing Measures: FDA believes that there are appropriate screening measures, such as medical history interview, and physical and clinical signs, to detect sepsis.

Symptoms of sepsis are discussed in Section III.F.6 of this document. Screening measures for sepsis are discussed in Sections III.E, III.F. and III.G. of this document.

Vaccinia

Risk of Transmission: FDA believes that there is a risk of transmission of vaccinia (the virus used in smallpox vaccine) through HCT/Ps because vaccinia is potentially transmissible by HCT/Ps and has sufficient incidence and/or prevalence to affect the potential donor population, as follows:

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. 19). 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. 20, 21). 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. 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 close contacts that touch the vaccination site or dressing (Ref. 22). 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. 23). 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. 24, 25).

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 (www.cdc.gov/nip/smallpox/supp_recs.htm). 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, and Egypt (Ref. 26). Implementation and review of these policies appear to be ongoing (Ref. 27). According to the DoD Smallpox Vaccination Program website (updated 3/25/2004) (Ref. 28), more than 600,000 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 will be sufficient to warrant its addition to the list of relevant communicable diseases.

Severity of Effect: Vaccinia virus can be fatal or life threatening, can result in permanent impairment to a body function or permanent damage to a body structure, and can necessitate medical or surgical intervention to preclude permanent impairment or permanent damage to a body structure.

The potential consequences of vaccinia infection can include severe complications of vaccinia infection (see Appendix 4). These consequences may be more likely in HCT/P recipients who are immunocompromised or who have burns, or other serious skin conditions. In addition, vaccinia virus infection can rarely cause severe complications such as encephalitis and severe generalized vaccinia in otherwise healthy people. It is possible that vaccinia infection transmitted via HCT/P may result in different or more severe infections than when acquired percutaneously, since the route of infection can influence the severity (Ref. 29). 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 (Vaccine Information Sheet, new Reference 13 above).

Availability of Screening and/or Testing Measures: FDA believes that there are appropriate screening measures, such as medical history interview, and physical and clinical evidence, to detect vaccinia.

Symptoms of vaccinia are discussed in Section III.F.4 of this document. Screening measures for vaccinia are discussed in Sections III.E, III.F. and III.G. of this document. (See Ref. 29 for further information regarding the background and rationale for vaccinia deferral.)

Severe Acute Respiratory Syndrome (SARS)

Risk of Transmission: FDA believes that there is a risk of transmission of SARS through HCT/Ps because it is potentially transmissible by HCT/Ps and it has sufficient incidence and/or prevalence to affect the potential donor population, as follows:

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have been investigating a worldwide outbreak of unexplained atypical pneumonia referred to as Severe Acute Respiratory Syndrome (SARS). As of July 2003, 8,427 probable cases of SARS have been reported to WHO from 29 countries (Ref. 30, 31). In the United States as of July 2003, about 418 cases were reported to CDC from about 30 states—with only eight laboratory-confirmed cases and no significant local spread (Refs. 30, 31). About 95% of cases reported in the United States were in people who had traveled to outbreak areas listed in the case definition within 10 days before the onset of clinical illness, and the remainder had a history of close contact with a person with suspected SARS. The majority of patients recovered or stabilized clinically without specific antiviral therapy; no fatalities have been reported in the United States as of July 2003 (Refs. 29-37).

The potential for transmission of SARS through HCT/Ps is not certain. The new Coronavirus that is the identified cause of SARS, SARS-CoV, has been isolated from infected kidney, lung, and bronchoalveolar-lavage fluid (Ref. 38) but has not been isolated from blood or serum of infected individuals (Refs. 38-42), though data are limited. Detection by nucleic acid amplification of SARS-CoV in blood specimens from persons acutely infected with SARS has been reported in a single patient (Ref. 42). Persons with SARS could potentially be viremic before the onset of symptoms and/or after resolution of symptoms. Transmission of SARS via HCT/Ps recovered during these time periods may be possible. The incidence or prevalence of SARS within the United States is limited; however, we believe these limitations were achieved by a coordinated public health response, and that the incidence and prevalence of SARS are sufficient to require screening measures during outbreaks.

Severity of Effect: FDA believes that SARS can be fatal or life threatening, can result in permanent impairment to a body function or permanent damage to a body structure, and can necessitate medical or surgical intervention to preclude permanent impairment or permanent damage to a body structure.

Approximately 10% of cases have been fatal worldwide, and the overall case-fatality rate can increase to >50% in persons older than age 60 (Ref. 31).

Availability of Screening and/or Testing Measures: FDA believes that appropriate screening measures have been developed for SARS.

Travel is an important source for new infections. We currently think that the donor medical history interview is an important method for detecting potential donors who have had this disease. The genetic sequence of the Coronavirus (SARS-CoV) responsible for SARS has been published, so it is anticipated that tests may become available in the future for detecting SARS-CoV (Refs. 43, 44). There are nucleic acid and serological diagnostic tests for SARS currently under investigational use (Ref. 45). However, our current recommendation is only for donor screening since no appropriate donor screening test for SARS-CoV has been licensed, approved, or cleared for such use by FDA. Symptoms of SARS are discussed in Section III.F.6 of this document. Screening measures for SARS are discussed in Sections III.E, III.F. and III.G. of this document. We may update our current thinking as more information becomes available about SARS. (See Ref. 45 for further information regarding the background and rationale for SARS deferral.) Information about diagnosing and reporting SARS may be obtained at the CDC website at http://www.cdc.gov/ncidod/sars/index.htm or by calling CDC at 888-246-2675. At this time, since there are no SARS-affected areas, you do not have to screen for SARS. No one knows if, when, or where person-to-person transmission of SARS-CoV will recur. FDA, as well as the CDC (Ref. 31), believes that SARS-CoV is capable of a very rapid spread of infection with high levels of associated morbidity and mortality. Because of this, FDA believes it is prudent to recommend donor screening for this illness **when CDC lists SARS-affected areas on their website.** (See Section III.E. of this document for more details).

