Summary (7/11/01)

Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC)

June 28 & 29, 2001

TOPIC 1

Deferral of Blood Donors Potentially exposed to the Agent of Variant Creutzfeldt-Jakob Disease (vCJD)

Issue: FDA asked the TSEAC for advice to help decide if deferral of additional blood and plasma donors potentially exposed to the agent of bovine spongiform encephalopathy (BSE) can be safely implemented to reduce further the theoretical risk of transmitting vCJD by blood, blood components and plasma derivatives while maintaining adequate national and regional supplies.

FDA asked the committee to consider the following three options, taking into account new information about BSE and CJD:

Option #1 (policy consistent with advice offered by TSEAC in January 2001)

- Defer donors traveling or resident for any cumulative period of ten years or more in France, Portugal, or the Republic of Ireland from 1980 to the present.
- Defer donors traveling or resident for any cumulative period of six months or more in UK 1980-1996. (This would be unchanged from current FDA policy.)
- Defer donors resident for any cumulative period of six months or more on a European DoD base from 1980-1996 (or 1980-1990 if all exposure after 1990 was on DoD bases North of the Alps).

  Estimated Impact: 2.2% donor loss; 44% reduction of current risk; 82% reduction of total risk.

Option #2 (policy proposed by the American Red Cross)

- Defer donors for cumulative travel or residence in Europe for any period of six months or more from 1980 through the present or in the UK for three months or more from 1980 to the present.
- Defer donors who received a transfusion in the UK at any time from 1980 through the present.
- ARC plans to implement the new deferral policy throughout their system in September 2001.

  Estimated Impact: 7.8 to 9.1% donor loss; 76% reduction of current risk; 92% reduction of total risk.

Option #3 (FDA proposal)

- Defer donors for cumulative travel or residence of five years or more in any European country except UK from 1980 to the present
- Defer donors who spent any cumulative period of three months or more in UK from 1980 through the end of 1996.
- Defer donors who spent more than six months on a European DoD base from 1980 through the end of 1996 (or 1980 through 1990 if all exposure after 1990 was on DoD bases North of the Alps)
- Defer any recipient of a blood transfusion in UK from 1980 to the present.
- Implement deferrals within six months of final FDA Guidance.

Estimated Impact: 4.6 to 5.3% donor loss; 72% reduction of current risk; 91% reduction of total risk

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The committee heard presentations on the estimated potential human exposures to the BSE agent in various countries, risk reduction and projected effects on the blood supply. Highlights of the presentations are as follows:

Geographic BSE Risk Assessment (GBR)
The ongoing GBR assessment conducted by a Scientific Steering Committee for the European Commission indicated that 14 countries have now reported BSE in native cattle herds, but that only the UK and Portugal continue to meet the criteria for inclusion in Category IV (over 100 infected cattle per million). The Czech Republic, previously designated Category III "low level BSE risk" recently reported a BSE case. This represents the first reported case from Eastern Europe. (Note: Following the TSEAC meeting, Greece reported a case of BSE this week, bringing the country count to 15.)

Potential Impact of a Deferral Policy on the Availability of Plasma for Fractionation
A spokesman for the EU noted that a decision to defer U.S. donors based on exposure in Europe could have a dramatic effect in reducing the availability of plasma and plasma derivatives worldwide. This is because European and non-European countries may decide to discontinue using European plasma for fractionated products. The result would be a marked increase in demand for U.S. plasma and U.S. plasma derivatives at a time when its availability would also be decreased.

Mathematical Modeling of BSE Risk Exposures.
In compliance with a recent directive, surveillance testing of healthy slaughtered cattle has now commenced throughout the EU. Early results indicate that the rankings of European countries by prevalence of pre-clinical BSE infection (via Western blot testing) do not parallel the rankings by reported incidence of clinical BSE. These data appear to support the theory that clinical BSE cases reflect only the visible tip of the epidemic. Rates of one or more BSE infections per 10,000 cattle were reported in Spain, Italy and Belgium, compared with rates between 0.1-0.3 in France, Germany, Netherlands and Republic of Ireland. (Data on 37 cases are pending from Portugal.) It was estimated that ~750,000 infected cattle have been consumed in the U.K. Recent testing data from the UK also support the concept that epidemic controls instituted and enforced there have markedly lowered the current risk of dietary exposure.

