Transmissible Spongiform Encephalopathies Advisory Committee
Meeting on June 28&29, 2001

Topic 2. Safety of FDA-Regulated Plasma Derivatives Prepared in Establishments Proposing to Use, on the Same Manufacturing Line, Plasma Which Does and Plasma Which Does Not Comply with Anticipated U.S. Standards with Regard to Donor Deferral for vCJD Risk Factors

Issue: FDA-licensed fractionators currently may use common manufacturing lines to process European and U.S. Plasma. If, as a vCJD precaution, the FDA recommends deferral of blood and plasma donors based on residence or travel in Europe, the agency will need to consider the safety implications of use of common manufacturing lines to process plasma which does and which does not meet FDA donor deferral recommendations for vCJD.

Background:

Most major manufacturers are licensed to use common equipment for the manufacture of plasma derivatives from U.S.-licensed plasma (for the U.S. market), and for European plasma, for non-U.S. products. The equipment is cleaned between sequential manufacturing campaigns[1], according to approved standard operating procedures. Common equipment is used in the preparation of anti-hemophilic factor (AHF), intravenous immune globulin (IGIV), albumin, and other plasma derivatives. A substantial proportion of the U.S. plasma derivative supply, including some unique products, may be affected by the issue under discussion. Some IGIV products, and potentially other investigational products which are under study for potential licensure in the U.S. also could be affected.

Since November 1999, FDA has recommended that blood and plasma not be collected from donors with a history of six or more months of residence or travel from 1980 through 1996 in the United Kingdom. Plasma from the United Kingdom also is not used for fractionation anywhere in Europe. At meetings in June 2000 and January 2001, the TSEAC was asked to review the current FDA policy in the context of current scientific data. At the January 2001 meeting, the TSEAC articulated concerns about the increasing BSE epidemic in Europe, and vCJD cases in France among people who had not lived in the United Kingdom. The TSEAC recommended deferral of donors who had lived in France, Portugal, or Ireland for 10 years or more between 1980 and the present, for risk of vCJD. FDA has considered this recommendation and, on June 28th, the TSEAC will be asked to provide additional advice on whether a donor deferral policy based on risk of BSE exposure should be adopted for all of Europe.

To date, no transmission of vCJD by blood or plasma derivatives has been reported. However, the possibility exists that plasma from a vCJD-incubating European donor could be processed with equipment that subsequently is used for processing of U.S.

[1] The same manufacturing lines may be used sequentially for different batches (pools) of plasma. A "campaign" refers to processing of an individual batch (pool) of plasma into plasma derivatives.

plasma, for U.S. licensed products. FDA seeks to be advised about a) the significance of the theoretical risk of contamination of U.S. products with vCJD based on plasma derivative manufacturing using common lines, and b) any additional precautions that should be taken to minimize such risks.

The scheduled presentations will provide the following information: (1) Review of the issue, with introduction of strategies to address the potential risk of vCJD contamination of U.S. products, (2) Review of scientific information about decontamination methods for TSEs, with attention to BSE/vCJD, and (3) Industry presentations on risk assessments, cleaning and decontamination methods currently in place, plans for cleaning and decontamination method validation for TSEs, studies relevant to TSEs in the setting of current common equipment usage, and effects upon supply of plasma derivatives in the U.S. and in Europe, if process changes or dedicated (i.e. separate) manufacturing lines were to be instituted.

Discussion:

Although epidemiological and laboratory-based studies have been negative to date, the risk of vCJD transmission by blood and plasma derivatives remains unknown. However, a single case of transfusion-transmission of BSE has been reported in a sheep, raising concerns that vCJD blood could be infectious (Lancet 356:999-1000, 2000 [In package for Issue 1]).

