

DRAFT ISSUE SUMMARIES

Transmissible Spongiform Encephalopathies Advisory Committee Meeting

18-19 January 2000

Issue 1.

Suitability of Blood Donors Who Traveled or Lived in BSE Countries: Further Consideration

FDA is committed to review regularly its policies concerning blood safety with regard to Creutzfeldt-Jakob disease (CJD) and new-variant CJD (vCJD). The Agency again asks the Transmissible Spongiform Encephalopathies (TSE) Advisory Committee (TSEAC) to consider whether the recent FDA recommendation to defer blood donors resident in the UK for any aggregate period of six months between 1980 and the end of 1996 is still appropriate and sufficient and whether a deferral policy should be adopted for donors who lived or traveled in other countries that have had bovine spongiform encephalopathy (BSE) in cattle ("BSE countries") as determined by the US Department of Agriculture. If changes in policy are entertained for residence in the UK, what should those changes be? If deferral policies are recommended for blood donors resident in other BSE countries, what are appropriate aggregate periods of residence and years of concern? Should the FDA attempt to distinguish different levels of risk for different countries?

Background and Discussion

Since the cases of vCJD were first described in the UK and France in 1996, the FDA and other national public health authorities have concluded that, in the absence of compelling evidence to the contrary, the disease must be considered to result from human exposure to the agent of bovine spongiform encephalopathy (BSE). Several lines of laboratory research later served to substantiate this position. Although the routes of human exposure are not completely clear, the epidemiology of BSE in cattle and other ruminants and in felines suggests that the oral route must be suspected. Since 1996 more than 80 cases of confirmed or probable vCJD have been recognized in the UK, three in France and one in the Republic of Ireland. Cases of vCJD continue to occur in the UK, probably at increasing annual rates.

For more than ten years the FDA has been concerned with the theoretical risk of transmitting CJD through blood and blood products. In large part, that concern has been prompted by the repeated demonstrations that rodents with several experimental TSEs have small amounts of infectivity in blood during both the asymptomatic incubation period and overt disease. For several years, prior to

1998, the FDA recommended withdrawal not only of blood and blood components from donors later recognized to have CJD or to be at increased risk of CJD but also of plasma derivatives prepared from pools to which they had contributed. However, in at least six epidemiological investigations of CJD, exposure to blood and blood products, including exposure to blood products to which donors with CJD contributed, has not been implicated as a risk factor. Furthermore, experimental studies with rodent-adapted TSE agents in blood showed that the processing of plasma greatly reduced or eliminated infectivity from fractions IV (immunoglobulins) and V (albumin). That information, plus the fact that most donors destined to develop sporadic CJD cannot be recognized during the prolonged incubation period, led the PHS and the FDA to recommend, in September 1998, that blood and plasma establishments continue to defer donors with all forms of CJD or known to be at increased risk of CJD and to withdraw their blood and all blood components including unprocessed plasma but no longer withdraw plasma derivatives. However, if a donor is recognized as having vCJD, then all plasma derivatives should also be withdrawn and intermediates quarantined.

The more conservative FDA policy for plasma derivatives from persons with vCJD is dictated by uncertainties regarding the pathogenesis of vCJD. New-variant CJD is an “emerging” infection with which there is much less experience than with previously known “classical” forms of CJD (sporadic, iatrogenic and familial CJD). It has a unique constellation of clinical and histopathological findings, including a marked accumulation of the pathological protease-resistant type of “prion” protein in lymphoid tissues not seen in classical CJD. Limited studies of the pathogenesis of natural and experimental BSE, based on assay of various bovine tissues and fluids injected into mice or calves, have not demonstrated detectable infectivity in blood of cattle. However a recent preliminary report of one study described transmission of disease by a large volume of blood drawn during the asymptomatic incubation period of a sheep experimentally infected with the BSE agent to healthy sheep obtained from a TSE-free source. The greater level of uncertainty about vCJD led the FDA and other national regulatory authorities to conclude that the risk for transmitting vCJD by human blood and blood products might be greater than the risk for other forms of CJD. That conclusion prompted not only a more stringent policy for withdrawal of plasma derivatives, should a plasma donor later be credibly suspected of having vCJD, but also a recommendation to defer certain donors who might have been exposed to the BSE agent while visiting or living in some BSE countries.

In June 1999 the TSEAC advised the FDA to recommend that persons who lived or traveled in the UK for some substantial period of time during the BSE epidemic be deferred from donating blood. Analysis of a survey of blood donors suggested that deferral of donors who had spent an aggregate period of six months in the UK was predicted to eliminate almost 87% of the total “donor days” in the UK while reducing the number of suitable donors by 2.2%. In guidance

issued in November 1999, the FDA then recommended deferral of blood donors who had spent an aggregate period of six months or more in the UK between the beginning of 1980 and the end of 1996--a period taken to extend from the probable beginning of the BSE outbreak in cattle in the UK to the full implementation by UK authorities of a number of measures expected to reduce markedly if not completely eliminate opportunities for human exposure to the BSE agent. The FDA also recommended deferral of donors who had been treated or who might have been treated with bovine insulin prepared from animals in the UK. That policy was recommended for implementation by April 17, 2000.

