

## ISSUE SUMMARY—TOPIC 4.

### TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE MEETING

July 18, 2003

#### **Methods to Decontaminate Facilities and Equipment Used in Recovery and Processing of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) to Prevent Contamination and Cross-Contamination by TSE Agents**

#### ISSUE

FDA requests advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) on specific methods to decontaminate facilities and equipment used in recovery and processing of ocular tissue, to prevent contamination and cross-contamination by TSE agents. Additionally, FDA asks whether the same methods should be applied when low-risk tissues are recovered and processed. Should these methods be used routinely, or only in cases of known or suspected TSE discovered post-donation?

#### BACKGROUND AND DISCUSSION

FDA is concerned about the transmission of TSE agents by transplantation of HCT/Ps, particularly those of high infectivity. WHO Infection Control Guidelines (1) has categorized infectivity into high, low and no detectable infectivity. The Guidelines list brain, spinal cord and eye as tissues of high infectivity. Low-infectivity organs and tissues include kidney, liver, lung, lymph nodes, spleen and placenta. Other tissues (adipose, gingival, heart muscle, skeletal muscle, peripheral nerve, glands) and secretions, including blood, are considered to have no detectable infectivity. The United Kingdom (UK) Creutzfeldt-Jakob Disease (CJD) Incidents Panel (2) has categorized infectivity into high, medium, and low categories, and has distinguished sporadic CJD (sCJD) from variant CJD (vCJD). Thus, brain, spinal cord, cranial and spinal ganglia, dura mater, optic nerve and retina are considered to be of high infectivity for both sCJD and vCJD; other eye tissues are considered to be of medium infectivity for both sCJD and vCJD; lymphoreticular tissues are of low infectivity for sCJD but of medium infectivity for vCJD. Blood and other tissues are considered to be of low infectivity for both sCJD and vCJD.

FDA currently regulates human cells and tissues (HCT/Ps) intended for transplantation, but FDA does not regulate solid organs for transplantation. Three approaches to reduce the risk of TSE transmission by human cells and tissues were discussed at the June 26, 2002, TSEAC meeting (3). One approach is to carefully screen and defer potential

HCT/P donors with risk factors for or clinical evidence of TSE disease (and to test donors, if and when validated screening tests become available). A second approach is to control the recovery and processing of HCT/Ps so as to prevent contamination and cross-contamination by TSE agents. A third approach is to introduce into the manufacture of HCT/Ps a step or steps to remove or inactivate TSE agents.

Regarding the second approach above, the committee was asked at that meeting to recommend specific methods for HCT/P recovery and processing to prevent contamination and cross-contamination by TSE agents. These methods included decontamination of instruments and surfaces used during manufacturing. The committee members did not vote on this question as stated. Instead, the Chairman posed the following revised question: Do the committee members recommend that FDA define validated inactivation procedures for TSE decontamination of instruments and surfaces, and propose methods for removal and/or inactivation of TSE agents from HCT/Ps that may be contaminated by TSE agents, differentiating high-risk from low-risk tissues? The committee voted unanimously in favor of this revised recommendation.

As a follow-up to this recommendation, FDA has presented for discussion several methods for TSE agent decontamination of facility surfaces and equipment/instruments, and now asks the committee to consider whether any of these methods should be added to the current conventional decontamination procedures for work surfaces and instruments used in recovery and processing of tissues, and, if so, whether these additional procedures should be performed routinely or only in cases of confirmed or suspected TSE. The high-infectivity tissues regulated by FDA are human dura mater and human ocular tissue. The discussion here will focus on ocular tissue, e.g., cornea and sclera, currently regulated by the Center for Biologics Evaluation and Research (CBER). At this time, processed human dura mater is regulated as a medical device by the Center for Devices and Radiological Health (CDRH), and has been previously discussed at TSEAC meetings.

TSE infectivity in ocular tissues varies (2). In scrapie-infected hamsters, the optic nerve and retina had infectivity levels similar to those in brain, i.e., high infectivity (defined as  $>10^7$  ID 50/g), while the cornea, choroid and lens had 10 to 100 times less infectivity than brain, i.e., medium infectivity (defined as  $10^4$  to  $10^7$  ID 50/g). In a single patient with vCJD, abnormal prion protein (PrP<sup>Sc</sup>) was detected in optic nerve (at 2.5% of the brain level) and retina (at 25% of the brain level), but not in sclera, aqueous and vitreous humor, lens, iris or cornea (meaning less than 0.25% of the brain level.) Both vCJD and sCJD contained similar levels of PrP<sup>Sc</sup> in these tissues. Corneas from patients with sCJD have transmitted infection to animals, in experimental studies.

