

Food and Drug Administration
Transmissible Spongiform Encephalopathies Advisory Committee

February 20, 2003

Issue Summary for Topic #1, “Consideration of Labeling Claims for Transmissible Spongiform Encephalopathy (TSE) Agent Clearance in Plasma Derivatives”

Issue: Do scientific data support labeling claims for TSE clearance in plasma derivatives?

FDA’s Approach to Ensuring TSE Safety of Plasma Derivatives

FDA is responsible for regulating the safety of plasma derivatives (e.g. FVIII, FIX, IGIV, albumin, alpha-1 PI). Several measures can prevent or markedly reduce the risk of contaminating plasma derivatives with infectious agents:

- Deferral of donors most likely to be infected
- Laboratory testing of donor blood to identify and eliminate potentially infectious units
- Use of manufacturing processes that inactivate or remove infectious agents

The combination of blood donor deferral, testing of donations, and use of manufacturing processes that clear pathogens has virtually eliminated the risk of transmitting hepatitis, AIDS, and bacterial infections including syphilis by plasma derivatives. Responding to the tragic experience with AIDS, FDA has taken a very conservative approach to ensuring blood product safety in the face of the theoretical risk from Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD). As such, efforts to develop suitable screening, testing and pathogen clearance strategies for TSE agents have been ongoing.

Transmission by human blood of the transmissible spongiform encephalopathies (TSEs), e.g. CJD and vCJD, has never been reported. Epidemiological studies have not established any relationship between CJD and blood transfusion, nor have any frequent recipients of blood products been diagnosed with CJD or vCJD. However, the power of epidemiological studies to detect low-frequency events is limited, since relatively small numbers of subjects are involved, and the asymptomatic incubation periods of TSEs in humans may last for decades (documented range < 2 yr to almost 40 yr).

Blood and plasma of animals experimentally infected with TSE agents (mice, hamsters, sheep, primates) sometimes contain small amounts of TSE infectivity (Hemophilia 8:63-75, 2002; Transfusion 42(5): 509-12, 2002). Recently, blood from sheep naturally infected with scrapie was also shown to transmit scrapie to naïve sheep by transfusion (J. Gen. Virol. 83(11): 2897-905, 2002). Blood of asymptomatic animals as well as sick

animals with TSE may contain infectivity. It seems unlikely that blood-borne TSE infectivity, which occurs regularly in experimental animals, is never present in humans and more likely that blood of persons incubating TSE agents may sometimes contain infectivity.

No blood test currently available can identify healthy individuals who may have been infected with a TSE agent. Since 1987, FDA has recommended precautionary deferral of blood and plasma donors who may be at increased risk of CJD. In 1999, FDA recommended additional deferral of some donors who may be at increased risk of vCJD, due to possible exposure to the agent bovine spongiform encephalopathy (BSE) in Europe—so-called “geographic” vCJD deferrals. The most recent revised FDA guidance recommending such donor deferrals was published on January 9, 2002 (<http://www.fda.gov/cber/guidelines.htm>).

Accumulating laboratory evidence and reassuring clinical experience suggest that methods used to prepare plasma derivatives have the ability to remove substantial amounts of TSE agents. However, the components of Whole Blood (packed red blood cells, platelets, and fresh frozen plasma) are only minimally processed, by methods that do not remove TSE agents. Based upon these observations, FDA recommended geographic deferrals for donors of Source Plasma that differ from those for donors of Whole Blood.

FDA recommends that candidate donors of *both* Whole Blood and Source Plasma be deferred if they:

- Lived or traveled in the U.K. for any total period of 3 months or more from 1980 through the end of 1996.
- Lived or worked on or traveled to U.S. military bases in Europe for any period of 6 months or more, from 1980 through 1990 (if north of the Alps) or 1980 through 1996 (if elsewhere in Europe). (Different bases had stopped procuring beef products from the U.K. by those dates.)
- Lived or traveled in France five years or more from 1980 to the present time.
- Received a transfusion in the U.K. from 1980 to the present time.
- Were treated with bovine insulin manufactured from U.K. cattle from 1980 to the present time.

However, FDA recommended that *donors of Whole Blood, but **not** Source Plasma donors*, also be deferred if they spent 5 years or more in any countries of Europe. The less stringent recommendation for donors of Source Plasma was based on the following information:

- Experimental validation studies demonstrated that several processes used to manufacture plasma derivatives removed substantial amounts of TSE agent spiked into process intermediates.