On June 1, 2000 the TSEAC was asked to reevaluate the new donor-deferral policy for the UK and to consider whether potential exposure to the BSE agent of donors who had lived or traveled in France and other BSE countries justified FDA recommending some policy of deferral for them as well. The TSEAC and the FDA concluded that BSE was less widespread among cattle in France and other BSE countries than it had been during the peak years of the BSE outbreak in UK and that, while UK beef products had been consumed in countries outside the UK, consumption was substantially less than in the UK. In France the consumption of UK beef might have been at least 5% of that in the UK itself. (The additional risk of exposure from consumption of beef products derived from the smaller number of BSE-infected French cattle was thought to be negligible when compared with the risk from imported UK beef.)

The TSEAC and the FDA recognized that, while the theoretical risk of transmitting vCJD by blood could be reduced further by deferring some additional donors who had been in BSE countries, that risk cannot be eliminated completely without deferring so many potential donors that the supply of blood would be jeopardized. The TSEAC accordingly advised that the FDA make no further changes in its recently announced blood-donor deferral policy.

On June 2, 2000 the TSEAC reviewed the possible effects that leukofiltration devices might have for reducing the risk of transmitting CJD. The committee concluded that, due to the many uncertainties about the distribution of TSE infectivity in blood and the unknown effects of various filtration devices on cell-associated infectivity, universal leukofiltration--whatever its other potential benefits--should not be recommended to reduce the risk of transmitting CJD and that the FDA should continue to recommend reliance on a policy of careful donor selection to do that.

During subsequent months, Canadian authorities have recommended deferring blood donors who were in France for any aggregate period of six months or more from 1980 through 1996 but not donors resident in any other BSE country except the UK. Several other countries have adopted blood-donor deferral policies similar to those of the USA.

Since the last deliberations of the TSEAC, the number of diagnosed cases of vCJD as well as annual rates of both new cases and of deaths from vCJD have continued to increase in the UK. Many more cases of BSE have been recognized in French cattle, and several countries not previously acknowledging the disease have recently diagnosed BSE in native cattle. Furthermore, the US Department of Defense has recognized that some US military personnel stationed in Europe as well as their dependents must have consumed beef products obtained from the UK and other BSE countries.

The FDA is committed to reevaluate frequently the potential exposures of blood donors to the BSE agent and implications that those exposures might have for the safety of the blood supply. The FDA is also cognizant of possible adverse effects on the blood supply expected to result from deferral of additional donors to reduce risks that remain theoretical. Once again, the Agency has asked the TSEAC to advise it concerning those issues.

The FDA now proposes that the TSEAC consider a deferral policy based on their previous estimate that exposure to the BSE agent by persons resident in France might have been at least one-twentieth of the exposure in the UK and that exposure in France probably continued after 1996. The FDA also agrees with an additional concern previously expressed by TSEAC, that possible human exposures to the BSE agent in other BSE countries are even more difficult to estimate than those in France and may be at least as great.

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Charge

The FDA again asks the TSEAC to evaluate new information concerning vCJD in the UK and France and BSE in the UK, France and other European countries where the disease has infected or may have infected cattle. The TSEAC should attempt to compare the risk that donors resident in various countries (including overseas US military personnel and dependents) might have been exposed to and infected with the BSE agent and consider implications for the safety of the blood supply.

The TSEAC should also consider, in the context of a risk-benefit estimate, effects that FDA blood-donor policies may have had on the blood supply in the US as well as effects to be expected if additional deferrals of blood donors are recommended.

Questions

1. United Kingdom

- a. Are recent data on prevalence of vCJD in the UK or the potential risk of transmitting vCJD by human blood or plasma sufficient to warrant a change in current FDA policies regarding deferrals of blood and plasma donors based on a history of travel or residence in the UK? Please comment.
- b. Have recommendations of FDA concerning blood-donor deferral because of residence in UK had an adverse effect on the blood supply sufficient to consider a change? Please comment.

2. France

- a. Should the FDA recommend deferral of blood or plasma donations by persons with a history of travel or residence in France for an aggregate period of ten years or more after 1980?
- b. If not, which years and aggregate duration of residence, if any, should be of concern?

3. Other BSE countries

- a. Should the FDA recommend deferral of blood or plasma donation from persons with a history of travel or residence in other countries identified by the USDA as having BSE in cattle for an aggregate period of ten years or more after 1980?

b. If not, which years and aggregate duration of residence, if any, should be of concern?

4. Should deferral of blood or plasma donors be recommended based on some combined aggregate duration of travel or residence in more than one BSE country, and, if so, how should that be estimated appropriately?

5. US Military Personnel and Dependents

a. Should the FDA recommend deferral of blood or plasma donations from persons with a history of six months aggregate potential exposure to UK beef and beef products during service or dependent status in the US military in Europe from 1980 to 1996?

b. If not, do members of the TSEAC suggest some other policy for deferral of US military personnel or dependents due to exposure to UK beef products?

c. Should the FDA recommend deferral of blood or plasma donations from persons with a history of ten years of potential exposure to beef and beef products from BSE countries other than the UK during service or dependent status in the US military in Europe after 1980?

d. If not, should some other aggregate duration of residence be of concern?