

Aventis Behring



October 8, 2001

Jay Epstein, MD, Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research
c/o
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry - Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products [Docket No. 97D-0318]

Dear Dr. Epstein:

Thank you for the opportunity to comment on the above-referenced draft Guidance for Industry. Aventis Behring strongly supports the draft guidance recommendation not to defer Source Plasma donors who have lived or traveled in Europe for a cumulative period of 5 years or more since 1980.

The FDA balanced concerns over risk by appropriately taking into consideration the low prevalence of vCJD in Europe outside of the United Kingdom as well as the likely ability of plasma fractionation processes to reduce Transmissible Spongiform Encephalopathies (TSE) infectivity. The FDA also correctly stated that the relative risk and benefits of excluding Source Plasma donors who have lived or traveled in Europe for 5 years or more have not been established. The draft guidance states that such a donor deferral for Source Plasma donors could have a significant impact upon the supply of life and health sustaining plasma derivatives. I personally applaud the FDA for this statement and can state unequivocally that such a donor deferral would have a major impact on the supply of life and health sustaining plasma derivatives worldwide, especially during this time of product shortages.

Aventis Behring does not use Recovered Plasma from Whole Blood donors in the manufacture of any products licensed in the United States, but we do have a concern with the draft guidance's recommendation that collection of Recovered Plasma from Whole Blood donors deferred for European residency should be discontinued. The FDA has recognized the appropriateness and safety of differentiating between donors of transfusion products and donors of plasma for fractionation. This distinction was made partially on the belief that the fractionation process reduces and possibly eliminates the risk of transmission of prions by fractionated products. The recommendation against collecting Recovered Plasma from Whole Blood donors as a means to prevent inappropriate use of blood and blood components for transfusion is consistent with the

geographic risk assessments in the guidance. However, I should state that in the production of plasma derivatives, Recovered Plasma collected from Whole Blood donors would be subjected to the same rigorous manufacturing and purification processes that have the ability to reduce the theoretical risk of TSE infectivity. Aventis Behring is of the opinion that Recovered Plasma, when available for fractionation, is a suitable and safe source material since it is subjected to the very same processes as Source Plasma. In this regard, it is Aventis Behring's position that it would be more appropriate for the final guidance to require that Recovered Plasma from Whole Blood donors may only be used in the manufacture of plasma derivatives. This way, additional base material that is subjected to the same rigorous manufacturing standards as Source Plasma would be available to produce life saving plasma therapies.

Another point of concern is the draft guidance citation of scientific evidence that blood from animals experimentally infected with TSE agents contains low levels of infectivity and TSE infection, including Bovine Spongiform Encephalopathy (BSE) that has been transmitted by transfusion in some experiments. The relevance and validity of such data is subject to significant scientific debate, particularly data regarding the experimental transmission of BSE from sheep to sheep via transfusion, as documented in a single transfused sheep (out of 21 donor/recipient pairs) as published by Houston, et al. It has now been a full year since the publication of this isolated observation, yet other animals have not become sick, nor is control data available as of yet. It is not clear whether these data should be cited as scientific evidence that blood contains infectivity that can be transmitted by transfusion.

There are significant new data that are not referenced in the draft guidance. Two articles appearing in the July 21, 2001 edition of *The Lancet* (volume 358, number 9277) report that prions were undetectable in the blood, plasma and buffy coat of patients with vCJD, despite the presence of prions in their lymphoid tissues (Bruce, et al., 2001; Wadsworth, et al., 2001). While the lack of detection by bioassay and/or Western blot in these studies does not definitively establish the ultimate absence of prions, these data do add to a growing body of evidence that continues to support the conclusion that prion infectivity in human blood cannot be found. Aventis Behring request that such data be contained in the final version of the guidance.

One last suggestion for the final guidance would be with regard to the formatting of the document. A blood or plasma collection center might benefit if a table was attached to the document classifying the donor and then determining the subsequent actions that are required. Such a table should provide for greater understanding and adherence to the new regulations incorporated in the guidance. I have taken the liberty of enclosing such a table and would ask that you consider this or some possible variation, for inclusion into a final document.