- Cattle in European countries other than the U.K and France had much lower rates of BSE compared to the U.K. (BSE rates are estimated to be at least 100-fold less than those in the U.K.)
- Very small numbers of vCJD cases have been recognized outside the U.K. and France, and most of those were in former U.K. residents.

Consideration also was given to the possibility that a policy to preclude donation of Source Plasma based on exposure in any part of Europe could precipitate a severe shortage of plasma derivatives in the U.S.

Clearance of Transmissible Spongiform Encephalopathy Agents from Plasma Derivatives During Manufacturing

Paradigm of validation studies showing clearance of viruses during manufacture of plasma derivatives

FDA has previously relied on experimental studies to provide evidence in support of claims that a manufacturing process removes viruses from plasma derivatives. Manufacturers submitted detailed data from the studies to FDA, to demonstrate that a specific process inactivated or removed pathogenic viruses from a raw material or intermediates used to manufacture the product. These validation studies are performed in the laboratory using a scaled-down model of the actual manufacturing process steps, and test materials from manufacturing intermediates. The scaled-down model is intended to mimic the actual production steps as accurately as possible. The validation data must establish the relevance of the scaled-down model to the actual manufacturing process by comparing critical process and operation parameters of the two processes. Viruses used in these validation studies are a selection of enveloped and non-enveloped DNA and RNA viruses, which are relevant viruses or specific models for such viruses. Whenever possible they have used the actual pathogen of concern, such as HIV. If a virus of concern, such as HCV, cannot be cultured, then surrogate viruses are used, although additional data sometimes can be obtained by observing removal/non-detectability of viral gene sequences. Surrogate viruses are selected based on taxonomical, and physical similarity to the virus of concern. Acceptable studies of virus removal consist of the following elements:

- Detailed description and validation of scaled-down procedure (which must generate the actual product, or the next intermediate)
- Description of virus and viral spike
- Demonstration of robustness of inactivation/clearance steps with controlled variation in process parameters (temperature, pH, ionic strength, etc.)
- Demonstrated reproducibility of clearance steps
- Demonstration of “mass balance” with regard to viral removal steps
- Validated infectivity assays to measure viral titers present in the starting material and remaining after the process step

Specificity of manufacturing methods that clear TSE agents

Plasma derivatives are manufactured using a variety of methods. No two manufacturers use precisely the same conditions to produce a product. Differences may be in overall method, such as use of column chromatography, rather than cold-ethanol fractionation. However, for a single “method,” such as cold-ethanol precipitation, process variations in pH, ionic strength, alcohol concentration, and protein concentration during each step can substantially influence the removal of proteins and other molecules and of viruses. Further variations are introduced by adding different viral clearance procedures or other steps to increase product purity and/or stability. Claims for removal or inactivation of pathogens from plasma derivatives have been based upon convincing viral validation data that are product and process-specific. Published evidence suggests that, as for viruses, removal of TSE agents during manufacturing of plasma derivatives depends upon specific process parameters. Many studies have used measurement of the abnormal prion protein that is associated with TSE infectivity (PrP^{Sc})¹. In vitro methods to measure PrP^{Sc} are typically faster and less expensive than animal assays of infectivity. Reductions in amounts of PrP^{Sc} have correlated well with reductions in infectivity measured by bioassays in animals. Variations in ethanol concentration, ionic strength, and pH have all affected the removal of the TSE agent (Biochem. Biophys. Acta 1597: 28-35, 2002). Other production steps have also varied in their effectiveness of TSE removal in a context-dependent fashion. For example, only higher concentrations of polyethylene glycol (PEG) effectively precipitated TSE infectivity (Transfusion 42(11): 1497-500, 2002). Other steps, such as depth filtration, in various experiments removed between one and 5 logs of PrP^{Sc}, depending on the filter type employed and solution being filtered (Vox Sang. 78:86-95, 2000; Vox Sang 83:137-45, 2002). Overall, both unpublished and published information suggests that no single manufacturing step can be considered “generically” effective in removing for TSE agents.

