

**TSE ADVISORY
COMMITTEE MEETING
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ISSUE 2

**Suitability Determination for Donors
of Human Cells, Tissues, and
Cellular and Tissue-Based Products:
CJD and vCJD**

Ruth R. Solomon, M.D.—CBER

**CURRENT AND PROPOSED
FDA REGULATION**

- **Current Regulation and Guidance on:**
 - Human Tissue Intended for Transplantation
 - Licensed Biologic Products—Somatic cell/gene therapies
 - Medical Devices—Dura mater, Heart Valve Allografts, Corneal Lenticules, Combination products (Skin + matrix)
 - NOT Hematopoietic Stem Cells
 - NOT Reproductive Cells and Tissues
 - NOT Vascularized Organs; Bone marrow

**HUMAN TISSUE INTENDED
FOR TRANSPLANTATION**

- Interim Final Rule—12/14/93
- Final Rule-7/29/97(eff. 1/26/98)—Part 1270
- includes bone, ligaments, tendons, fascia, cartilage, corneas, sclera, skin
- focuses on a determination of donor suitability through donor screening (risk factors/clinical evidence) and testing for:
- HIV-1, HIV-2, HBV, HCV

**DONOR SCREENING
(Relevant medical records)**

- Donor medical history interview—a documented dialogue with an individual knowledgeable about the donor's relevant medical history/social behavior
- Physical assessment
- Review of medical records; laboratory test results; coroner and autopsy reports; other information

**CORNEAS—LEGISLATIVE
CONSENT STATE LAWS**

- Donor medical history interview is not required
- Physical assessment required
- Available information reviewed
- Corneal tissue accompanied by statement that it was determined suitable in absence of interview, and was procured under legislative consent

**GUIDANCE FOR INDUSTRY
Screening/Testing of Donors
July 1997**

- Behavioral and High Risk Information
 - “Though not directly within the scope of 21 CFR 1270, FDA is aware that screening for possible risks of exposure to CJD is recommended in industry standards”:
 - (1) diagnosis or known family history of CJD
 - (2) receipt of human pit-hGH
 - (3) receipt of dura mater transplant

**GUIDANCE FOR INDUSTRY
Processed Human Dura Mater
CDRH--July 31, 1999**

- **Donor Qualification--Neurological Screen**
 - (1) diagnosis or known family history of CJD
 - (2) receipt of pit-hGH
 - (3) receipt of dura mater transplant
 - (4) degenerative or demyelinating disease (e.g., multiple sclerosis) or other neurologic disease (e.g., senile dementia, Alzheimer's)
 - (5) death in a neurological/psychiatric hosp

**GUIDANCE FOR INDUSTRY
Recommendations, cont.**

- Gross/histological examination of brain
- Archiving of brain and dura mater
- PrP-RES testing of brain or other validated test, when available
- CJD disinfection by validated procedure
- Manufacturing controls--aseptic recovery, procedures to prevent cross-contamination (no co-mingling)
- Record-keeping; tissue tracking

**CURRENT AND PROPOSED
FDA REGULATION**

- **Proposed Regulation and Guidance**
 - "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" 2/28/97
 - a unified, tiered approach with degree of regulation based upon risk/public health concerns
 - all human cells, tissue, cellular and tissue-based products intended for transplantation under one umbrella
 - 3 proposed rules; 1 or more guidances

SCOPE

- Human tissue (bone, ligament, tendon, fascia, cartilage, cornea, sclera, skin, and including dura mater; heart valve allografts)
- Somatic cell/gene therapy
- Medical devices (corneal lenticules, combination products, e.g., skin + matrix)
- Hematopoietic stem cells from peripheral blood or placental/umbilical cord blood*
- Reproductive cells and tissue*

PROPOSED RULE September 30, 1999

- “Suitability Determination for Donors of Human Cellular and Tissue-Based Products”
 - Donor Screening (all donors) for risk factors/clinical evidence of: HIV, HBV, HCV, TSEs including CJD*
 - Donor Testing (all donors) for: HIV-1, HIV-2, HBV, HCV, syphilis*