Statements about blood adequacy and consequences of blood supply shortages.
The major blood collection organizations (with the exception of the ARC), as well as patient advocates and numerous individuals representing healthcare institutions the New York area expressed major concerns about the potential shortages of blood and blood products that could accompany tightened donor deferral policies. Notably, Former Surgeon General (and current NY State Health Commissioner) Dr. Antonia Novella voiced strong support for the FDA, but urged that extreme care be taken to preserve blood resources, particularly in the New York metropolitan area. The American Red Cross acknowledged the severe projected donor losses that would be realized by implementation of its proposed deferral policy, but expressed confidence in the organization's ability to overcome these losses by an assortment of assertive donor recruitment and retention programs. In general, there appeared to be agreement that donor losses could be offset by the availability of adequate time and financial resources.

As detailed in the attached TSEAC Issue Summary, the Committee was presented with three policy options including: 1) the TSEAC January 18, 2001 recommendation; 2), the ARC deferral proposal, and 3) the proposed FDA deferral proposal. Also presented for each option were donor loss estimates, relative advantages and disadvantages, and risk reduction estimates based upon a relative risk model previously endorsed by FDA and CDC scientists. (UK=1; DoD = 0.35; France = 0.05, Other Europe = 0.015).

The Committee's discussion evaluated each of the component parts of the FDA proposed model culminating in several "straw" votes regarding the acceptance of these components.
Deferral for a history of transfusion in UK, deferral for 6 month exposure on a European base (recognizing the differences in N/S Europe exposure) and shortening the UK deferral to ≥ three months were accepted without major debate. Curtailing the UK deferral at 1996 was discussed in depth, but was ultimately approved based upon UK surveillance data showing greatly reduced current dietary BSE exposure. The most widely debated component of the FDA-proposed policy was the concept of a pan-European deferral,

in contrast to targeted deferrals for known BSE countries. While the uncertainty of BSE data accuracy and availability for individual countries was acknowledged, the severe supply impact of a pan-European deferral including a projected 35% blood loss in the New York area was of major concern. As a result of these deliberations, the Committee moved to add an amendment to the FDA deferral option recommending deferral actions only in concert with substantive Federally-funded programs for blood donor recruitment and blood supply monitoring. Ultimately, the entire FDA proposal (with amendments) was subjected to a formal vote and was accepted 10:7 without abstention.

Summary of Voting on Questions for the TSEAC

1. Do TSEAC members concur with the FDA proposal (Option #3) to defer additional blood and plasma donors based on potential exposure to the agent of BSE?

   After much discussion (see above) the committee voted on Option # 3 (question #1) which now included the TSEAC-initiated., "proposal to institute both a national recruitment campaign and a system to monitor adequate blood supply." The vote on Option 3--with this amendment--was: 10 yes votes, 7 no votes, and 0 abstentions.

   Since the answer to question 1 was "yes" the committee did not consider following three questions (2,3, and 4).

2. If not, do TSEAC members advise the FDA to recommend the blood and plasma donor deferral policy recently proposed by the American Red Cross (Option #2)?

3. If not, do TSEAC members advise the FDA to recommend the blood and plasma donor deferral policy proposed by the TSEAC on 18 January 2001 (Option #1)?

4. If not, do TSEAC members advise FDA to recommend some other revised policy to reduce further the risk of blood-borne transmission of vCJD while maintaining adequate regional and national supplies of blood and blood products? Please specify.

The committee then addressed question 5:

5. Please comment on steps that should be taken to monitor and ensure adequate national and regional supplies of blood, blood components and plasma derivatives if additional donors are deferred based on possible exposures to BSE agent.

