

ISSUE SUMMARY—TOPIC 1.

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE MEETING

June 26, 2002

Validation of Procedures to Prevent Contamination and Cross-Contamination with TSE Agents of Human Tissue Intended for Transplantation

ISSUE

FDA requests advice from TSEAC on measures for donor screening and tissue processing that are appropriate to prevent contamination and cross-contamination of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) by TSE agents, and on the design of scientific studies to validate clearance of TSE agents in processing.

BACKGROUND AND DISCUSSION

Classic CJD has been transmitted through the transplantation of certain human tissues, i.e., dura mater and cornea, as well as by human cadaveric pituitary-derived hormones. FDA is concerned about the actual and theoretical transmission of TSE agents by transplantation of these and other human cells, tissues, and cellular and tissue-based products (HCT/Ps). There are at least three approaches to reduce the risk of TSE transmission by such products. One is by careful screening of the potential HCT/P donor for risk factors for TSEs, and for TSE disease (including testing of the donor, if and when validated screening tests become available) and deferral of these donors. A recently published draft guidance for industry, focusing on donor screening recommendations, addresses this approach. 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 would be to introduce into the manufacture of HCT/Ps a step or steps to remove or inactivate TSE agents. FDA is asking the TSEAC to consider which of these approaches—donor eligibility, tissue recovery and processing measures and controls, and/or validated TSE clearance processes—might be appropriate to reduce the risk of contaminating or cross contaminating HCT/Ps with TSE agents.

Iatrogenic transmission of CJD through transplantation of dura mater allograft (currently regulated by FDA as a device) and cornea (regulated by FDA as a “361” tissue) has been reported. There have been more than 100 cases of transmission of CJD by dura mater allografts worldwide, including three cases in the U.S. The mean interval between receipt of dura mater and onset of disease was 8.6 years, with the longest latent period being 18.2 years (1). The first case was reported in 1987, in a 28-year-old woman who had received a lyophilized, irradiated human cadaveric dura mater graft (a product never

cleared by FDA), imported into the U.S. from Germany through Canada (2). This patient died 22 months after receiving the graft. A case in New Zealand and four cases in Spain, all involving the same brand of dura mater grafts, were subsequently reported. A second U.S. case associated with a dura mater graft in a 28-year-old woman was reported in 1994 (3). Before 1987, the involved product had been prepared using a method that commingled dura mater from many cadavers in the same container during processing. In 1998, a third U.S. case occurred in a 39-year-old woman who had received dura mater made by a different manufacturer; that dura mater had not been intentionally commingled (4). The donor had been inadequately screened, and the dura had been soaked for one hour in a solution of sodium hydroxide, but at 0.1N rather than 1.0 N as recommended by FDA. The majority of CJD transmissions from dura mater have occurred in Japan since 1985. Japan has recognized at least 67 cases – almost all in patients believed to have received dura mater made in a commingled process (5).

Transmissions of CJD by ocular tissue have included one definite case in the United States (6), one possible case in Japan (7), and one possible case in Germany (8). There was concern about the potential for transmission of CJD after the transplantation, and subsequent explantation, of two corneas and sclera donated by a Scottish woman who was later determined to have CJD (9). 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. 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 had histological changes typical of CJD at autopsy; full details about the donor were not published, but a link between her disease and a previous corneal transplant was asserted. The German case, published in 1997, was that of a 45-year-old woman who developed neurological symptoms and EEG signs of CJD. She had no family history of CJD, no genetic markers of familial CJD, and was homozygous for methionine at codon 129 of the PRNP gene on chromosome 20. She had received a corneal transplant thirty years earlier. Although the pathology slides from the donor were no longer available for review, the original medical records and necropsy reports indicated the donor had died of CJD. No autopsy was performed on the recipient.

There is no reason to believe that there would be any less risk of transmitting variant CJD by transplantation of dura mater and cornea. In addition, there is some risk of transmitting both CJD and vCJD by other tissues (10).

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 are currently in effect, and others have been proposed and are being finalized.

FDA regulations currently in effect address preventing transmission of HIV, HBV, and HCV through the transplantation of human tissue by screening and testing the potential tissue donor. Current regulations also require that written procedures be prepared, validated, and followed to prevent infectious disease contamination or cross-contamination by tissue during processing (11).

Current FDA guidance recommends excluding potential donors of tissue (musculoskeletal, ocular, integumental) who are diagnosed with sporadic CJD or who have risk factors for iatrogenic or familial CJD. In an FDA guidance for industry on screening and testing tissue donors (12), the agency recommends that the donor medical history interview include questions to defer potential donors with a diagnosis of CJD, with a known family history of CJD, or who have received human pituitary growth hormone or dura mater transplants. In another FDA guidance for industry specifically about human dura mater (13), donor evaluation includes all of the above recommendations, and in addition, FDA recommends exclusion of donors with any degenerative or demyelinating disease of the CNS and donors who died in a neurological/psychiatric hospital. This last guidance also recommends performing gross and histological examination of the brain (full autopsy) of each dura mater donor, use of processing controls such as disinfection by a method validated to reduce CJD infectivity, and the prohibition of batch processing.

In March 2002, FDA published a final guidance entitled “Validation of Procedures for Processing of Human Tissues Intended for Transplantation” (14). This guidance reminds all tissue establishments of the requirement to prepare, validate, and follow written procedures to prevent contamination or cross-contamination with infectious disease agents during tissue processing, and explains that contamination may be caused by a variety of infectious disease agents, including viruses, bacteria, fungi, and TSE agents (TSE-associated prions). The document defines validation and gives examples of methods to obtain validation data. FDA now expects validation of methods used to prevent contamination and cross-contamination of HCT/Ps with viruses, bacteria, and fungi. Validation of methods to prevent contamination or cross-contamination by TSE agents would be required routinely if and when such methods are agreed upon by scientific experts and become available.

