Plasma Protein Therapeutics Association

Date: March 31, 2020 **VIA WEB**

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

SUBJECT: Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt Jakob Diseases by Blood and Blood Components; Draft Guidance for Industry
Docket No. FDA-2012-D-0307

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance for industry "Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt Jakob Diseases by Blood and Blood Components" January 2020 (hereinafter "Draft Guidance"). We will describe in this letter why we support, with a few exceptions, what is described in the Draft Guidance as it would be beneficial in simplifying donor eligibility requirements and expanding a larger donor pool to increase Source Plasma collection.

PPTA encourages FDA to continue dialogue with global regulators to seek convergence in policies to the extent possible. Regulatory convergence facilitates the manufacture of Source Plasma and plasma-derived therapies, which are global resources. Areas of continued disparity are noted in the specific comments.

PPTA is the standards-setting and global advocacy organization that represents the private sector manufacturers of plasma-derived and recombinant analog therapies, collectively known as plasma protein therapies, and the collectors of Source Plasma used for fractionation. Plasma protein therapies are primarily used in the treatment of a particular set of rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies include among others, blood clotting factors for individuals with bleeding and coagulation disorders, immunoglobulins (IG) to treat persons with antibody deficiencies, autoimmune disorders, and certain neurological conditions, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult-onset emphysema and substantially limits life expectancy, albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings in shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

The Draft Guidance provides blood establishments, including Source Plasma establishments (SPE), with revised recommendations intended to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood components. This Draft Guidance replaces the document entitled "Amendment to 'Revised Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products,' Draft

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Guidance for Industry, dated December 2017." The revised or removed recommendations for screening blood (and plasma) donors include: 1) Geographic risk of possible exposure to bovine spongiform encephalopathy, including time spent on U.S. military bases in Europe; 2) receipt of a blood transfusion in certain vCJD risk countries; 3) risk factors for iatrogenic CJD (i.e. a history of taking human cadaveric pituitary-derived growth hormone; 4) having blood relative with CJD; and 5) history of injecting bovine insulin.

PPTA has the following 15 comments:

Comment 1: Section I. Introduction

When describing Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD), the common term of transmissible spongiform encephalopathies (TSE) should be used and all forms should be mentioned: Sporadic Creutzfeldt-Jakob disease (sCJD), familial Creutzfeldt-Jakob disease (fCJD), iatrogenic Creutzfeldt-Jakob disease (iCJD), vCJD, Gerstmann-Stäussler Scheinker (GSS) and fatal familial insomnia (FFI). Please consider using the term "classical CJD" when referring to sCJD and fCJD (as both diseases have similar age of onset, length of duration, clinical and pathological presentation). GSS and FFI are not CJD (as both have different age of onset, length of duration, clinical and pathological presentation from CJD and between each other).

Comment 2: Section II. Background, A. CJD and vCJD

In the first paragraph, it states "a small percentage (less than 1%) of CJD cases are iCJD and are acquired through transplantation of dura matter or cornea allografts from donors with CJD or through injections of human cadaveric pituitary-derived growth hormone (hGH) from contaminated preparations." Please consider clarifying "from donors with CJD" to include donors that might have had any form of TSE/CJD, excluding vCJD. Also, please consider changing "contaminated preparations" to "preparations contaminated with TSE/CJD." "Cornea allografts" are mentioned in this background but not elsewhere in the document. Please note that the European Union (EU) Blood Directive requires donor deferral for corneal transplants. Please provide rationale why FDA does not provide guidance regarding corneal transplants.

Later in the first paragraph, it states, "CJD is rapidly progressive, with a median duration of illness of 4-5 months from onset of symptoms." This is true for sCJD and some forms of fCJD and FFI, but it is not true for many GSS cases in which the disease progresses over number of years.

In the third paragraph, it states that "the following notable features distinguish vCJD from CJD and form the basis of a clinical diagnosis of suspected vCJD." As there is limited use to provide diagnostic criteria for vCJD if criteria for sCJD are omitted, please include the criteria as presented in the 2016 version of the Guidance.