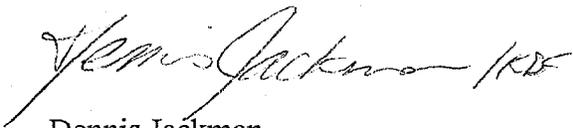
Aventis Behring will continue to treat this theoretical risk as if it were real through the implementation of precautionary measures. Further, Aventis Behring will maintain a sustained research and development effort designed to seek answers to further minimize the theoretical risk of transmission of vCJD through the use of plasma-derived products.

This effort includes our recent collaboration with Stanley Prusiner, MD, a former member of the FDA's Advisory Committee on TSE and recipient of the 1997 Nobel Prize for Medicine. This collaboration has led to the development of a sensitive test for prions which Aventis Behring currently uses internally to measure prion levels as they might change during the manufacturing process.

In conclusion, Aventis Behring strongly supports the provisions of the draft guidance as they relate to Source Plasma. This position balances theoretical risk while taking into account legitimate product supply concerns. The policy also acknowledges the likely ability of the plasma fractionation and purification processes to significantly reduce prion infectivity.

Aventis Behring is grateful for the opportunity to comment on the draft guidance and pledges to continue its research efforts regarding the theoretical risk of vCJD. Please do not hesitate to contact me if I may be of any assistance or if you have any questions concerning the comments of Aventis Behring.

Sincerely,

A handwritten signature in cursive script, appearing to read "Dennis Jackman".

Dennis Jackman
Vice President
Industry and Health Policy

CC: Jay Epstein, MD (at HFM 340, 1401 Rockville Pike)
Mark Weinstein, MD
Dorothy Scott, MD
David Asher, MD
William Freas, Ph.D.
Stephen Nightingale, MD

Draft Guidance - vCJD Document - Suggestion

| Donor Suitability Question or Post Donation Information | Frequency of question | Donor Classification | Deferral Status | Products for transfusion and further manufacture under control of manufacturer | Required Reporting | Consignee Notification (Unpooled Source Plasma) | Pooled Source Plasma, Intermediates and Plasma Derivatives |
|---|---|---------------------------------|---|--|-----------------------|--|---|
| <p>Have you or any of your blood relatives had Creutzfeld-Jakob Disease or have you ever been told that that your family is at increased risk for Creutzfeld-Jakob Disease?</p> <p>Have you ever received human pituitary-derived growth hormone?</p> <p>Have you received a dura mater (or brain covering) graft?</p> | First donation and each annual physical | Donor at increased risk for CJD | Indefinitely defer, and appropriately counsel | Immediately retrieve and quarantine for subsequent destruction | None required | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | No action |
| <p>Have you visited or lived in the United Kingdom (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands) from 1980 through 1996? If so, have you spent a total time of 3 months or more in the United Kingdom from 1980 through 1996?</p> | | | | | | | |
| <p>As a current or former member of the U.S. military, a civilian military employee, or a dependent, have you been stationed in Belgium, the Netherlands, or Germany, for 6 months or more, between 1980 and 1990?</p> <p>As a current or former member of the U.S. military, a civilian military employee, or a dependent, have you been stationed in Spain, Portugal, Italy, Turkey, or Greece for 6 months or more, between 1980 and 1996?</p> | | | | | | | |
| | Once | Geographic risk of BSE exposure | Indefinitely defer | Immediately retrieve and quarantine for subsequent destruction | None required | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | No action |

Draft Guidance - vCJD Document - Suggestion

| Donor Suitability Question or Post Donation Information | Frequency of question | Donor Classification | Deferral Status | Products for transfusion and further manufacture under control of manufacturer | Required Reporting | Consignee Notification (Unpooled Source Plasma) | Pooled Source Plasma, Intermediates and Plasma Derivatives |
|--|--|--|--------------------|---|-----------------------|--|---|
| Phase I Have you visited or lived in France since 1980? If so, have you spent a total time of 5 years or more, between 1980 and the present? | Intervals no greater than every 3 months | Geographic risk of BSE exposure | Indefinitely defer | Immediately retrieve and quarantine for subsequent destruction | None required | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | No action |
| Phase II (Not required for Source Plasma donors - maintain Phase I) Have you visited or lived in Europe between 1980 and the present? If so, have you spent a total time of 5 years or more in BSE risk countries in Europe between 1980 and the present? (Please include time spent in the U.K. from 1980 through 1996) | | Additional geographic risk of BSE exposure | | No retrieval and subsequent destruction of Recovered Plasma from Whole Blood collected prior to start of Phase II | | No consignee notification regarding Recovered Plasma from Whole Blood collected prior to start of Phase II | |
| Have you received a transfusion of blood, platelets, or plasma in the United Kingdom, between 1980 and the present? | | Geographic risk of BSE exposure | | Immediately retrieve and quarantine for subsequent destruction | | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | |
| "Have you at any time since 1980 injected bovine (beef) insulin?" | | ? | | | | | |