Iatrogenic transmissions of CJD by corneal transplantation have included one definite case in the United States (4), one probable case in Japan (5), and one possible case in Germany (6). In addition, a case of potential transmission of CJD was reported in 1997, involving the transplantation and subsequent explantation of two corneas and sclera donated by a Scottish woman who was later determined to have CJD (7). The first case, described in the U. S. in 1974, was that of a 55-year-old woman who received a cornea from a donor who had died of a neurological illness characterized by ataxia, memory

deficit, myoclonus, and other involuntary movements. It is unlikely that this transmission would have occurred if current FDA recommendations (8) and industry standards for donor suitability had been followed (i.e., the donor would have been excluded because of clinical CNS disease of unestablished diagnosis). After the cornea was transplanted, the donor's autopsy revealed spongiform changes consistent with CJD. The recipient became ill 18 months after transplantation and died 8 months later; her autopsy revealed spongiform encephalopathy consistent with CJD. The Japanese report in 1994 was that of a 63-year-old woman who developed neurological symptoms 15 months after receiving a cornea. She died 40 months later, and her brain had histological changes typical of CJD at autopsy; full details about the donor's history were not published, but brain autopsy reportedly showed CJD changes, and a link between her disease and the previous corneal transplant was suggested. The German case, published in 1997, was that of a 45-year-old woman who developed neurological symptoms and EEG findings of CJD. She had received a corneal transplant 30 years earlier. An autopsy was refused upon her death 8 months later. Although the pathology slides from the donor were no longer available for review, the original medical records and necropsy reports indicated the donor had a 3-month history of neurological symptoms, and spongiform encephalopathy was observed at autopsy.

Under the legal authority of section 361 of the Public Health Service Act, FDA has promulgated regulations and recommendations to prevent the introduction, transmission and spread of communicable disease through cell and tissue transplantation. Some of these rules are currently in effect, and others have been proposed and are being finalized. The following is a summary of the current and proposed requirements and recommendations regarding controls for facilities and equipment used in the manufacture of HCT/Ps, designed to prevent contamination and cross-contamination.

Current regulations require that written procedures be prepared, validated, and followed to prevent infectious disease contamination or cross-contamination by tissue during processing (9). FDA guidance for industry, published in March 2002, explained the agency's current expectations with regard to viruses, bacteria and fungi, but stated that, at the time of publication, there was no adequate validation method for procedures intended to prevent contamination with TSE agents. As technology progressed and validated procedures became available, the TSE agents would be included in the requirement, when appropriate (10).

FDA's proposed rule regarding eligibility of HCT/P donors would require that all donors be screened for human TSE, including CJD, by reviewing the donor's relevant medical records and performing a donor history interview and physical assessment (11). FDA draft guidance for industry, published in June 2002, provided more detailed information about the risk factors for and clinical evidence of sCJD and vCJD (12).

FDA's proposed rule regarding current good tissue practice would require that procedures be established and maintained to ensure that HCT/Ps do not become contaminated during any steps in manufacturing, not just processing. This requirement would include tissue recovery (13). These procedures would include establishing and

maintaining effective controls over facilities, personnel, equipment, environment, incoming materials, labeling, and storage, as well as process controls and validation, record keeping, reporting of adverse reactions and product deviations, and tracking of HCT/Ps from the donor to the recipient and vice versa.

Specific to today's discussion about decontamination of facilities and equipment, FDA's proposed good tissue practices include the following requirements:

1. Facilities used for recovery and processing must be maintained and cleaned according to schedule, with documentation—e.g., ensuring that contact surfaces are cleaned with appropriate disinfecting agents, according to instructions, before each donation is processed and between donors.
2. Equipment used in recovery and processing must be cleaned, maintained, and calibrated as appropriate, according to schedule, with documentation—e.g., ensuring that refrigerators are maintained at proper temperatures; thermometers calibrated.
3. Instruments used in recovery and processing must be decontaminated and sterilized as appropriate—e.g., ensuring that decontamination solutions and procedures are adequate; sterilizer cycles are verified with each use, in that pressure, time and temperature meet established parameters, and biological indicators are used in each load.
4. Supplies and reagents must be verified to meet specifications—e.g., ensuring that reagents are not contaminated upon receipt or during use.
5. Equipment, instruments and reagents must be tracked to HCT/s.
6. Environmental monitoring must take place—e.g., ensuring that laminar flow hoods are monitored for microbial growth.