Proposed FDA regulations (15) would require screening, to include obtaining a medical history for all potential donors regarding risk factors and clinical evidence of relevant communicable diseases, including HIV, HBV, HCV, and TSEs (e.g., CJD), and screening some donors of particular cells and tissues for other relevant diseases. The proposed regulations would also require testing the blood of all donors for relevant communicable diseases, including HIV, HBV, HCV, and syphilis, and testing some donors of particular cells and tissues for other relevant diseases. Other proposed regulations (16) would define current good tissue practices (cGTPs) and require that cGTPs be followed during all aspects of manufacture of the cells or tissues. These practices 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. More specifically, the proposed GTP rule states that human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacture of the HCT/P. However, the proposed rule would allow a cell or tissue establishment to request an exemption or alternative from any GTP requirement, provided that, after reviewing valid scientific data submitted in the request, FDA finds that the exemption or alternative is consistent with the goals of preventing the introduction, transmission, and spread of communicable disease. If a request for an exemption from the pooling prohibition were to be submitted, FDA would weigh the potential increased risk of contamination and cross-contamination with emerging infectious disease agents (e.g., TSE agents) against the potential benefit of improved elimination of conventional infectious disease agents (e.g., viruses, bacteria, or fungi) in determining whether or not to grant the request. The donor eligibility and the GTP proposed rules are being finalized.

In the process of developing guidance on TSE issues, FDA requests advice on any additional measures for donor screening and tissue processing that TSEAC considers to be appropriate. The committee might consider, among other matters, risk assessment, including models for estimating the risk of transmitting TSE by human tissue, the possibility of requiring autopsy for each donor or the potential value of post-mortem transorbital needle biopsy in situations where full brain autopsy may not be feasible, lessons learned from batch processing of human pituitary growth hormone, effects on risk from limiting batch size, the value of requiring single-donor aseptic recovery and processing techniques, specified methods of decontamination of facilities and equipment, process validation data that are currently required by FDA for processes used to clear conventional infectious agents, validation data from several large tissue processors, and TSE clearance studies in experimental models.

In deliberating these issues, the TSEAC may consider, in the context of risk and benefit analysis, the potential effects that various FDA policies might have not only on safety but also on supply of HCT/Ps.

References

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11. Human Tissue Intended for Transplantation. Final rule. 62 Federal Register 40429-40447; July 29, 1997.
12. Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation, July 1997.
13. Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater, October 1999.
14. Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation, March 2002. (***enclosed**)
<http://www.fda.gov/cber/tissue/docs.htm>
15. Suitability of Donors of Human Cellular and Tissue-Based Products; Proposed Rule (64 FR 52696) September 30, 1999. (***enclosed**)
<http://www.fda.gov/cber/rules/suitdonor.pdf>.
16. Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule (66 FR 1508), January 6, 2001. (***enclosed**)
<http://www.fda.gov/cber/rules/gtp010801pr.htm>

CHARGE

FDA asks the TSEAC to evaluate the appropriateness of several measures and controls to prevent the transmission of TSEs to the recipients of human cells, tissues, and cellular and tissue-based products. The TSEAC might consider whether FDA should recommend imposing donor eligibility criteria in addition to screening potential donors for CJD, vCJD, and risk factors for these diseases, as discussed in more detail in topic 2 below, such as setting an upper age limit for donors or excluding donors who died of head trauma. FDA recognizes that recommending such exclusions might seriously reduce tissue supply.

The TSEAC might also consider whether the agency should recommend that an autopsy—or failing that, a brain biopsy validated to show that it is predictive of an autopsy diagnosis of TSE—be performed on some or all HCT/P cadaveric donors.

In addition, FDA asks the TSEAC to consider the appropriateness of requiring that specified methods be introduced to prevent contamination and cross-contamination by TSE agents during recovery and processing of HCT/Ps. Should the agency recommend or require any specific procedures to decontaminate surfaces and instruments, or require manufacturing steps to remove and/or inactivate TSE agents in HCT/Ps? Should co-mingling of HCT/Ps from different donors during manufacturing ever be permitted? If so, what controls should FDA require in assessing whether a request for an exemption from the proposed pooling prohibition should be granted?

Finally, FDA asks the TSEAC to comment on the design of TSE agent clearance studies validating the effectiveness of methods to prevent contamination and cross-contamination of HCT/Ps by TSE agents.

QUESTIONS

1. Which of the following measures and controls is (are) appropriate to prevent TSE agent transmission to the recipients of human cells, tissues, and cellular and tissue-based products?

A. Recommend additional donor eligibility criteria:

- Upper age limit
- Head trauma exclusion
- Negative brain autopsy or biopsy

B. Recommend specified methods for HCT/P recovery and/or processing to prevent contamination and cross-contamination:

- Decontamination of instruments and surfaces used for recovery and processing
- Methods for removal and/or inactivation of TSE agents from accidentally contaminated HCT/Ps
- Single-donor aseptic processing or permit pooled processing under certain circumstances with adequate controls

C. Other

2. Please comment on the design of a satisfactory TSE agent clearance study for HCT/Ps, in terms of the following criteria:

- A. Suitable TSE agent strains and animal models
- B. Accept measurement of abnormal forms of prion protein alone or require assays for infectivity

- C. Accept substantial reduction (how much?) or require complete elimination of detectable prion protein and/or infectivity
- D. Accept a single validated method or require that more than one validated method for eliminating TSE agents be included in the study
- E. Other