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

FDA intends to recommend screening and testing for additional infectious diseases if we believe that an infectious disease meets the definition of relevant communicable disease

(§ 1271.3(r)(2)). In addition, FDA intends to notify you, in guidance, in the event that the agency concludes that a disease identified as "relevant" under § 1271.3(r)(2) no longer meets the criteria as a "relevant" diseases for purposes of the donor eligibility regulations.

E. What procedures must I establish and maintain?

Under § 1271.47, 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. A responsible person must review and approve all procedures before their implementation.

Procedures must be available to personnel either in the area where the procedures are performed, or if this is not practical, in a nearby area.

Under § 1271.47(d), you must record and justify any departure from a procedure at the time of its occurrence, but you do not have to obtain approval at that time for making the departure. 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. However, before distributing an HCT/P manufactured under a departure from procedure, a responsible person must determine that the departure did not increase the risk of communicable disease transmission.

The regulation authorizes the use of 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 the regulations. For instance, 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.

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

Under § 1271.55 you must provide the following records with each HCT/P:

- 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 or directed reproductive donations, 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.

The summary of records 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 communicable disease tests performed on the donor;
- 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).

G. What records must I retain, and for how long?

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. If this date is not known, then you must retain records at least 10 years after the date of distribution, disposition or expiration, whichever is later. These records would include results and interpretation of all donor screening and testing performed, the name and address of the testing laboratory, and the name of the responsible person who made the donor eligibility determination, and the date (§ 1271.55(d)(1)). All records must be accurate, indelible, and legible (§ 1271.55(d)(2)).

H. What do I do with the HTC/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) & (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 and to track 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.

I. 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,*** under that regulation, the HCT/P must be kept in quarantine and must be accompanied by records that:

- identify the donor by a distinct identification code affixed to the HCT/P container, but not by name (except in the case of an autologous or directed donation);
- 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), described in Section VII.C. of this document.

J. 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), described in Section VII.B. of this document.

FDA believes there are a number of ways in which you may comply with this requirement. Examples include employing separate refrigerators or freezers, using separate shelves in a single refrigerator or freezer, and using an automated designation system. Since § 1271.47(a) requires you to establish and maintain procedures for complying with these donor eligibility regulations, you should describe the method you choose to comply with this regulation in your standard operating procedures (SOPs).

III. 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 for risk factors for, and clinical and physical evidence of, relevant communicable disease agents and diseases and for communicable disease risks associated with xenotransplantation unless one of the exceptions identified in § 1271.90(a) applies. You must also screen donors of reproductive cells and tissue for the additional diseases identified as relevant to those HCT/Ps. (See section II.C., above, for discussion of relevant communicable disease agents and diseases.)

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

We recommend screening both the birth mother and the infant when a donor is one month of age or less.

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, clinical evidence, and physical evidence of the relevant communicable diseases listed in section III. A. (§ 1271.75(a)). Risk factors are described in section III. E., clinical evidence in section III. F., and physical evidence in section III. G.

Relevant medical records 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;(3) ***other available records*** (§ 1271.3(s)). 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.

    FDA believes that this is a step in determining donor eligibility. Accordingly, standard operating procedures (SOPs) governing the conduct of the ***donor medical history interview***, including direct questions about risk behavior, would be required (§ 1271.47). FDA believes that the medical history interview may take place in person or by telephone.

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)). Since this is a step in determining donor

eligibility, FDA recommends that you 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). FDA believes that examples of these records include: medical examiner report, police records, and information from other tissue or medical establishments.

FDA believes that "available" means that the record or information exists and is obtainable within a reasonable amount of time. A "reasonable" amount of time is a period of time that would allow the effort to collect important information without compromising the usefulness of the tissue.

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 is 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 usefulness of the tissue, perhaps because your HCT/P needs to be released within a limited timeframe, you would not wait to review the final report of autopsy results. Instead, FDA recommends that you take into consideration and document the presumed cause of death and other pertinent preliminary autopsy findings.

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 screening procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including changes in relevant social behavior".

FDA recommends that, if you perform an abbreviated screening:

- You do not need to conduct a new physical examination or a new review of relevant medical records.
- We recommend that you remind the donor about behaviors that could put him/her at risk of a relevant communicable disease. 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.
- We recommend that you ask the donor if there have been any changes in donor history or risk factors since the previous donation.

E. What risk factors 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)).

FDA believes that the following conditions and behaviors increase the donor's relevant communicable disease risk. Except as noted in this section, we recommend that you 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 five years (Refs. 46, 47);
2. persons who have injected drugs for a non-medical reason in the preceding five years, including intravenous, intramuscular, or subcutaneous injections (Ref. 46);
3. persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates (Ref. 46);
4. persons who have engaged in sex in exchange for money or drugs in the preceding five years (Ref. 46);
5. persons who have had sex in the preceding 12 months with any person described in the previous 4 items of this section or with any person known or suspected to have HIV infection (Refs. 46, 47), clinically active hepatitis B infection (Ref. 38), or hepatitis C infection (Ref. 49);
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., needlestick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 46, 48);

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

   - if 18 months of age or younger, or
   - if breastfed within the preceding 12 months;

Note: FDA does not recommend that you decline to accept as a donor 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 breastfed 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. 46).

