Aventis Bio-Services

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Director, Regulatory Affairs

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

26 October 2001

RE: Docket 97D-0318
Draft Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeld-Jakob Disease (CJD) and Variant Creutzfeld-Jakob Disease (vCJD) by Blood and Blood Products

Dear Sir or Madam:

Aventis Bio-Services wishes to thank the FDA for the opportunity to comment on this draft guidance for industry. This guidance document addresses a very complex set of issues, i.e., the theoretical risk of transmission of BSE or perhaps other transmissible spongioform encephalopathies through blood and blood products. The FDA is to be commended for addressing such a complex series of issues in a set of guidelines that considers and balances both the safety and the supply of blood and blood products.

Specific comments, related primarily to the collection and use of Source Plasma, follow.

Format of the document:

Given the complex nature of the guidance that is provided, the format of the document is at time difficult to follow, and does not always clearly specify actions that are to be taken in response to the receipt of information regarding a specific donor.

When the plasma industry first becomes aware of information about a donor, either through the donor's answers to the posed questions, or as a report of post donation information, there are several steps that must be performed promptly and correctly. First, the donor must be properly classified, e.g., as a donor with increased risk for CJD, or as a donor with increased risk for exposure to BSE, etc.

97D-0318 C35

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Based upon this classification, the following actions must be performed:

- The donor must be deferred.
- Products under the control of the manufacturer, i.e. the plasmapheresis center, must be quarantined for subsequent disposition.
- Consignees of products shipped by the manufacturer must be notified. For the plasma industry, there are at least two categories of products that must be considered:
  - Source Plasma that has been shipped to a consignee, e.g., a fractionation facility, but has not yet been pooled.
  - Source Plasma that has been pooled, or has been processed into intermediates and plasma derivatives.
- The event must be reported to the FDA, either as a Biological Product Deviation (required to be reported within 45 days of discovery), or, depending upon the classification of the donor, in a more urgent fashion.

We are concerned that the format and language of the draft guidance makes it difficult to easily determine the correct course of action for a specific donor. For example, a variety of terms are used to describe different categories of donors. Terms such as donors with "risk for exposure to BSE, " or "potential exposure to vCJD" are used. The consistent use of standardized terms is recommended.

Simplifying this information and presenting it in the form of a table would likely improve industry's ability to comply with these guidelines. As an example of what might be considered as more useful, a copy of a table that was created based upon the information presented in the draft guideline is attached. The first column of the table lists the information that would make the donor eligible for consideration under this guideline, and subsequent columns describe the specific actions that are to be taken for donors and products that fall within that category. Please note that the table represents an attempt to map the information contained in the document, and due to differences in interpretation, may not reflect the true intent of the document. Information that may not have been clearly stated in the document is indicated by a question mark "?."

The process of attempting to populate the various cells in the attached table has revealed some points that require additional clarification.

Section V. Recommendations for Product Retrieval and Quarantine

Section V. A. "Blood and Blood Components Intended for Transfusion or Further Manufacture from the Following: Donors with CJD or **vCJD** (emphasis added), Donors with CJD Risk Factors, and Donors with Potential Exposure to vCJD (as described in sections IV. D. 1., and IV. D. 3)"

Section V. C. "Blood and Blood Components, Including Source and Recovered Plasma, from Donors with **vCJD** (emphasis added), or suspected vCJD"

Please note that:

- **"Donors with vCJD"** (emphasis added) are listed in both Section V. A. and Section V. C.
  - Section V. C requires that the FDA be notified as soon as possible of donors that are considered as having vCJD, but Section V. A. does not.
- Donors with a "physician's clinical or pathological diagnosis of CJD and age less than 55 years" is first mentioned in Section V. C.
  - It is not clear from document if these donors are to be considered as donors with vCJD or as donors with "suspected" vCJD. This distinction becomes important in determining the disposition of pooled Source Plasma, intermediates and plasma derivatives.

When the guideline states that the FDA should be notified, the exact reporting requirements should be more clearly stated. The document states that the report should be made as soon as possible, and a telephone number is provided. However, the reference to the current regulations that require reporting of biological product deviations is somewhat confusing, since these are only required to be reported within 45 days of discovery. Clarification is requested as to whether reporting in addition to a Biological Product Deviation Report is required.

Section IV. D.

The guideline states that donors of Source Plasma should be asked Question 4 and Question 5 at intervals no greater than every three months. Introducing a requirement to ask donors questions at a three-month interval would complicate the donor screening process in that a mechanism would have to be devised to alert staff when the two additional questions would have to be asked of each donor. Donors could be effectively managed by asking both of these questions during the physical exam, which occurs on an annual basis.