DONOR SCREENING (Relevant Medical Records)

- Donor medical history interview--a documented dialogue with the donor, if living, or with an individual knowledgeable about the donor's medical history/relevant social behavior
- Physical Assessment/Examination
- Review of medical records; laboratory test results; coroner and autopsy reports; other information

**CORNEAS--LEGISLATIVE
CONSENT STATE LAWS**

- Proposed regulation requires a donor medical history interview, even if corneas are procured under legislative consent.
- **WHY?**-Risk factors, signs and symptoms of TSE would be expected to be uncovered in a donor medical history interview, but would be less likely to be found during other parts of the screening process.
- FDA specifically requested comments.

**COMMENTS RECEIVED ON
INTERVIEW
REQUIREMENT**

- 57 comments opposed
- 10 comments supported

**USE OF CELLS/TISSUES
FROM AN UNSUITABLE
DONOR**

- **Not prohibited IF :**
 - for family-related allogeneic use
 - reproductive tissue from a directed donor
 - there is a documented **urgent medical need:** no comparable cell/tissue is available and the recipient is likely to suffer serious morbidity without this product

Provided that:

- The product is labeled biohazard
- The physician was notified of screening/testing results
- The physician authorized the use
- The physician explained the risks to the recipient or authorized representative
- The physician agreed to obtain consent

DRAFT GUIDANCE DOCUMENT

- Under development
- May contain specific information to assist in complying with the rule
- May contain specific questions to ask regarding risk factors for and clinical evidence of TSE

**GUIDANCE FOR INDUSTRY
November 1999**

- “Revised Precautionary Measures to Reduce the Possible Risk of Transmission of CJD and nvCJD by Blood and Blood Products”
 - Recommended donor deferral criteria:
 - diagnosis (CJD or vCJD) or CJD family history
 - receipt of pit-hGH or dura mater transplant
 - 6 months or more cumulative time in UK from 1980 to 1996
 - injection of bovine insulin since 1980, unless not made from cattle in UK

**RATIONALE FOR UK
DEFERRAL OF BLOOD
DONORS**

- Variant CJD appears to be distinct from classic CJD clinically and biologically.
- UK residents have an increased risk of developing vCJD.
- Precautionary measure--lack of sufficient studies on epidemiology, risk of transmission by blood components and derivatives.

**TSEAC
RECOMMENDATIONS**

- 12/18/98--TSEAC recommended deferring donors who have traveled to or resided in UK and could have been exposed to vCJD agent, but requested additional information on the impact of deferrals on the blood supply, in order to provide more specific advice about duration of residence.

- 6/2/99--TSEAC reaffirmed recommendation, and based upon survey data, recommended 6 month cumulative residence--90% of risk captured; 2% of blood supply impacted.

QUESTION #1

- Compared to the risk of transmission of variant CJD by blood transfusion, is there a significant risk of transmission of vCJD from human cells, tissues, and cellular and tissue-based products that are transplanted, implanted, infused, or transferred?
 - What are the relative risks for different cells and tissues?

QUESTION #2

- The committee has previously assessed the risk of transmission of vCJD by blood, and has made recommendations accordingly. Based on the committee's assessment of the risk of transmission of vCJD by human cells and tissue, and considering the potential impact on supply, should FDA recommend donor deferral criteria for possible exposure to the BSE agent?

Continued

- A. If no, are there additional data that should be gathered that might alter this decision?
- B. If yes, what deferral criteria should FDA recommend:
 - Exclusion only for certain types of cells and tissues (which ones?)
 - UK? UK and France? Other BSE countries?
 - Time period of exposure—limit to 1980-1996?
 - Duration of exposure—limit to 6 months?

QUESTION #3

• If a deferral policy were to be put into place, how can information about the donor's risk factors for CJD and vCJD be obtained—is a donor medical history interview required?

– Currently, several states permit the recovery of corneas under legislative consent, whereby an interview with the next of kin may not take place. Should FDA require an interview for all cornea donors?