8. current inmates of correctional systems (including jails and prisons) and individuals who have been incarcerated for more than 72 consecutive hours during the previous 12 months (Ref. 50);
9. persons who have had close contact within 12 months preceding donation with another person having clinically active viral hepatitis (e.g., living in the same household, where sharing of kitchen and bathroom facilities occurs regularly) (Ref. 51);
10. persons who within 12 months of donation have undergone tattooing, ear piercing, or body piercing in which shared instruments are known to have been used (Ref. 51);
11. persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after age 11 (Ref. 52), unless evidence from the time of illness documents that the hepatitis was identified as hepatitis A (e.g., a reactive IgM anti-HAV test);
12. persons who have known or suspected sepsis at the time of death, or at the time of donation in the case of a living donor;
13. persons who have had recent smallpox vaccination (vaccinia virus) (Ref. 29);
    a. For persons who had no vaccinia complications (see Appendix 4 for definition of vaccinia complication) we recommend that:

       - The donor be deferred until after the vaccination scab has separated spontaneously, or for 21 days post-vaccination, whichever is the later date, and until the physical exam 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, the donor be deferred for two months after vaccination.

       Note: For 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, FDA recommends that you consider the donor to be eligible.

b. For persons who have experienced vaccinia complications (Appendix 4) we recommend that:

- The donor be deferred until 14 days after all vaccinia complications have completely resolved.

Note: For 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, FDA recommends that you consider the donor to be eligible.

14. persons who acquired a clinically recognizable vaccinia virus infection by close contact with someone who received the smallpox vaccine (Ref. 29);

- For living donors who developed skin lesions as a result of close contact with someone who received the smallpox vaccine, we recommend that you question the donor regarding the loss of the scab, and that you examine the skin. For cadaveric donors, we recommend that you examine the skin.
- If no scab is present, FDA recommends that you consider
  - a cadaveric donor to be eligible;
  - a living donor to be eligible if the scab spontaneously separated; or
  - a living donor whose scab was otherwise removed to be eligible after three months from the date of vaccination of the vaccine recipient.
- If a scab is present, FDA recommends that you consider
  - a cadaveric donor to be ineligible; or
  - a living donor to be deferred until the scab spontaneously separates.
- We recommend that persons who developed complications of vaccinia infection acquired through close contact with a vaccine recipient be deferred until 14 days after all vaccinia complications have completely resolved.

Note: For a cadaveric donor who previously had complications of vaccinia acquired through close contact with a vaccine recipient, but has no visible signs of vaccine complications – if the date of resolution of the vaccinia complications is

unknown FDA recommends that you consider the donor to be eligible.

Close contacts who never developed skin lesions or other complications of vaccinia infection need not be deferred.

15. persons who have had a medical diagnosis of WNV infection (including diagnosis based on symptoms and laboratory results, or confirmed WNV viremia) (Ref. 8), we recommend that:

    - The donor be deferred for at least 28 days from onset of symptoms or diagnosis; or
    - until 14 days after the condition is considered to be resolved, whichever is the **later** date.

16. persons who have had both a fever and a headache (simultaneously) during the 7 days before donation (Ref. 8), we recommend that:

    - The donor be deferred from donation; or
    - The donor be deferred for 28 days after the interview for living donors who may donate at a later date.

Note: We recommend that numbers 17, 18, and 19 regarding SARS be applied only when person-to-person transmission of SARS-CoV is occurring in the world. We recommend that you routinely and periodically refer to the CDC website (http://www.cdc.gov/ncidod/sars/index.htm) or call CDC (888-246-2675) to obtain the up-to-date information concerning areas affected by SARS.

17. persons who are suspected to have SARS or who are known to have SARS or treatment for SARS within the previous 28 days (Refs. 31-33, 45);
18. persons who have had close contact within the previous 14 days with persons with SARS or suspected SARS (Refs. 33, 45);
19. persons who have traveled to or resided in areas affected by SARS within the previous 14 days (Refs. 33, 45);
20. persons who are xenotransplantation product recipients or intimate contacts of a xenotransplantation product recipient (Ref. 53).
    a. FDA recommends that you use the following xenotransplantation definitions:

        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. FDA does 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 donor has received a xenotransplantation product, or is the intimate contact of a person who has received a xenotransplantation product, we recommend that you ask if 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 xenotransplantation product recipient is the potential donor or his/her sexual partner, FDA recommends that you defer the donor. If the recipient is a member of the potential donor's household, we recommend that you determine whether the potential donor has been exposed to blood, saliva, or other body fluids from the xenotransplantation product recipient (e.g., through deep kissing, shared toothbrushes, razors, or needles, or through open wounds or sores). If any of these are the case, FDA recommends that you defer the donor.

FDA believes that certain ex vivo exposures to xenotransplantation products (e.g., exposure to a well-characterized cell line, or

exposure across a physical barrier) may not provide a basis to defer a potential donor who may have been either a recipient or intimate contact of a recipient of certain xenotransplantation products. FDA would need to evaluate the circumstances, such as what cell line is used and its extent of characterization, in each case. For instance, an advisory committee recommended and FDA concurs 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. For this reason, intimate contacts of Epicel™ recipients need not be deferred from tissue donation (Ref. 54). (Note: FDA recommends deferral of Epicel™ recipients from tissue donation.)

