

## ISSUE SUMMARY—TOPIC 4 Part 2

### TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE MEETING

July 18, 2003

#### **Cleaning Procedures for Equipment Used in Manufacture of Plasma Derivatives, to Reduce the Theoretical Risk of Transmitting TSE Agents**

##### **Background**

##### Use of Common Equipment for Manufacturing of U.S. and European Plasma in the Context of vCJD Risk

Many major plasma derivative manufacturers are licensed to use the same equipment to produce plasma derivatives from U.S.-licensed plasma for the U.S. market and from European plasma for non-U.S. products. The risk of carryover contamination of any kind from one manufacturing lot to another is minimized by rigorous cleaning of common equipment between lots and use of dedicated tangential-flow membranes and chromatographic resins. All licensed facilities use specifically validated, FDA-approved cleaning methods. Typical practices include cleaning of tanks and other stainless steel equipment with solutions of sodium hydroxide and/or sodium hypochlorite followed by rinsing. These procedures often are carried out at elevated temperatures. Cleaning effectiveness is usually assessed by testing for residual protein or total organic carbon and/or by checking ionic strength of rinsing solutions. In some cases, notably columns that are reused for affinity chromatography, only mild cleaning methods can be used, so as to maintain column integrity. Common equipment is used in the preparation of anti-hemophilic factor (AHF), intravenous immune globulin (IGIV), albumin, and other plasma derivatives. Validated methods for decontamination of equipment potentially exposed to TSE agents have not yet been established, in part because the relevant scientific information has not been generated. At this meeting, the committee will hear presentations about ongoing studies that are relevant to equipment decontamination.

##### Comparison of U.S. and European Donor Deferrals for vCJD Risk

Donor deferrals for risk of exposure to vCJD in the U.S. differ from those in Europe (see below).

	<u>U.K</u>	<u>France</u>	<u>Europe</u>
U.S. Source Plasma <sup>2</sup>	≥ 3 months <sup>1</sup>	≥ 5 years <sup>4</sup>	no deferral

<sup>1</sup> For residence between 1980 and 1996

<sup>2</sup> Plasma collected by plasmapheresis

	<u>U.K</u>	<u>France</u>	<u>Europe</u>
U.S. Recovered Plasma <sup>3</sup>	≥ 3 months <sup>1</sup>	≥ 5 years <sup>4</sup>	≥ 5 years <sup>4</sup>
Europe Plasma for fractionation	≥ 6 months- 5 years <sup>1,6</sup>	0 – 6 months <sup>5</sup>	no deferral

U.S. Source Plasma donors are not deferred for residence in most European countries, based both upon lower estimated risk of human dietary exposures to the BSE agent in other parts of Europe compared to the UK and France and upon the experimentally demonstrated ability of manufacturing processes to remove TSE agents. These laboratory-based studies use samples of product intermediates spiked with TSE agents that are then subjected to the manufacturing step being studied for TSE clearance. Types of processes that can remove TSE agents under specific conditions include some precipitations, some filtrations, and the use of chromatographic resins. However, it remains the case that donors residing in Europe may have an increased risk of exposure to the BSE agent, compared to donors in the U.S., and that plasma manufactured from European donors may have a slightly higher chance of containing a donation from someone who is incubating vCJD. The risk that a European donor may be incubating vCJD is unknown. The vCJD epidemic in the UK is believed to be declining (Lancet. 2003 Mar 1; 361(9359): 751-2). To date, 132 deaths from probable or definite vCJD have occurred in the UK, 6 in France, and single cases in Italy and Ireland ([http://www.doh.gov.uk/cjd/cjd\\_stat.htm](http://www.doh.gov.uk/cjd/cjd_stat.htm); <http://www.who.int/mediacentre/factsheets/fs180/en/>; [http://www.invs.sante.fr/publications/mcj/donnees\\_mcj.html](http://www.invs.sante.fr/publications/mcj/donnees_mcj.html)).