Draft Guidance - vCJD

Document - Suggestion

| Donor Suitability Question or Post Donation Information | Frequency of question | Donor Classification | Deferral Status | Products for transfusion and further manufacture under control of manufacturer | Required Reporting | Consignee Notification (Unpooled Source Plasma) | Pooled Source Plasma, Intermediates and Plasma Derivatives |
|---|-----------------------|----------------------|----------------------------|--|---|--|--|
| Physician's clinical or pathological diagnosis of CJD | NA | Diagnosis of CJD | Permanently defer if alive | Immediately retrieve and quarantine for subsequent destruction | None required | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | No action |
| Physician's clinical or pathological diagnosis of CJD and age < 55 years | NA | Possible vCJD | Permanently defer if alive | Immediately retrieve and quarantine for subsequent destruction | Director, Office of Compliance and Biologics Quality, FDA ASAP, BPDR? | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | To be determined by FDA in conjunction with CDC |
| Any or all (?) of the findings listed below: <ul style="list-style-type: none"> ♦ Numerous widespread kuru-type amyloid plaques, surrounded by vacuoles, in both the cerebellum and cerebrum ("florid plaques"); ♦ Spongiform change most evident in the basal ganglia and thalamus, with sparse distribution in the cerebral cortex; and ♦ High density accumulation of abnormal prion protein, particularly in the cerebrum and cerebellum as shown by immunohistochemistry. | NA | Diagnosis of vCJD | Donor will be deceased | Immediately retrieve and quarantine for subsequent destruction | Director, Office of Compliance and Biologics Quality, FDA ASAP, BPDR? | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | Immediately retrieve and quarantine for subsequent destruction any pooled plasma, intermediates, derivatives, and any other material containing plasma |

Draft Guidance - vCJD

Document - Suggestion

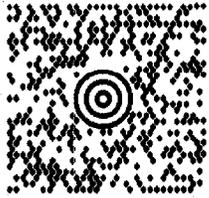
| Donor Suitability Question or Post Donation Information | Frequency of question | Donor Classification | Deferral Status | Products for transfusion and further manufacture under control of manufacturer | Required Reporting | Consignee Notification (Unpooled Source Plasma) | Pooled Source Plasma, Intermediates and Plasma Derivatives |
|---|--------------------------|---|-------------------------------|--|---|---|---|
| <p>All of the findings listed below:</p> <ul style="list-style-type: none"> ◆ Current age (if alive) or age at death <55. ◆ Persistent painful sensory symptoms and/or psychiatric symptoms at clinical presentation. ◆ Dementia, and delayed development ≥ 4 months after illness onset) of ataxia, plus at least one of the following three neurologic signs: myoclonus, chorea, or dystonia. ◆ A normal or abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD. ◆ Duration of illness of at least 6 months. ◆ Routine investigations do not suggest an alternative, non-CJD diagnosis. ◆ A history of possible exposure to BSE, e.g., having been a resident or traveler to a BSE-affected country from 1980 to the present. ◆ No history of iatrogenic exposure to CJD, such as receipt of a dura mater graft, or human pituitary-derived hormones. ◆ Absence of a prion protein gene mutation, or, if this has not been determined, no history of CJD in a first degree relative. | NA | Clinical diagnosis of "suspected" vCJD | Permanently defer if alive | Immediately retrieve and quarantine for subsequent destruction | Director, Office of Compliance and Biologics Quality, FDA ASAP, BPDR? | Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction | Not clearly specified in document |
| Aventis Bio-Servcies, Inc. | | | | | | | |

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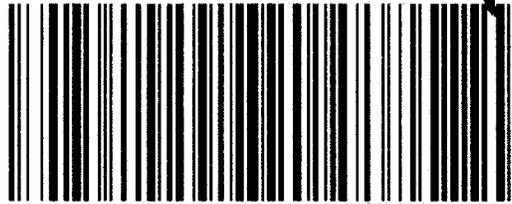


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