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

You must review relevant medical records to determine that potential donors are free from clinical evidence of relevant communicable disease agents and diseases (§ 1271.75(a)). For cadaveric donors, we recommend you determine whether an autopsy was not performed due to infectious criteria or, if an autopsy was performed, if any special precautions were taken that would suggest risk of a communicable disease in the donor. This information should be considered in light of other information obtained about the donor in making a donor eligibility determination.

FDA recommends that you look for the following examples of clinical evidence of relevant communicable disease:

1. HIV infection:

    - a prior 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) of longer than one month;
    - unexplained temperature of > 100.5°F (38.6°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. 55).

2. Hepatitis infection:

- a prior reactive screening test for hepatitis B virus or hepatitis C virus;
- unexplained jaundice;
- hepatomegaly; and/or
- past diagnosis of clinical, symptomatic viral hepatitis after age 11 (Ref. [52]52), unless evidence from the time of illness documents that the hepatitis was identified as hepatitis A (e.g., a reactive IgM anti-HAV test).

Note: Records of the following laboratory data may 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. 56). If these tests are abnormal, but a cause other than viral hepatitis was established, FDA believes that the donor may be eligible.

3. Syphilis infection

- persons who have had or have been treated for syphilis or gonorrhea during the preceding 12 months (Ref. 55). FDA recommends that, after 12 months, the donor may be re-entered after presenting evidence of successful treatment for syphilis (Ref. 57).

4. Vaccinia infection

- recent smallpox vaccination
- eczema vaccinatum
- vesicular rash indicative of generalized vaccinia in person who has had recent smallpox immunization or who is a close contact of someone with recent smallpox immunization
- progressive necrosis in an area of vaccination consistent with vaccinia necrosum
- postvaccinial encephalitis
- vaccinial keratitis (Ref. 29).

5. WNV infection (Ref. 8) (Because signs and symptoms of WNV can be nonspecific, consider these clinical signs and symptoms in light of other information obtained about the donor in making a donor eligibility determination .)

- mild symptoms may include fever, headache, body aches, or eye pain;
  - mild symptoms may also occasionally be accompanied by a skin rash on the trunk of the body; or
  - swollen lymph glands.

- severe illness;
  - severe illness may include encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis.
  - signs and symptoms of severe illness may include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, and muscle weakness or paralysis.

6. SARS infection (Refs. 31, 32, 36, 37) (Signs and symptoms of SARS-CoV can be nonspecific; we recommend you consider these clinical signs together with known or suspected exposure to the SARS virus when there is known person-to-person transmission of SARS-CoV occurring in the world. We recommend that you routinely and periodically refer to the CDC website (http://www.cdc.gov/ncidod/sars/index.htm) or call CDC at 888-246-2675 to obtain the up-to-date information concerning areas affected by SARS.)

   - Asymptomatic or mild respiratory illness;

   Note: No instances of SARS-CoV viremia have been detected in persons who are asymptomatic. However, SARS-CoV antibody has been detected in persons who have not experienced known clinical SARS infection (Ref. 58). At this time, data are insufficient to exclude the possibility of asymptomatic infection with SARS-CoV and the possibility that such persons can transmit the virus.

   - Moderate respiratory illness;
     - Temperature of >100.4º F (38º C), and
     - One or more clinical findings of lower respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia).
   - Severe respiratory illness;
     - Temperature of >100.4º F (38º C), and
     - One or more clinical findings of lower respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), and
       - radiographic evidence of pneumonia, or
       - respiratory distress syndrome, or
       - autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.
   - Although not diagnostic, the following laboratory abnormalities have been seen in some patients with laboratory-confirmed SARS Co-V disease:
     - lymphopenia with normal or low white blood cell count;
     - elevated hepatic transaminases;

- elevated creatine phosphokinase;
- elevated lactate dehydrogenase;
- elevated C-reactive protein; and/or
- prolonged activated partial thromboplastin time.

7. Sepsis (includes, but not limited to, bacteremia, septicemia, sepsis syndrome, systemic infection, or septic shock) (Ref. 59)

If bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock is specifically noted in the medical records, the donor is ineligible (see Section III. F. 12.).

Sepsis is often described by the following clinical evidence, but we recommend that these signs be considered 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 $PaCO_2$ <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 may be associated with the above signs.

8. HTLV infection

- a prior reactive screening test for HTLV;
- unexplained paraparesis; and/or
- adult T-cell leukemia (Refs. 60, 61).

G. What physical evidence do I look for?

Relevant medical records include the report of the physical assessment of a cadaveric donor or the physical examination of a living donor (§1271.3(s)). FDA recommends that you review those records 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. The following are examples of physical evidence to look for:

1. Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis, chancroid;
2. For a male donor, physical evidence of anal intercourse including perianal condyloma;
3. Physical evidence of nonmedical percutaneous drug use such as needle tracks, including examination of tattoos, which may be covering needle tracks;
4. Physical evidence of recent tattooing, ear piercing, or body piercing;
5. Disseminated lymphadenopathy;
6. Oral thrush;
7. Blue or purple spots consistent with Kaposi's sarcoma;
8. Unexplained jaundice, hepatomegaly, or icterus.
   Note: Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed.
9. Physical evidence of sepsis, such as unexplained generalized rash;
10. Large scab consistent with recent smallpox immunization;
11. Eczema vaccinatum;
12. Generalized vesicular rash (generalized vaccinia);
13. Severely necrotic lesion consistent with vaccinia necrosum; and/or
14. Corneal scarring consistent with vaccinial keratitis. (Ref. 29)

IV. DONOR TESTING: GENERAL (§ 1271.80)

A. Who may perform donor testing?

Required testing must be performed by a laboratory: (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 CMS in accordance with those provisions (§ 1271.80(c)). Examples of the latter include Veterans Administration hospital laboratories, laboratories in states that have received exemptions from CMS, and laboratories that have been accredited by organizations approved by CMS.