### Blood and Blood Component Risk of TSE Infectivity

To date, no transmission of vCJD has been attributed to exposure to human blood, plasma, or plasma derivatives. The UK CJD Incidents Panel has categorized blood as a low-infectivity tissue (<http://www.doh.gov.uk/cjd/consultation>). Experimental studies with animal TSE models suggest that blood and plasma may contain low titers of TSE agents. The possibility exists that plasma from a European donor incubating vCJD might

<sup>3</sup> Plasma from units of whole blood

<sup>4</sup> For residence from 1980 to the present

<sup>5</sup> Most European countries do not have a donor deferral for France; 2 countries have a 6 month donor deferral for Ireland and France, and one country has a 6 month deferral for France alone.

<sup>6</sup> The majority of the European countries have a 6-month deferral for UK between 1980-1996.

be processed with equipment that is subsequently used to process plasma for U.S.-licensed products.

In June 2001, the TSEAC was asked whether FDA should be concerned about the potential for cross-contamination of U.S. products with the vCJD agent from European plasma during plasma fractionation. The TSEAC was also asked whether any scientifically supported measures should be taken to minimize such risks. The committee heard presentations about methods and models for TSE removal and inactivation. Industry presented information that demonstrated the complexity of manufacturing lines. At that time, the Plasma Protein Therapeutics Association (PPTA) stated that about 50% of IGIV distributed in the U.S. was manufactured in facilities that also manufacture separate batches of non-U.S. plasma for the worldwide market. Some unique products, such as fibrin sealant, were manufactured only in facilities that also process non-U.S. plasma. PPTA contended that the manufacturing of plasma derivatives in dedicated lines reserved for U.S. plasma would not be feasible, because it would require construction of new facilities and regulatory approvals that might take years. The costs would be substantial, and disruption of plasma derivative supplies would be inevitable. The TSEAC commented that, based on existing studies, the risk of vCJD transmission by blood and plasma derivatives remains unknown but is probably very low. They also stated that precautions should be taken but that complete segregation of manufacturing lines for European and U.S. plasma is unwarranted, given the very low risk of significant cross-contamination. The TSEAC also urged development of validation methods to assess the removal of TSE agents, in order to provide information about the ability of cleaning methods under specific (context-dependent) circumstances (<http://www.fda.gov/ohrms/dockets/ac/cber01.htm#Transmissible%20Spongiform>).

In this session the committee will hear an update of methods and models to address the scientific question of how best to prevent TSE cross-contamination of batches during manufacturing of products derived from human plasma, a low-risk tissue. Specific to today's discussion of facilities and equipment used in plasma fractionation, the committee is asked to consider the following points:

- ?? The risk that the starting material (plasma) might be contaminated with the agent of vCJD
- ?? The likelihood that existing, conventional cleaning methods, especially those that include exposure to solutions of sodium hydroxide and/or sodium hypochlorite as cleaning agents for stainless steel equipment—methods that are validated by assessment of remaining total protein and/or total organic carbon—may clear contaminating TSE agents
- ?? The removal of TSE infectivity by precipitations, filtrations, and discarding of resins during plasma processing
- ?? Experimental observations that TSE infectivity may be retained by chromatographic columns
- ?? The current state of knowledge about effective cleaning methods for TSE agents

## Questions

Considering current facility cleaning practices, the low risk of vCJD infectivity in human plasma, and the ability of plasma fractionation methods to clear TSE agents:

1. Does the committee feel that current facility cleaning methods, e.g., the use of solutions of sodium hydroxide or sodium hypochlorite followed by extensive rinsing cycles, are adequate to minimize the possibility that an infectious dose of the vCJD agent may be carried over from one manufactured lot into the next?
2. Are the available scientific data sufficient for FDA to recommend specific methods for cleaning of equipment used in the manufacture of plasma derivatives with respect to TSE agent clearance or inactivation?
  - a. If so, please identify which methods can be recommended.
  - b. If not, please describe what additional studies would assist in development of such recommendations.