Comment 3: Section II. Background, B. TSE Agents and Blood

In this section, there is no mention of plasma or the safety of plasma-derived therapies. Please consider adding in the applicable paragraph from the 2016 Guidance: "At this time, plasma derivatives have not been implicated in vCJD transmission in any country other than the U.K. To date, no U.S.-licensed plasma-derived products have been manufactured from a donor known to have developed vCJD and no cases of vCJD have been reported from use of a U.S.-licensed plasma derivative. In addition, published studies and information submitted to FDA

show that certain plasma derivative manufacturing steps can remove TSE infectivity, although such experiments have inherent limitations (Refs. 51[1], 57[2]). Based on animal studies as well as on FDA risk assessments, the possibility of vCJD transmission by a U.S.-licensed plasma derivative is extremely small." We also recommend adding the reference from Cai et al (2013)[3] and Roth et al (submitted 2019)[4] highlighting prion removal capacity of plasma protein manufacturing processes.

In the second paragraph, it states, "In contrast to vCJD, no transfusion-transmitted cases of CJD have been described to date, and the risk remains theoretical." Please consider changing "CJD" to "any form of TSE, including sCJD, fCJD, iCJD, GSS and FFI." Corresponding changes should also be made throughout the Draft Guidance.

The second paragraph references two studies which conclude that "there have been no cases of any type of CJD identified among the transfusion recipients to date." However, data from a new study should also be referenced. Holmqvist et al (2020)[5] concluded "Using data from a large, bi-national database of transfused patients, we find no evidence of sCJD transmission. Our data adds to the growing body of evidence indicating that sCJD is not transfusion transmitted."

In the third paragraph, it states, "Abnormal prion protein accumulates in lymphoid tissues in persons with vCJD, but not in persons with sCJD or genetic CJD, possibly reflecting the different propensity for detection of the agent in blood and transmission of vCJD by blood transfusion." However, according to Glatzel et al (2003)[6] and Rubenstein and Chang (2013)[7], the abnormal prion protein was found in lymphoreticular tissues of a proportion of patients with sCJD.

Comment 4: Section III. Discussion, A. Rationale for Revised CJD Recommendations

In the first paragraph, it states "FDA is revising its recommendations on reducing the possible risk of transmission of CJD and vCJD transmission [*sic*] by blood and blood components." In order to clarify the differences between the various forms of CJD, please consider changing

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[1] Foster, P. R. (2004). Removal of TSE agents from blood products. *Vox Sang* 87 Suppl 2: 7-10.
[2] Lee, D.C., Streland, J.C., et al. (2001). A direct relationship between the partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. *Transfusion*. 41: 449-55.
[3] Cai K, Gröner A, Dichtelmüller HO, Fabbrizzi F, Flechsig E, Gajardo R, von Hoegen I, Jorquera JI, Kempf C, Kreil TR, Lee DC, Moscardini M, Pölsler G, Roth NJ. (2013). Prion removal capacity of plasma protein manufacturing processes: a data collection from PPTA member companies. *Transfusion*. Sep;53(9):1894-905.
[4] Roth NJ, Dichtelmüller HO, Fabbrizzi F, Flechsig E, Gröner A, Gustafson M, Jorquera JI, Kreil TR, Misztela D, Moretti E, Moscardini M, Poelsler G, More J, Roberts P, Wieser A, Gajardo R. Nanofiltration as a robust methodology contributing to viral safety of plasma-derived therapeutics. 20 years' experience of the plasma protein manufacturers. A data collection from PPTA member companies. Submitted 20 November 2019 (under revision, 25 December 2019).
[5] Holmqvist J, Wikman A, Pedersen OBV, Nielsen KR, Rostgaard K, Hjalgrim H, Edgren G. (2020). No evidence of transfusion transmitted sporadic Creutzfeldt-Jakob disease: results from a bi-national cohort study. *Transfusion*, doi: 10.1111/trf.15751. [Epub ahead of print]
[6] Glatzel M, Abela E, Maissen M, Aguzzi A. (2003). Extraneural pathologic prion protein in sporadic Creutzfeldt-Jakob disease. *N Engl J Med*. Nov 6;349(19):1812-20.
[7] Rubenstein R, Chang B. (2013). Re-assessment of PrP(Sc) distribution in sporadic and variant CJD. PLoS One. Jul 3;8(7): e66352. doi: 10.1371/journal.pone.0066352.