B. What type of test must I use?

You must use 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)).

- FDA recommends that you choose a test that is the best available for the purpose of reducing disease transmission. Over time, as new and improved tests are made available, older tests may no longer adequately and appropriately reduce the risk of disease transmission. We list in

section V tests that we consider to meet this requirement as of the date of this guidance.

- We believe that, in some instances, you may need to conduct more than one test to adequately and appropriately test for a single disease agent.
- If you are testing a specimen of cadaveric blood—i.e., taken from a donor whose heartbeat has ceased—FDA believes that a test specifically labeled for cadaveric specimens would be more appropriate than a more generally labeled test, when such a test is applicable and available (§ 1271.80(c)). A list of donor screening tests that have been licensed for use with cadaveric serum can be found on CBER's website, http://www.fda.gov/cber/tissue/prod.htm. We intend to update the website periodically as additional tests are labeled for this use and become available.

C. How do I interpret test results?

You must interpret test results according to the manufacturer's instructions in the test kit's package insert (§ 1271.80(c)).

We are aware that some HCT/P establishments rely solely on the test results obtained by an organ procurement organization (OPO). As described by the Centers for Disease Control and Prevention (CDC), an OPO may run an enzyme immunoassay initially in triplicate (Ref. 46). If that is the case, and you are relying solely on such triplicate testing, we recommend that you obtain the results of the three individual tests performed in a single run. FDA believes that, in such a case, three nonreactive results in a single run would constitute a negative test result. If any other results are obtained, 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)).

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, if this is not feasible, within seven days before or after the recovery of cells and tissue (§ 1271.80(b)).

In the case of anonymous semen donors who donate repeatedly, you do not have to test the donor at each donation, but you must test him the first time and at least every six months. You must not release the semen unless you have quarantined it for at least six

months, collected and tested a new specimen from the donor, and found him to be negative for all required infectious disease testing (§§ 1271.80(b) and 1271.85(d)).

In the case of peripheral blood hematopoietic stem/progenitor cell (HPC) transplantation, we realize that the recipient may begin myeloablative chemotherapy more than seven days before the transplant. The identified allogeneic donor may need to be qualified before this time, and the qualification would include screening and testing the donor for relevant communicable diseases. In this situation, you may collect the donor specimen up to 30 days before the peripheral blood HPC recovery (§ 1271.80(b)).

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

Transfusion or infusion may dilute plasma, making test results unreliable. 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)).

FDA recommends that, for adult donors who have suffered blood loss, certain volumes of transfusions and/or infusions (described below) should be suspected of affecting test results. Blood loss includes blood lost within the body cavity and blood lost outside of the body. For donors twelve years of age or younger, you should suspect any transfusion or infusion of affecting test results regardless of blood loss. There may be other clinical situations involving transfusion or infusion that should also be suspected of affecting test results. FDA believes that 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.

Some Useful Definitions from the Regulations:

a. *Blood component* means a product containing a part of human blood separated by physical or mechanical means (§ 1271.3(i)).
b. *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)).
c. *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, or 5 percent dextrose in water (§ 1271.3(k)) .

d. *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)).

1. Adult Donor (§ 1271.80(d))(2)

Under the regulations, a risk of plasma dilution sufficient to suspect that test results may be affected occurs in a donor over twelve years of age in 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 is taken post-mortem;

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 is taken post-mortem; or

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 section IV.F.1.

2. Pediatric Donor (§ 1271.80(d)(2)(ii))

Under the regulations, a risk of plasma dilution sufficient to suspect that test results may be affected occurs in a pediatric donor (12 years of age or under), regardless of whether or not blood loss has occurred, when the donor has received:

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 taken post-mortem; and/or
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 taken post-mortem.

3. Other Clinical Situations

We cannot provide guidance that anticipates every possible clinical situation where plasma dilution may affect test results. You may be aware of additional circumstances in which plasma dilution may affect test results. We recommend that your SOPs identify any additional circumstances where you believe plasma dilution may have occurred, and that you 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 IV.F.1. and 2. Nevertheless, FDA recommends that you 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 sampling;
- 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, we recommend that the SOPs indicate how the situation will be handled; for example, by consulting the medical director.

4. Pre-Transfusion/Infusion Specimen

We recommend that your SOPs 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 (§ 1271.47(a)). You must perform tests in accordance with the manufacturer's instructions (§ 1271.80(c)), including any instructions concerning factors that may affect specimen acceptability.

5. Algorithms

If you use an algorithm, it must evaluate the fluid volumes administered in the 48 hours before collecting the specimen from the donor, to ensure 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, we recommend that you 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 we recommend that you not use the post-transfusion/infusion specimen for testing. We recommend against using further procedures attempting to qualify the ineligible specimen.