Additional considerations for clearance of TSE agents

Removal of TSE agents during manufacturing of plasma derivatives is complicated by uncertainties regarding the nature of this pathogen. The physico-chemical characteristics of TSE agents in human blood, if present there, remain unknown. Thus the appropriate form of TSE agent that best represents theoretical blood infectivity for spiking test materials is disputed. Samples of human TSE agent preparations are limited, and infectivity is hard to assay; consequently, most TSE clearance studies have been performed using animal-adapted TSE agents. Since titers of TSE infectivity are low in other tissues, brain-derived preparations have generally been used to spike sufficient infectivity to demonstrate robust clearance, and PrP^{res} assayed rather than infectivity. In vitro detection of PrP^{res}, if properly validated against infectivity assays, could be used as a surrogate test to reduce complete reliance on animal infectivity assays, particularly to establish the reproducibility of a clearance step. In addition, the use of several different animal models, and spiking with more than one form of infectivity (e.g., crude tissue

¹ PrP^{Sc} denotes the abnormal prion protein that is associated with TSE infectivity. The more specific term, PrP^{res}, denotes abnormal prion protein identified by its resistance to protease digestion, rather than by other techniques that do not use protease digestion.

homogenate, partially purified membrane-bound infectivity and membrane-free infectivity), may partially overcome the limitations of animal infectivity assays.

The theoretical risk of transmitting infection by plasma derivatives and the amount of agent removal sufficient to assure safety may differ between viruses and TSE agents. With regard to viruses, the overall reduction should be greater than the maximum possible virus titer that could potentially occur in the source material. This has been interpreted as having at least two major clearance steps in a manufacturing process, each step clearing more than 4 logs of enveloped viruses, with total log reduction of > 10 logs for viruses such as HIV, HCV, and HBV. Clearance of several logs in excess of maximum viral titers is built into these requirements. In contrast to viruses, the estimated titers of TSE infectivity in blood of animals is low - approximately 10 to 100 LD₅₀ (fifty-percent intracerebral lethal doses of TSE agent per ml of blood). A few blood samples from vCJD patients have been assayed for infectivity in mice and for PrP^{Sc}; none was positive, although neither assay was sensitive enough to detect small amounts of infectivity (Lancet 358:208-9, 2001; Lancet 358: 171-80, 2001). However, in evaluating TSE removal, the limitations of animal models, and whether or not all potential vCJD infectivity would be removed by the same mechanisms, need to be considered.

Labeling Claims for TSE removal in Plasma Derivatives

Among other purposes, product labeling communicates risk to the public. Risk has two dimensions, first, what is the likelihood of any risk, and second, what is the potential amount of risk. In 1999, FDA recommended labeling for possible risk of transmitting TSE by plasma derivatives. The following recommended statement is contained in the Warnings section of package inserts for plasma derivatives:

?? “Because [this product] is made from human blood, it carries a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

Labeling may also communicate details concerning risk reduction that occurs during manufacturing. For example, many package inserts describe the amount of virus that has been removed from a product during experimental studies of its manufacture. A science-based labeling claim of specific TSE agent clearance might serve to inform the public and provide an incentive for industry to study and to pursue reduction of TSE risk via manufacturing processes. This incentive is particularly important because validated and licensed blood screening tests for detecting donors incubating TSEs seem unlikely to be available in the near future. Furthermore, blood and plasma supplies would almost certainly be strained if programs attempted to impose additional geographic vCJD deferrals of donors, which have been projected to contribute little additional risk reduction to that already achieved. The current donor deferrals are estimated to have already reduced the theoretical vCJD exposure risk (taken as person-days of exposure adjusted for the risk of BSE agent in meat products of various countries) by about 90%. A robust single manufacturing step may remove over 4 logs of TSE agent infectivity. Deferring all travelers to BSE countries would severely diminish the blood supply. The most feasible strategy for significantly reducing risk at this time, is removal of potential

TSE infectivity by manufacturing procedures. Once made, labeling claims may be modified later as science advances and additional information is submitted to FDA. For example, new labeling was adopted to describe the reduced risk of transmitting HIV and HCV after universal screening of blood components by ELISA was implemented and labeling may eventually reflect the additional improvement in safety afforded by viral nucleic acid testing (NAT).

It is important to assure that if a TSE agent enters plasma pools, that infectivity does not remain or accumulate on processing equipment. This issue was addressed by the TSEAC in June, 2001, where it was determined that more research was needed on methods of cleaning validation for TSE's. FDA plans to present this issue in the near future, for further consideration.

The TSEAC is asked to consider the following questions:

- o Assuming adequacy of decontamination procedures in product manufacturing, should FDA consider labeling claims for TSE clearance in plasma derivatives, based upon specific demonstration of TSE removal during manufacturing?
- o If so, please comment on whether such data would support the following draft wording for labeling:
 - “Because this product is made from human plasma, it carries the risk of transmitting infectious agents, e.g. viruses, and, theoretically, the CJD agent. It has been demonstrated that [the manufacturer]’s manufacturing process provides substantial clearance of agents similar to those causing CJD and vCJD. Thus the theoretical risk of transmission of CJD or vCJD is considered extremely remote.”