   Before the committee voted on Option # 3, they had discussed their concern regarding its predicted effect on the blood supply, especially in the New York City metropolitan area, as well as the need to further reduce the theoretical risk of transmitting vCJD in blood and blood components. Their amendment to Option 3 (to institute both a national recruitment campaign and a system to monitor adequate blood supply) was their proposed response to FDA's request for a recommendation.

   One committee member expressed a serious concern that food protective measures in the UK might not yet have reduced the potential human exposure to the BSE agent sufficiently to reassure the FDA that risk after 1996 was negligible. Another requested that the FDA obtain information concerning reliability of CJD surveillance in continental European countries; knowing that, the committee could better evaluate the significance of the fact that vCJD has not been recognized on the European continent except in France.

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.

At FDA's request, the TSEAC addressed the questionof safety of FDA-regulated plasma derivatives made in facilities which process both European and U.S. plasma, in the setting of anticipated deferral of European donors for vCJD risk. Manufacturers are currently licensed to process U.S. plasma for U.S. markets, and European plasma, for other markets, using the same equipment, with cleaning procedures in-between campaigns. In the setting of increased theoretical risk of vCJD in donors from Europe, the committee considered 1) the likelihood of cross-contamination with vCJD from European to U.S. plasma, 2) whether labeling of products made in European facilities should be instituted, 3) whether additional cleaning of facilities directed towards vCJD should be examined, and 4) the strategy of instituting segregated manufacturing equipment for U.S. plasma. While forma! votes were not taken, the TSEAC stated that based on existing studies, the risk of vCJD transmission by blood and plasma derivatives is unknown, but probably low. The committee discussed the usefulness of additional labeling, since the warning section of products already states that there is a theoretical risk for CJD, and because even U.S.-manufactured products are not definitely risk-free. Members agreed that segregation of manufacturing lines is a complex issue, worthy of more detailed review by FDA and industry. The committee favored exploration of facility cleaning and decontamination methods, and emphasized that research was needed into cleaning methods, and cleaning validation.

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.
   The committee stated that based on existing studies, the risk of vCJD transmission by blood and plasma derivatives remains unknown, but probably very low. However there was concern that the infectious agent could accumulate in columns used in the purification of plasma components.

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?
The committee rnembers stated that while precautions should be taken, segregation of manufacturing lines is a complex issue, and a subject for more detailed review by FDA and industry to determine its feasibility.

If so, which of the following steps should FDA consider at this time?

a. labeling to identiify campaigned manufacturing involving potential exposure to European plasma

Members of the committee felt that labeling should be considered, but a vote was not taken. Members in favor of labeling felt that patients should be aware of products produced in European facilities, as a matter of disclosure and to enable choice of products. Other members expressed that current CJD labeling was adequate, and in the setting of a theoretical risk, labeling about production in European facilities would cause undue concern among consumers. It was also noted that vCJD risk, if it exists, probably could not be completely eliminated even from U.S. plasma.

b. use of additional decontamination procedures
The committee felt that enhanced cleaning was a worthwhile endeavor, but that such an effort would require additional research relevant to facilities and materials in question. Validation methods, in particular, would need to be developed.

c. use of dedicated manufacturing lines
The committee did not feel that dedicated lines should be mandated.

d. other measures (please specify)
The committee encouraged additional research into methods, which would elucidate the possibility of equipment contamination, using relevant models, and methods of facility cleaning.

TOPIC 3

Update: Interim results of a new study on the inactivation of TSE agent by the manufacturing process of gelatin

During this portion of the meeting, the Committee heard updates on the interim validation study results on the inactivation of BSE through the gelatin manufacturing process, from the Gelatin Manufacturers of Europe (GME). This was an information sharing discussion; no questions were posed to the Committee.

The committee reviewed the study design and preliminary data. They requested to receive a presentation of the final study results as soon as they are available. Policy recommendations should not be made until the final results are presented and reviewed.

The committee also requested additional information on slaughterhouse operations and additional studies to determine the titer of prions in all types of bovine tissue derived from infected animals in order to better understand the potential exposure to the infectious agent.