Calculating blood and plasma volumes for donors in the 45-100 kilogram range, where there is blood loss with replacement:

We recommend that you calculate and assess both blood volume and plasma volume as follows:

- You may 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.
- You may 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)

V. 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 as 1-5 of this section, as required in § 1271.85(a). You must use an FDA licensed, approved, or cleared test, and if a test specifically labeled for use with cadaveric specimens is available, you must use that test, if applicable to your HCT/P. (§ 1271.80(c)). At this time we recommend that you use the tests listed in parentheses because we believe these tests 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* (Ref. 55));
2. HIV, type 2 (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2*) (Ref. 55);
3. HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) (Ref. 51) and for total antibody to Hepatitis B core antigen (anti-HBc)--(IgG+IgM)) (Ref. 62);
   Exception for cord blood collection and storage: When the maternal sample tests negative for HBsAg and reactive for core antibody, cord blood units may be collected and stored in quarantine. Use of these cord blood units, if there is no comparable cord blood unit for the recipient, is not prohibited in cases of urgent medical need (§ 1271.65(b)). If the maternal sample is reactive for HBsAg, you must not collect the cord blood (§ 1271.50(b)).
4. HCV (FDA-licensed screening test for anti-HCV);
5. *Treponema pallidum* (FDA-cleared serological test for syphilis).

Exception for syphilis test results: A donor whose specimen tests reactive on a non-Treponemal screening test for syphilis and negative on a specific Treponemal confirmatory test may nevertheless be considered eligible, as long as all other required testing and screening are negative. A donor whose specimen tests reactive on a Treponemal confirmatory test is not eligible (Ref. 57).

Nucleic Acid Testing (NAT): Although there are FDA-licensed NAT tests for HIV and HCV blood donor screening, these tests have not been validated for use with cadaveric blood specimens. FDA is working with industry to encourage development of NAT that is validated for use with cadaveric blood. As more information becomes available, FDA may recommend these tests for use in cadaveric tissue donors. FDA does recommend that living donors of HCT/Ps (e.g., hematopoietic stem/progenitor cell donors, semen donors) be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV.

p24 Antigen Tests: We are aware that the HIV-1 p24 antigen test may not be readily available. Therefore, we are not recommending the HIV-1 p24 antigen test for HCT/P donors at this time. (Ref. 63)

Nonrecommended tests: You or someone else might perform additional testing not listed in section V.A. (for example, NAT). If you perform donor testing for relevant communicable diseases using tests in addition to those listed in section V.A. 1-5, or if you are aware that other establishments are performing such tests and the test results are

* At the time of publication of this guidance, the only test for anti-HIV that is approved by FDA for use on cadaveric blood specimens is a combination test for detection of anti-HIV-1 and anti-HIV-2.

available, such test results would be included in the donor's medical record. (§ 1271.3(s)(1) and (s)(2)). Since they 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 usefulness of the tissue.

> *Example:* An eye bank is aware that a tissue bank performs HIV NAT 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 NAT results before releasing the corneas. FDA recommends that the eye bank inform the consignee that NAT results are pending.

Confirmatory tests: If you perform a confirmatory test, negative results on a confirmatory test would *not* override a reactive screening test (except for syphilis).

> *Example:* You perform a confirmatory test on a potential donor who has tested reactive for Hepatitis B surface antigen on an enzyme immunoassay. The confirmatory test is negative. Despite the negative confirmatory test, you determine the donor to be ineligible because the screening test was reactive.

Hepatitis B surface antibody test (anti-HBs): If you obtain a reactive anti-HBs test in the absence of any other markers for Hepatitis B infection, the donor may be eligible.

> *Example:* Your contract laboratory routinely performs 3 different tests for HBV: HBsAg, anti-HBc, and anti-HBs. You have a donor who is negative for HBsAg and anti-HBc, but 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.

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 V.A. (§ 1271.85(b)). You must use an FDA licensed, cleared, or approved test where such a test is available (§ 1271.80(c)).

   We recommend that you use the tests listed in parentheses:

   a. Human T-lymphotropic virus, types I and II (FDA-licensed screening test for anti-HTLV I/II)) (Refs. 60, 61)
   b. Cytomegalovirus (FDA-cleared screening test for anti-CMV).

Special note on CMV: CMV is not a relevant communicable disease or disease agent. However, establishments are required to test donors of viable, leukocyte-rich cells or tissues for CMV. A donor who tests reactive for CMV is not necessarily ineligible to donate HCT/Ps. You must establish and maintain an SOP governing the release of HCT/Ps from donors whose specimens test reactive for CMV (§ 1271.85(b)(2)). We recommend that the SOPs be based on current information on the potential for disease transmission from the type of HCT/P to be made available for use and that the SOP limit use of an HCT/P based on the CMV-reactive status of the recipient.

2. FDA believes that examples of viable, leukocyte-rich cells or tissue include, but are not limited to:

    - hematopoietic stem/progenitor cells
    - semen

    FDA recommends that you consider cells and tissues to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing may remove leukocytes.

3. FDA believes that examples of cells or tissue that are not both viable and leukocyte-rich include, but are not limited to:

    - corneas
    - skin
    - heart valves
    - dura mater
    - bone
    - tendons
    - ligaments
    - cartilage
    - oocytes
    - embryos

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

Currently, FDA does not recommend testing for TSE. Although reagents for Protease-Resistant Prion Protein (PrP^{Res}) testing are available from certain research laboratories, this testing is currently a research/investigational-use tool. Because there is no FDA-approved PrP^{Res} test marketed for the screening of CJD in brain tissue, FDA does not recommend its use.

FDA made recommendations for screening donors for TSE in the draft "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. 3). We intend to issue a single final guidance document that incorporates the guidance on CJD and vCJD into a final guidance on donor eligibility determination.

In addition, 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, we recommend that 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.

