

Summary and Rationale for Draft Guidance: “Revised Preventive Measures to Reduce the Possible Risk of Transmission of CJD and Variant CJD by Blood and Blood Products”

In this draft guidance document, published on August 27, 2001, FDA proposes an expansion of the currently recommended blood donor deferrals for potential exposure to Bovine Spongiform Encephalopathy (BSE) and variant Creutzfeldt-Jakob Disease (vCJD), to further reduce the possible risk of transmission of vCJD from blood and blood products. The recommendations expressed in this draft guidance reflect TSEAC opinions, as well as internal discussions within the PHS.

Background

CJD is a rare, fatal degenerative disease of the central nervous system, with a prolonged incubation period. In 1996, a new form of this disease, variant CJD (vCJD) was reported in the United Kingdom (U.K.). Since then, over 100 cases of vCJD have been diagnosed, mostly in the United Kingdom, although several have occurred in France, and among former U.K. residents. Consumption of BSE-infected cattle is believed to be the cause of human disease. The BSE epidemic began in the U.K. around 1980, and spread to Europe primarily via contaminated meat-and-bone meal exported from the U.K., which was used to feed cattle.

No cases of transmission of CJD or vCJD by human blood have been reported, and long-term epidemiological studies suggest that transmission of CJD by blood or blood products is rare or nonexistent. However, sufficient time has not elapsed for similar reassurances to be made about vCJD. vCJD differs from CJD clinically, and histopathologically. In particular, the presumed causative agent, an abnormal prion protein, accumulates at higher levels in the lymphoid tissue of vCJD patients, compared with CJD patients, thus enhancing concerns that blood of people incubating vCJD, could be infectious.

Since tests to identify donors who are incubating vCJD do not exist, the only method of reducing the risk that this agent may be present in blood or blood products is deferral of donors who may have been exposed to BSE. Based upon BSE exposure, on November 11, 1999, FDA published a guidance recommending deferral of blood and plasma donors who had resided in the U.K. for 6 months or more, from 1980 through 1996. This donor deferral was expected to remove 87 % of the BSE exposure risk (in the U.K.), with an estimated loss of 2.2% of donors. The limit of the deferral period to the end of 1996 reflected the assessment that adequate controls were implemented in the U.K. by this time to prevent entry of infected beef products into the human food chain.

Since 1999, additional events have triggered the need to consider expansion of donor deferrals. These include:

- Increasing vCJD epidemic in the U.K.
- Increasing BSE epidemic in Europe – including increased number of cases in some countries, and new countries reporting BSE
- European active surveillance programs for BSE have not been uniformly instituted, therefore epidemic size, and presence in some countries remains uncertain
- European food safety controls to prevent entry of BSE into human food have not been uniformly instituted
- Transfusion transmission of BSE (1 sheep) was been reported (Lancet 2000, 356: 999-1000). This finding supports the theoretical concern that human blood could be infectious.

The TSEAC considered new donor deferrals, which would reflect European exposure to BSE, in January, and in June 2001. As a result, FDA published this draft guidance reflecting the TSEAC deliberations of June, 2001. The new proposed donor deferrals are summarized, below. In addition, measures have been taken both within the guidance, and external to the guidance, to address concerns about the impact of European donor deferrals on the supply of blood, blood components, and plasma. These include phased implementation of deferrals, recommendations for pilot studies if more stringent deferrals are undertaken, HHS initiatives to monitor blood supply, and non-deferral of Source Plasma donors who have traveled to or lived in Europe.

Proposed Recommendations for Donor Deferrals for Risk of Exposure to BSE or vCJD:

Phase I donor deferrals, for implementation May 31, 2001, for donors of all blood and blood components

- ≥ 3 months residence in United Kingdom (U.K.) 1980- 1996
- ≥ 5 years residence in France, 1980- present
- ≥ 6 months residence in U.S. military bases North of the Alps 1980- 1990, or South of the Alps 1980- 1996 (risk from consumption of British beef purchased by the military)
- Transfusion in the U.K., 1980- present

Phase II donor deferrals, for implementation October 31, 2002, for blood, but not Source Plasma donors

- > 5 years residence in Europe 1980- present

Rationale for not Recommending Pan-European Deferral for Source Plasma Donors

The Guidance does not propose deferral of Source Plasma donors who have lived in Europe (other than the U.K. and France) for several reasons:

- Published experimental evidence shows that processes that are used in the manufacture of plasma derivatives remove TSE agents.

These processes include ethanol precipitation, PEG precipitation, depth filtration, nanofiltration, and column chromatography. Additionally, unpublished information evaluated by FDA, suggests that the vCJD agent behaves similarly to other TSE's in plasma fractionation.

- The incidence of vCJD in Europe, with the exception of France, is estimated to be low, and the current estimates suggest that at worst, the BSE epidemic in Europe is approximately 60-fold less than that of the U.K. Therefore it is estimated that the risk, if any, for transmitting vCJD by plasma, would be low for donors who lived in Europe, and that plasma processing would further reduce such a risk. The magnitude of estimated risk reduction conferred by plasma processing is far greater than that which can be achieved by donor deferral.
- It is possible that a shortage of nationwide and worldwide supplies of life and health-sustaining plasma derivatives could result if donors who resided in Europe are deferred.

FDA continues to evaluate TSE removal during plasma derivative processing, and will present this issue to the TSE in the future.

Predicted Effects of Expanded Donor Deferrals on the U.S. Blood Supply

The effects of deferring donors for an unproven, but theoretically possible risk, were weighed against the potential for shortage of life-saving and health-sustaining blood products. In June 2001, the TSEAC evaluated three deferral options, both for the amount of theoretical risk removed, and for the effects of each option on the blood supply. The deferral proposal favored by the TSEAC, and incorporated into the draft guidance, could result in an estimated 5 % loss of blood donors. This may be substantially higher in urban coastal areas. Furthermore, the largest supplier of blood in New York, the New York Blood Center (NYBC) obtains approximately 25% of its supply from Europe, under the Euroblood program. The following steps have been taken by FDA and HHS to reduce the possibility of shortages:

- Phased implementation of donor deferrals recommended
- Pilot studies of supply effects for more stringent donor deferrals recommended

- Initiation of nationwide monitoring of blood supply and demand, beginning prior to institution of donor deferrals
- Encouragement of cooperation among blood banks to prevent regional shortages

Final Guidance

The current guidance is regarded as an interim recommendation, based upon evolving science. Publication of a final guidance is anticipated after TSEAC discussion, and public comments to the docket have been considered. The public comment period ends on October 28, 2001.