Information obtained in response to Question 4 would be documented in the donor record file (DRF), and could be reviewed on a regular basis and updated as necessary. Regular review of this information would allow donors to be effectively managed on a donor-by-donor basis.

For Question 5, donors are already asked, prior to every donation, if they have received a blood transfusion in the past 12 months. If a donor answers affirmatively to this question, they could be further questioned to determine where the blood transfusion was received. If the transfusion had been obtained in the U.K., the donor could then be deferred for the appropriate time period. i.e.,

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indefinitely deferred if the transfusion had been received in the U.K., or certain countries in Africa, and for 12 months if the transfusion had been received in the U.S.

Section II. Background

The document recommends proactive planning to ensure blood supply adequacy before, during and after implementation of the guideline, and recommends that "Steps to moderate supply impact may include **assertively increasing collection volume prior to implementation** (emphasis added), and careful monitoring of the blood supply and demand factors before, during, and after implementation." This statement implies that collections should be increased prior to implementation, because after implementation fewer donors will remain eligible to serve as donors of either blood or plasma. However, once new screening questions have been implemented, it is generally accepted practice to consider donors who are deferred based upon the new questions as having provided post donation information, and to retrieve for subsequent destruction any units previously donated. Given this requirement, it would make sense to require that the new questions be implemented **prior** to assertively increasing collection volume. This would improve product safety by preventing the collection of these units, rather than relying on the lookback process to retrieve the units that may already be in the production process.

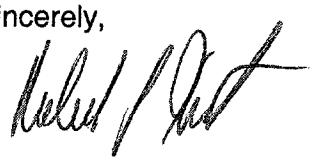
General Comment

Finally, the document contains a great deal of complexity in the form of several specific questions that are ostensibly intended to allow a greater number of donors to remain eligible to donate. The number of donors that will actually continue to donate must be weighed against the risk of a compliance failure due to the increase in operational complexity imposed by this guidance document.

Again, thank you for the opportunity to comment on this document, which contains much useful information and guidance on a very complex issue.

Please do not hesitate to contact me if you have any questions regarding these comments.

Sincerely,



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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
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?	First donation and each annual physical	Donor at increased risk for CJD	Indefinitely defer, and appropriately counsel	Immediately retrieve and quarantine for subsequent destruction	BPDR (?)	Within one week, notify consignees to immediately retrieve and quarantine for subsequent destruction	No action
Have you ever received human pituitary-derived growth hormone?							
Have you received a dura mater (or brain covering) graft?							
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?	Once	Geographic risk of BSE exposure	Indefinitely defer				
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?							
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?							

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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	BPDR (?)	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?"		?					

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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	BPDR	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		Possible vCJD			Director, Office of Compliance and Biologics Quality, FDA ASAP, (BPDR?)		To be determined by FDA in conjunction with CDC
Any or all (?) of the findings listed below: • 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.		Diagnosis of vCJD	Donor will be deceased		Director, Office of Compliance and Biologics Quality, FDA ASAP, (BPDR?)		Immediately retrieve and quarantine for subsequent destruction any pooled plasma, intermediates, derivatives, and any other material containing plasma

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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
All of the findings listed below: ♦ 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	Immediately retrieve and quarantine for subsequent destruction any pooled plasma, intermediates, derivatives, and any other material containing plasma OR (?) To be determined by FDA in conjunction with CDC (Not clearly stated in document)

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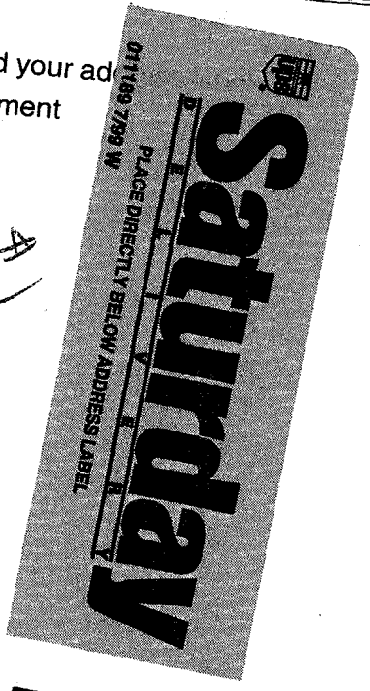

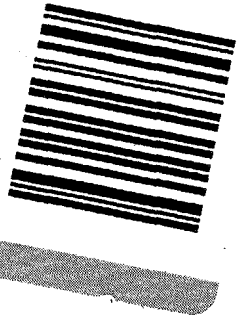

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