VI. ADDITIONAL SCREENING AND TESTING REQUIREMENTS FOR DONORS OF REPRODUCTIVE CELLS AND TISSUES (§§ 1271.75, 1271.80, 1271.85, AND 1271.90)

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

The regulations do not require screening and testing of the donor of reproductive cells or tissue who is a sexually intimate partner of the recipient (§ 1271.90(a)(2)). These individuals are excepted from the screening and testing requirements of anonymous and directed donors. Special label requirements apply in this instance (§ 1271.90(b)), and they are discussed in section VII.

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

Reproductive HCT/P donors who are not sexually intimate partners are subject to the screening required for all HCT/P donors and, if applicable, the screening requirements for viable, leukocyte-rich cell and tissue donors. In addition, 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*.

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, you must test the donor of reproductive cells or tissue 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, 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)).

Exception from testing requirement:

If the reproductive cells or tissue are procured 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 these tests are not required. (§ 1271.85(c))

Example: FDA believes that the retrieval of oocytes by laparoscopic methods would ensure freedom from contamination of the cells or tissue by infectious disease organisms that may be present in the genitourinary tract. However, most oocyte retrievals are not performed by laparoscopic methods, but rather through the vagina.

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

At least 6 months after donation, you must collect a new specimen from the donor and repeat all 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.

Example: A donor tests negative for HBsAg and Hepatitis B core antibody. He is retested 6 months later, and is still negative for HBsAg, but is reactive for Hepatitis B core antibody. The donor is ineligible.

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.

F. Are you required to screen and test a donor of reproductive HCT/Ps for communicable disease agents and diseases if the HCT/Ps were initially collected for use in a sexually intimate partner, but subsequently intended for anonymous or directed donation?

Yes. When reproductive HCT/Ps are originally collected for use in sexually intimate partners, and then a decision is made to donate these HCT/Ps for anonymous or directed use, all screening and testing requirements in §§1271.75, 1271.80, and 1271.85 for screening and testing of anonymous and directed donors would apply. The only exception is in situations as described in § 1271.90 (a)(3) (See section VII.A.).

Example: Sexually intimate donors have cryopreserved embryos, ova, or semen, and decide to donate those tissues to anonymous or directed recipients. They would then be considered either anonymous or directed donors.

- To be able to donate an embryo, both donors would have to be initially screened and tested at the time of the in vitro fertilization treatment cycle. The male partner would also have to be retested at least six months later in the case of an anonymous donation.
- In the case of semen initially stored for the sexually intimate partner's use and then donated, the requirements for directed or anonymous donation of semen would apply.
- We recommend that this information be included with the informed consent at the time the HCT/Ps are collected, so that sexually intimate donors understand the restrictions that would apply to a directed or anonymous donation if the donors do not consent to be screened and tested.

Another example is the case of an individual who cryopreserves his semen for donation in the future to a sexually intimate partner, directed recipient, or anonymous recipient.

- If the semen were donated in the future to a sexually intimate partner, no screening or testing of the donor would be required.
- If the semen were used as a directed donation, then only initial screening and testing of the donor would be required.
- If the semen is to be donated anonymously, initial screening and testing of the client depositor, six-month quarantine of the semen, and retesting of the donor would be required.
- We recommend that this information be included with the informed consent at the time the semen is donated so that the donor understands the restrictions that apply to a directed or anonymous donation if the donor does not consent to be screened and tested.

VII. EXCEPTIONS

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. FDA understands 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 container, or (2) a printed label affixed as a tie-tag to the immediate container of the HCT/P.

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

There are three situations in which you are not required to make a determination of donor eligibility or to perform donor screening and testing. Special label requirements apply if you do not screen and test.

Donor eligibility determinations are not required for:

1) Cells and tissue for autologous use;
2) Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or
3) Cryopreserved cells or tissue for reproductive use, originally excepted under (1) and (2) at the time of donation, that are subsequently intended for directed donation, provided that

    (i) 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
    (ii) appropriate measures are taken to screen and test the donor(s) before transfer to the recipient.

This exception addresses the situation where the donor(s) was not screened and tested at the time of the donation and where the donor(s) cannot make additional donations (perhaps because 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(s) wishes to make a directed donation of the cryopreserved semen or embryos to someone the donor(s) knows. Under these circumstances, we recommend that the semen or embryos be cryopreserved for at least 6 months and that when the decision is made to donate, the donor(s) be screened and tested, and the directed donation 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. (See VII.C.2.)

If the donor(s) cannot be tested due to death or inability to locate the donor(s), FDA recommends that you use a recent specimen from the donor(s) to perform

the testing required under § 1271.85(a) through (c). (See section IV.E.) If you cannot locate for testing a specimen from the donor(s) collected at or after the time of donation, FDA believes that appropriate measures could not be taken to test the donor(s), and that this exception would not apply.

To meet the donor screening requirement, 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).

Special label requirements (§ 1271.90(b)):

- If the HCT/Ps are stored for autologous use, then you must label the HCT/Ps "FOR AUTOLOGOUS USE ONLY."

- If you do not test and screen a donor, then you must label the HCT/Ps from that donor "NOT EVALUATED FOR INFECTIOUS SUBSTANCES." This requirement applies even if you perform some testing and screening, but not all that would otherwise be required for the donor of the same type of cells or tissue.

  Example: A man wishes to donate semen for use in his wife. You test the man for HIV-1 and HIV-2 before he donates the semen but do not test for any of the other relevant communicable diseases for which anonymous or directed sperm donors would be required to be tested. You must label the semen "NOT EVALUATED FOR INFECTIOUS SUBSTANCES."

