DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20852-1448

20 April 2012

Louis M. Katz, MD
Chairman, Transfusion Transmitted Diseases Committee
AABB

Mississippi Valley Regional Blood Center
5500 Lakeview Parkway
Davenport, IA 52807

Dear Dr. Katz:

This is a response to your letter of 25 May 2011 in which you asked FDA to consider simplifying FDA *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* (dated May 2010)[1] by changing FDA's current recommendation at section IV.A.2 to defer indefinitely "... donors with one or more blood relatives diagnosed with CJD... [because they are] considered to be at increased risk of CJD..." by recommending deferral of only those donors with "... one or more **first-degree** relatives diagnosed with CJD."

As we explained previously in our prepared oral response to the same request to FDA at the AABB Transfusion Transmissible Diseases Committee Liaison Meeting on 09 September 2011, OBRR continues to believe that restricting the recommended deferral to donors with first-degree relatives diagnosed with CJD would not be in the public interest and that there is a valid scientific basis for continuing to recommend deferral of any donor having any blood relative diagnosed with CJD. We want to share our reasoning with you and to respond to several specific comments you offered in your letter to FDA of 25 May 2011 as follows:

1. We have indeed not further defined the term "blood relative" in the guidance, however we believe that the generally accepted meaning is clear: a "blood" relative is a relative "by birth"—genetically related rather than related by marriage or adoption—and that definition should be easily understood by most donors.

[1] The Guidance is available through the Internet at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf.

2. While we find informative and somewhat reassuring the recent report by Dorsey and colleagues[2] to which you eluded in your letter (no cases of transfusion-transmitted **sporadic** CJD demonstrated), we note that only one of the donors in that series had a familial CJD. As you know, experience with blood transfusions from donors incubating **variant** CJD has been quite different from that with sporadic CJD, in that four transfusion-transmitted vCJD infections have already been reported in the UK. We do not believe that we can confidently predict the transfusion risk from donors incubating familial forms of CJD from past experience with either sporadic or variant forms of CJD.
3. FDA does not agree that "familial risk for CJD is concentrated in first-degree relatives." We acknowledge that medical histories of first-degree relatives are usually more accessible to donors than are histories of more distant relatives. However, as you know, in persons with mutations in the prion-protein-encoding (*PRNP*) gene associated with familial CJD and similar disorders, disease is expressed as an autosomal dominant trait—fortunately with incomplete penetrance in some kindreds. While only 25% of second-degree relatives of an index case are expected to bear the mutation, that rate greatly exceeds the rate in the general US population.
4. Regarding the definition of familial CJD in the cited report of a WHO Consultation[3] ("... CJD plus definite or probable CJD in a first degree relative ..."), we note that the document cited is expressly described as "... not a formal publication of the World Health Organization ..." The WHO Consultation Report proposing the definition did not explain the reasons why consultants adopted the limited criteria for diagnosis of familial CJD. Therefore, FDA does not agree with the definition in the Consultation Report (please see previous paragraph).
5. FDA is especially concerned about the observation that many patients with CJD who are found to bear a mutation in the *PRNP* gene have had no family history of CJD or similar disease. In one large European series[4] involving several

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[2] Dorsey K et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009;49:977-84

[3] WHO/EMC/ZDI/98.9. Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a. WHO Consultation. Geneva 1998, available through the Internet at www.who.int/entity/csr/resources/publications/bse/whoemczdi989.pdf

[4] Kovács GG, et al. Genetic prion disease: the EUROCJD experience. Hum Genet 2005;118:166-74

countries, 12% to 88% of CJD cases with *PRNP* mutations had no family history of CJD. (Figures for such cases in the US are probably much lower, although a number of US cases initially diagnosed with sporadic CJD have also been found to bear an unexpected mutation in the *PRNP* gene.) Some such cases may result from incomplete penetrance of disease in relatives of the index case, by expression of disease in a relative but only at an advanced age, or by early death of the mutation-bearing parent. For example, the most common *PRNP* mutation associated with familial CJD is E200K, which not only has incomplete penetrance in some populations but also has relatively late onset (and a clinical presentation often indistinguishable from that of sporadic CJD). Even in a clinical series where the penetrance of E200K was relatively high[5], fewer than 20% of cases had onset of clinical illness before the age of 50 years, reaching 50% only at age 60 years. For a relatively young healthy blood donor with the E200K mutation (or a similar mutation) who has young parents and no older siblings, the most likely way to detect the increased risk of familial CJD would be through diagnosis of CJD in a second-degree relative.

6. We understand the practical difficulty of evaluating a blood donor with a history of CJD in a relative. The guidance has attempted to ease several problems. Note that at IV.B "If the donor is not familiar with the term 'Creutzfeldt-Jakob disease' you may take that as a negative response."

[5] Chapman J, et al. The risk of developing Creutzfeldt-Jakob disease in subjects with the PRNP gene E200K mutation, Neurology 1994;44:1683-6

Furthermore, the guidance clarifies at IV.C:

> If you defer a donor because of family history of CJD, you may reenter that donor if
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> 1. The diagnosis of CJD in the family members(s) is confidently excluded, or CJD in the family member(s) is iatrogenic, or the family member(s) is (are) not a blood relative(s); or
> 2. Laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD.

If you need any further clarification, please feel free to contact us.

Best wishes.

Sincerely,

David M. Asher

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