Abundant evidence exists that classical CJD transmission by blood is rare or non-existent. Furthermore, laboratory studies with several different TSE agents have suggested that plasma fractionation results in reduction of TSE infectivity (Refs. 1-3). However, little information is available to determine whether the vCJD/BSE agent behaves similarly to other TSE agents with regard to removal by plasma processing. Additionally, it is not well understood whether susceptibility of the vCJD agent to inactivation is similar to that of more thoroughly studied TSE agents. It is well established, however, that different TSE strains may demonstrate different levels of resistance to inactivation procedures. In the context of these uncertainties, FDA has chosen to address the issue of manufacturing equipment which could be exposed to vCJD contamination from European plasma, and which is subsequently used for U.S. products. The options to be considered include:

- Risk assessment to determine likelihood of vCJD contamination in U.S. products, from European plasma, without further action required if risk determined to be low. Currently, facility cleaning occurs between campaigns of U.S., and non-U.S. plasma. Some of these procedures already include the use of 1N to 4N NaOH. The infectivity of vCJD plasma, the prevalence of vCJD in European donors, and the ability of fractionation processes to remove the vCJD agent are all unknown. Is it possible to use risk assessments to determine the level of concern, and the level of action advisable, in addressing the question of cross-contamination? What parameters, in addition to those above, should be considered in risk assessment? Can sufficiently low risk assessment substitute for taking other measures? In conjunction with low

risk assessment and in the absence of other actions, should a labeling statement be devised for such products, concerning theoretical risks of contamination with the vCJD agent?

- Development and validation by industry of cleaning/decontamination procedures to remove the vCJD agent, to be used between U.S. and non-U.S. plasma campaigns. This approach could require some time for implementation, and repeated exposure of equipment, such as columns, to harsh chemical treatments may not be feasible. Does the committee think that FDA should work with industry on cleaning validation for TSEs as an alternative to the use of separate manufacturing lines? How relevant are non-BSE models in studies of vCJD decontamination? What, if any, short-term steps should be taken to minimize possible contamination of U.S. products with the vCJD agent? Given that there are many specific differences in manufacturing processes, and in the make-up of fractionation equipment, is enough information available for FDA to draft recommendations for such procedures, or should these be considered on a case-by-case basis?

- The use of dedicated manufacturing lines, for U.S. plasma, for U.S. products. If there is a real possibility of vCJD transmission from one plasma pool campaign to the next, the advantage of this approach is clear-cut, but there would be some attendant considerations. It is possible that implementation would take considerable time, and that U.S. plasma processing would thus be delayed, with potential for shortages of plasma derivatives. In light of the information presented, do members of the committee feel that this is a viable and important approach to be considered?

Questions for the Committee:

In the light of the TSEAC's recommendations on donor deferral for risk of BSE exposure, and considering the available scientific data on risk of vCJD from transfusion, removal of TSE agents in plasma fractionation, and inactivation of TSE infectivity by standard decontamination procedures,

1. Please comment on the significance of the vCJD risk from campaigned manufacturing involving exposure to European plasma.

2. Do the committee members believe that any additional steps should be taken at this time to address use of common manufacturing lines for European and U.S. Plasma?

3. If so, which of the following steps should FDA consider at this time?
   a. labeling to identify campaigned manufacturing involving potential exposure to European plasma
   b. use of additional decontamination procedures
   c. use of dedicated manufacturing lines
   d. other measures (please specify)

REFERENCES [included with package]

1. Brown, P., Cervenakova, L., McShane, L.M., Barber, P., Rubenstein, R., Drohan, W.N. Further studies of blood infectivity in an experimental model of tranmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans. Transfusion 1999; 39:1169-78.

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4. Rutala, W. A. and Weber, W.J. Creutzfeldt-Jakob Disease: Recommendations for disinfection and sterilization. Clin. Inf. Dis. 2001; 32:1348-56.

5. Taylor, D.M. Inactivation of transmissible degenerative encephalopathy agents: a review. The Veterinary Journal 2000; 159: 10-17.

6. Section 6, WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies, at www.who.int/emc-documents/tse/whocdscsraph2003c