At the June 26, 2002, TSEAC meeting, the committee learned about the controls used to ensure safe corneal transplantation. In addition to donor screening for risk factors and clinical evidence of CJD, aseptic techniques are used during recovery and processing (e.g., a sterile field is established, and sterile protective apparel is worn). Most processing is performed under a laminar flow hood. The hood is cleaned with disinfectants between donors. The equipment used for processing includes sterile surgical instruments (a separate set for each donor), slit lamp and specular microscopes, and refrigerators. Decontamination of surgical instruments involves mechanical cleaning, followed by autoclaving. [It has been estimated that the first cleaning step would remove 2-3 logs of TSE agent infectivity, while autoclaving would reduce infectivity by 3-6 logs, giving a combined effect of at least a 5-log reduction. Subsequent decontamination cycles probably have much less effect (2). Microscopes cannot be autoclaved; however, the cornea is immersed in a vial of disinfectant/preservative solution during examination under the microscope, and it does not touch the equipment.]

Speakers will discuss the current procedures for decontamination and sterilization of surgical instruments, the effect of current procedures on the longevity of these instruments, and the possible use of disposable instruments when recovering and processing ocular tissue.

A WHO Consultation on Infection Control for TSEs (1) recommended general measures for cleaning instruments and the environment. Instruments should be kept moist and mechanically cleaned prior to decontamination. The WHO Guidelines listed both ineffective and sub-optimal liquid chemical and gaseous disinfectants and physical processes, and effective decontamination methods (two or more different methods used in combination, when possible). [Please refer to the Appendix for these lists.] The most effective methods involve immersion in solutions of sodium hydroxide or sodium hypochlorite for various periods of time, followed by autoclaving and then cleaning and routine sterilization. It is important to note that, in principle, sodium hydroxide does not necessarily corrode stainless steel instruments, although in practice some types of stainless steel can be damaged. Sodium hypochlorite is corrosive both to stainless steel and autoclaves, and, if used, must be completely rinsed off before autoclaving.

The WHO document also recommended that decontamination procedures for confirmed or suspected cases of TSE and persons with known risk factors for TSE be considered with regard to the level of infectivity of the tissue involved. Instruments and surfaces in contact with tissues of low or no detectable infectivity would generally undergo routine cleaning and disinfection, and no additional decontamination steps would be required, whereas contact with tissues of high infectivity would require additional decontamination procedures.

Various risk assessment models for HCT/Ps were presented at the June 2002 TSEAC meeting. It was pointed out that, while certain components of a risk assessment model are known (e.g., age-specific CJD deaths; age-specific tissue donations), other components (variables) are less well known (e.g., the extent that the amount of TSE agent might be reduced during processing steps; the extent of possible cross-contamination by instruments or equipment used during processing). Additional data about these variables are needed in order to provide more accurate estimates of risk of exposure to infected tissues.

In deliberating these issues, the TSEAC may appropriately consider—as it has for donor deferral criteria—the potential effects that various recommendations might have not only on safety but also on supply of corneas. In any estimate of the risks and benefits for a life-enhancing product, one important risk is an insufficient supply. Eye banks are small entities that may lack the resources to comply with additional requirements.

## References

1. World Health Organization Infection Control Guidelines for Transmissible Spongiform Encephalopathies—Report of a WHO Consultation, March 1999. <http://www.who.int/csr/en>
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3. Transcript of TSEAC meeting on June 26-27, 2002  
<http://www.fda.gov/ohrms/dockets/ac/cber02.htm#TransmissibleSpongiform>
4. Duffy P., Wolf J., et al. Possible person-to-person transmission of Creutzfeldt-Jakob disease. *New England Journal of Medicine*. 1974; 290:692-3.
5. Uchiyama K, Ishida C, et al. An autopsy case of Creutzfeldt-Jakob disease associated with corneal transplantation. *Dementia* 1994; 8:466-73.
6. Heckmann JG, Lang CJG, Petruch F, et al. Transmission of Creutzfeldt-Jakob disease via a corneal transplant. *Journal of Neurology, Neurosurgery & Psychiatry* 1997; 63: 388-90.
7. Hogan, RN; Brown, P, et al. Risk of prion disease transmission from ocular donor tissue transplantation. *Cornea* 1999; 18(1): 2-11. **[attached]**
8. Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation, July 1997.  
<http://www.fda.gov/cber/tissue/docs.htm>
9. Human Tissue Intended for Transplantation. Final rule. 62 FR 40429, July 29, 1997.  
<http://www.fda.gov/cber/tissue/docs.htm>
10. Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation, March 2002. **[attached]**
11. Suitability Determination for Donors of Human Cellular and Tissue-Based Products. Proposed rule. 64 FR 52696, September 30, 1999.  
<http://www.fda.gov/cber/tissue/docs.htm>
12. 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), June 2002.  
<http://www.fda.gov/cber/tissue/docs.htm>
13. Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule. 66 FR 1508, January 6, 2001.  
<http://www.fda.gov/cber/tissue/docs.htm>

