

**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES  
ADVISORY COMMITTEE MEETING**

**28- 29October2010**

**Issue Summary**

**Informational Topic:** FDA's Geographic Donor Deferral Policy to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products and Human Cells, Tissues and Cellular and Tissue-based Products

**Issue:** FDA wishes to update the Committee on the current regulatory considerations relating to Relevant Communicable Disease Agents and Diseases (RCDADs), of which TSEs are a part, for human cell, tissue, and cellular and tissue-based products (HCT/Ps), and also would like to identify current criteria that would render an HCT/P donor ineligible as a result of TSE risk. There is no decisional issue for the committee at this time.

**Regulatory Background:**

The Office of Cellular, Tissue and Gene Therapies (OCTGT) within CBER regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) in order to prevent the introduction, transmission, or spread of communicable diseases. HCT/Ps cover a broad range of individual products. The regulations define HCT/Ps (21 CFR 1217.3(d)) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Donors of HCT/Ps may be either living or deceased (i.e., cadaveric). Examples of HCT/Ps include bone, ligament, skin, dura mater, heart valve, and cornea from deceased donors; hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, cells transduced with gene therapy vectors, epithelial cells on a synthetic matrix, and semen or other reproductive tissue from living donors.

The following articles are **not** considered HCT/Ps:

- Vascularized human organs for transplantation;
- Whole blood or blood components or blood derivative products subject to listing under 21 CFR § 607 and 207, respectively;
- Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;
- Minimally manipulated bone marrow for homologous use and not combined with a drug or a device (except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

- Ancillary products used in the manufacture of HCT/P;
- Cells, tissues, and organs derived from animals other than humans; and
- In vitro diagnostic products as defined in 21 CFR §809.3(a).

### **Relevant Communicable Disease Agents or Diseases and Donor Screening**

HCT/Ps carry the risk of communicable disease transmission from the donor to the recipient. To minimize this risk, FDA has established regulatory requirements designed to prevent the introduction, transmission, or spread of communicable disease by screening and testing the donor, and ensuring that the cells or tissues are not contaminated during recovery, processing, storage or distribution.

Individuals who have communicable diseases that their donated tissues can transmit to transplant recipients are not eligible to serve as donors. In accordance with the risk-based approach developed for 21 CFR Part 1271 certain exceptions are made for use of HCT/Ps from donors who are determined to be ineligible. These include HCT/Ps from a:

- First degree or second degree blood relative for hematopoietic stem cell donors,
- Directed (known) reproductive donors
- Donors where there is a documented urgent medical need

In order for there to be a requirement to screen or test HCT/P donors for an infectious agent, that agent must be considered by FDA to be a relevant communicable disease agent or disease (RCDAD). RCDADs are designated two ways in the regulations; some diseases are specifically listed in the regulation 21 CFR §1271.3(r)(1), while others must meet certain criteria, listed in 21 CFR §1271.3(r)(2) to be considered a RCDAD. The provisions in 1271.3(r)(2) were established to allow FDA to address emerging infectious diseases.

Disease agents specifically listed in 21 CFR 1271.3(r)(1) include the following for all HCT/Ps:

- 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 to the above list of RCDADs for all HCT/Ps, a communicable disease agent or disease meeting the following criteria (Sec. 1271.3(r) (2)), but not specifically listed, is relevant if it is one:

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

- i. is potentially transmissible by an HCT/P; and
  - ii. either (1) has sufficient incidence and/or prevalence to affect the potential donor population (Sec. 1271.3(r)(2)(i)(B)(1)), or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (Sec. 1271.3(r)(2)(i)(B)(2));
- b. That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (Sec. 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 (Sec. 1271.3(r)(2)(iii)).

The following are additional RCDADs for all HCT/Ps that were added according to the 1271.3(r)(2) definition:

- West Nile Virus;
- Sepsis; and
- Vaccinia (the virus used in smallpox vaccine).

## Current requirements for Donor Screening and Testing

Relevant communicable disease agents or diseases for which a donor must be screened or screened and tested include:

Agent	HCT/Ps for which evaluation is required	Screening	Testing
HIV-1 and -2	All	X	X
Hepatitis B	All	X	X
Hepatitis C	All	X	X
Syphilis	All	X	X
TSE*	All	X	
WNV	All	X	
Sepsis	All	X	
Vaccinia (recent smallpox vaccination)	All	X	
HTLV-I and –II	Viable, Leukocyte-Rich	X	X
CMV**	Viable, Leukocyte-Rich		X
<i>Chlamydia trachomatis</i>	Reproductive	X	X
<i>Neisseria Gonorrhoea</i>	Reproductive	X	X

\* Including CJD and variant CJD

\*\* Although CMV is not a relevant communicable disease agent or disease, donors of viable, leukocyte-rich HCT/Ps must be tested for evidence of infection due to CMV in order to adequately and appropriately reduce the risk of transmission

Examples of viable, leukocyte-rich HCT/Ps include hematopoietic stem/progenitor cells and semen. FDA interprets reproductive HCT/Ps to include semen, oocytes, and embryos to which the donor contributed the spermatozoa or oocyte.

The term “donor screening” has a specific meaning in the context of HCT/Ps. In some circumstances, the term donor screening may also encompass donor testing. However, the HCT/P regulations distinguish between donor screening (medical history interview, physical assessment and medical record review) and donor testing. HCT/P donors are tested using donor screening tests.

The screening process includes:

- **Physical** assessment or examination
- **Review** of potential donor’s medical records
- **Interviewing** donor (if the donor is living) about his or her social behavior

- **Interviewing** person who is knowledgeable about the donor’s social behavior (if the donor is non-living)

The key information needed to determine donor eligibility is:

- **Relevant risk factors** (e.g., non-medical drug injection during the past five years, geographic regions living in/ visited)
- **Clinical or physical evidence** of communicable disease agents that could be transferred to a recipient of donated HCT/Ps
- **Results of testing** for relevant communicable disease agents

### **HCT/P Donor Screening for TSE, including vCJD**

The current TSE risk factors for which HCT/P donors should be excluded from donation are as follows<sup>1</sup>:

19. Persons who have been diagnosed with vCJD or any other form of CJD.

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

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

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

<sup>1</sup> Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm#DONORSCREENING1271.75>

22. Persons who have a history of CJD in a blood relative unless:

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

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

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

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

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