- 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, you must label the HCT/P with the Biohazard legend shown in § 1271.3(h).
- If reproductive tissue is being donated to a directed recipient under § 1271.90(a)(3), you must label the HCT/P, "Warning: Advise patient that donor screening and testing were not conducted at the time of donation."

B. Can cells or tissue from a donor ever be used before the donor eligibility determination is completed?

Yes. We do not prohibit such use if there is a documented urgent medical need, but you must comply with the following labeling and authorization requirements (§ 1271.60(d)).

1. If an HCT/P is made available based on physician's request for urgent medical use before completing the donor-eligibility determination, you must document the physician's request 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 (This activity may be performed at the time that the initial consent for the procedure is obtained); and
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.

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

Yes. We do not prohibit the use of an HCT/P from a donor who has been determined to be ineligible, based on required testing and/or screening, in three instances:

1. the HCT/P is for allogeneic use in a first-degree or second-degree blood relative;
2. the HCT/P consists of reproductive cells or tissue from a directed donor; 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)).)

Any 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 test results, "WARNING: Reactive test results for (*name of disease agent or disease*)." The records required under § 1271.55 (§ 1271.65(b)) must accompany the HCT/P. The records required under section § 1271.55 (Section II.F. 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 instances, you must document that you notified the physician using the HCT/P of the results of screening and testing (§ 1271.65(b)).

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.

D. Are there any other uses for human cellular and tissue-based HCT/Ps from donors determined to be ineligible?

Yes. You are not prohibited from using such HCT/Ps for ***nonclinical*** uses, so long as they bear the Biohazard legend and are labeled "For Nonclinical Use Only" (§ 1271.65(c)).

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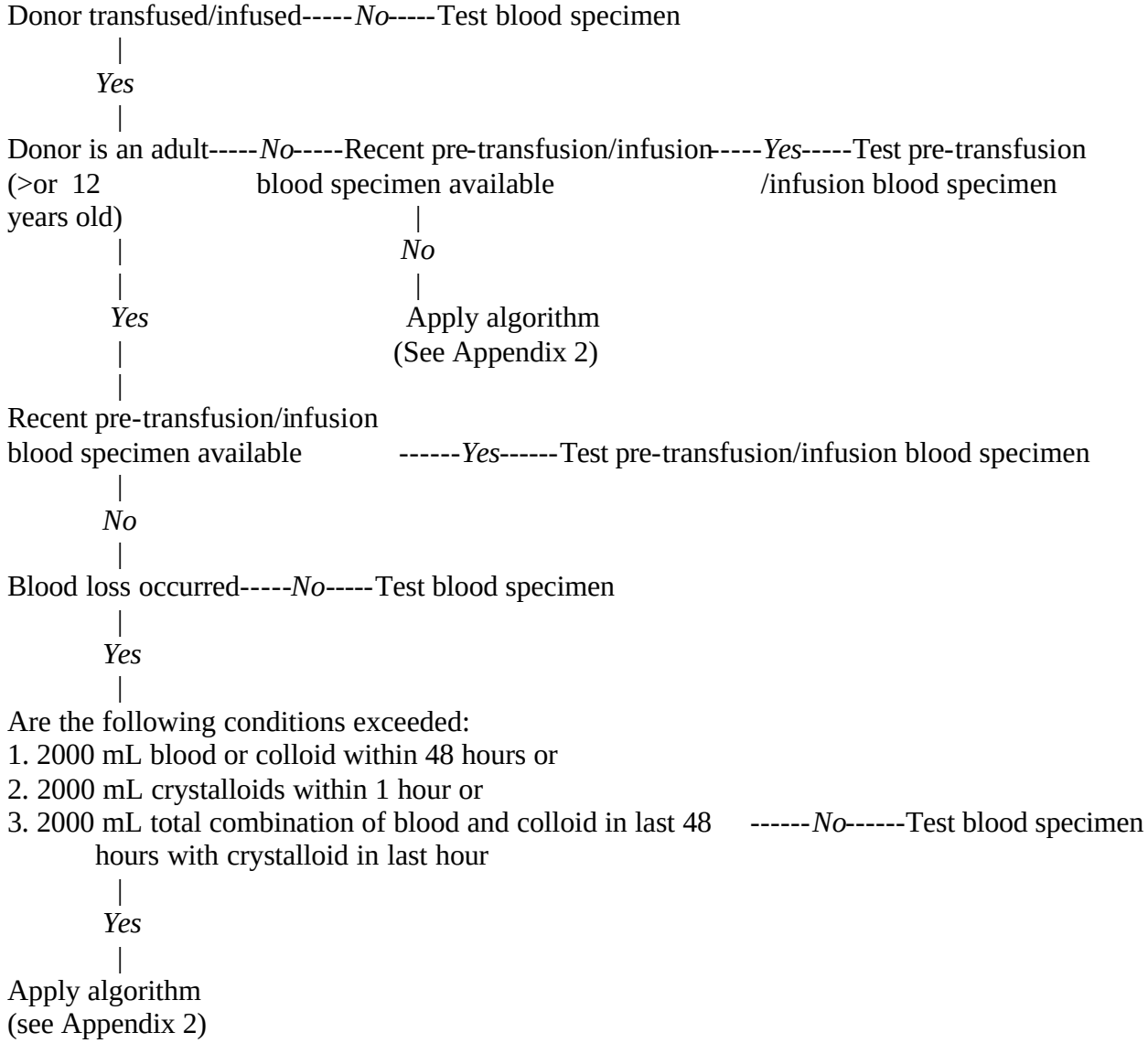
APPENDIX 1

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 both 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.