## CHARGE

FDA asks the TSEAC to consider whether specific methods for decontamination of facility work surfaces and surgical instruments should be introduced at this time, to prevent contamination and cross-contamination by TSE agents during recovery and processing of ocular tissue, in cases where post-donation information reveals that a donor had or may have had a TSE. Should these methods be used routinely by eye banks, or only as additional procedures in cases of known or suspected TSE in a donor? Should these methods be used in recovery and processing of other tissues with low risk of containing TSE infectivity, either for cases of known or suspected TSE or routinely?

## QUESTIONS

Considering (a) current practices using conventional methods of decontaminating facility work surfaces and equipment/instruments used in the recovery and processing of human tissues for transplantation, (b) other precautions currently in place (e.g., aseptic techniques, donor screening for TSE), and (c) concerns about availability of tissues---

1. With regard to the recovery and processing of ocular tissue from donors later discovered to have TSE or possible TSE:
  - A. Does the committee believe that surgical instruments used in recovery and processing should be destroyed by incineration, if practical?
  - B. If destruction of instruments is not practical, does the committee believe that, at this time, there exist established, effective methods that are adequate for decontaminating instruments and surfaces?
  - C. If so, please comment on the specific methods listed in the WHO Guidelines (see Appendix). In particular, does the committee consider that only those WHO methods using sodium hydroxide or sodium hypochlorite are adequate?
  - D. If so, should such methods be employed by eye banks in the circumstance noted above?
  - E. Does the committee believe that the number of decontamination cycles performed with the instruments after the index donor tissue was recovered and processed should determine whether or not these additional specified decontamination procedures are needed? A decontamination cycle involves two stages: physical cleaning, typically using a mechanical washer/drier, followed by inactivation of any remaining infectious material, e.g., by autoclaving (2).

2. With regard to the recovery and processing of ocular tissue, should additional decontamination procedures discussed in question #1 be used routinely, i.e. even when TSE has not been suspected?
3. Should similar decontamination procedures be used for instruments and surfaces used to recover and process other tissues with a low risk of TSE infectivity from cases of known or suspected TSE?
4. With regard to the recovery and processing of other tissues with a low risk of TSE infectivity, should additional decontamination procedures be used routinely, i.e. even when TSE has not been suspected?

## **Appendix**

### **WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies**

#### ***Annex III Decontamination methods for Transmissible Spongiform Encephalopathies***

The following recommendations are based on the best available evidence at this time and are listed in order of more to less severe treatments. These recommendations may require revision if new data become available.

Annex III lists the decontamination methods recommended by the consultation in order of decreasing effectiveness.

#### **1. Incineration**

1. Use for all disposable instruments, materials, and wastes.
2. Preferred method for all instruments exposed to high infectivity tissues.

#### **2. Autoclave/chemical methods for heat-resistant instruments**

1. Immerse in sodium hydroxide (NaOH) and heat in a gravity displacement autoclave at 121 C for 30 min; clean; rinse in water and subject to routine sterilization.
2. Immerse in NaOH or sodium hypochlorite for 1 hr; transfer instruments to water; heat in a gravity displacement autoclave at 121 C for 1 hr; clean and subject to routine sterilization.
3. Immerse in NaOH or sodium hypochlorite for 1 hr; remove and rinse in water, then transfer to open pan and heat in a gravity displacement (121 C)

or porous load (134 C) autoclave for 1 hr; clean and subject to routine sterilization.

4. Immerse in NaOH and boil for 10 min at atmospheric pressure; clean; rinse in water and subject to routine sterilization;
5. Immerse in sodium hypochlorite (preferred) or NaOH (alternative) at ambient temperature for 1 hr; clean; rinse in water and subject to routine sterilization.
6. Autoclave at 134 C for 18 minutes.

### **3. Chemical methods for surfaces and heat sensitive instruments**

1. Flood with 2N NaOH or undiluted sodium hypochlorite; let stand for 1 hr; mop up and rinse with water.
2. Where surfaces cannot tolerate NaOH or hypochlorite, thorough cleaning will remove most infectivity by dilution and some additional benefit may be derived from the use of one or another of the partially effective methods listed in Section 5.1 (Table 8).