"vCJD" to "any form of TSE except vCJD or CJD (sCJD and fCJD if other forms are not included in consideration) and vCJD." Additionally, there is a repletion of word "transmission."

In the second paragraph, it states, "There is currently no screening measure that can identify individuals who will later develop CJD." However, fCJD, GSS and FFI can be detected by genetic analysis except for cases with de-novo mutations. Please consider clarifying the statement in the Guidance.

Comment 5: Section III. Discussion, A. Rationale for Revised CJD Recommendations, 1. Donor Deferral for Receipt of Human Growth Hormone (hGH)

This section discusses the history of iCJD and hGH. We recommend for clarity to indicate when the last case of iCJD occurred in the United States.

Comment 6: Section III. Discussion, A. Rationale for Revised CJD Recommendations, 2. Donor Deferral for Having a Blood Relative with CJD

In the first paragraph, it states, "In the 2016 guidance, we recommended that prospective blood donors should be indefinitely deferred if they report having a blood relative with CJD." However, this is incorrect. In the 2016 guidance, it actually states, "We also recommended permanent deferral of donors with CJD or CJD risks, unless, in cases of a family member with CJD, the donor underwent genetic testing that demonstrated absence of a familial-CJD-associated abnormality (mutation) of the prion protein gene—generally requiring complete nucleotide sequencing of both PRNP genes." We recommend updating this section accordingly.

The first paragraph continues, "However, almost all cases reported are sCJD, not a genetic form of CJD." Please consider using different wording for consistency and clarity, such as "According to statistical data, the majority of reported donors who later developed the disease were diagnosed as having sCJD not a fCJD or gCJD." However, not each patient is subjected to autopsy and not in each patient is the genetic analysis is performed. Reference supporting this statement will be appropriate.

Also in the first paragraph, it states that the "rare genetic forms of CJD (e.g. fCJD, GSS, FFI) share pathophysiological features with sCJD" although this is not correct. GSS and FFI are not fCJD or genetic forms of CJD. Only some features are shared between these genetic forms of TSEs. We advise to make appropriate corrections.

The final sentence in the first paragraph states, "We recommend that establishments may stop asking prospective donors about having blood relatives with CJD." This is a problematic recommendation because not enough data are available on transmissibility of genetic forms of the disease by blood transfusion. To avoid all possible risks, especially when transfusions are made to children, please consider keeping this question in place. Additionally, without the question what would trigger a donor's voluntary admission of a family history of CJD?

Guidance continues in the next paragraph that "establishments quarantine and retrieve in-date blood and blood components upon receipt of post-donation information about a known family history of CJD." We believe it would be more effective to prevent the donation from happening in the first place by asking the question about family history of any form of TSE/CJD but agree that when information is obtained, either at the time of donation or post-donation, "establishments quarantine and retrieve in-date blood and blood components" from that donor.

This section concludes with FDA's recommendation that "donors that have one or more family members with genetic CJD (e.g. fCJD, GSS or FFI) are not eligible for re-entry." If the donor provides the documented result of the testing as being negative, he/she should be treated as a healthy normal donor. Therefore, we recommend having 2016 recommendation noted in this section. This comment is also applicable for all instances where family members with genetic CJD is mentioned in the Draft Guidance (i.e., Section IV, A. 3 and Section IV, B. 1).

Comment 7: Section III. Discussion, A. Rationale for Revised CJD Recommendations, 3. Donor Deferral for Receipt of a Dura Mater Transplant

This paragraph states that FDA is "not changing our recommendations to defer donors who receive human (cadaveric) dura mater allografts because such transplantation is still performed in the U.S. and presents a remote risk of iCJD." It is our understanding that the risk is not remote if the donor of the graft is later diagnosed with TSE.

Comment 8: Section III. Discussion, B. Rationale for Revised vCJD Recommendations, 1. Donor Deferral for Geographic Risk of [bovine spongiform encephalopathy] BSE Exposure.

The first paragraph states that "FDA developed a quantitative risk assessment based on a global geographic risk-ranking model that estimated the contributions of donors potentially exposed to BSE in various countries…The model also evaluated the potential additional risk afforded by leukocyte reductions of RBC." We request that FDA also comment on the continued safety of plasma derived therapies considering the changes to the geographic risk deferrals. Additionally, in this section, it states that "the model indicated that U.K., Ireland, and France, the three countries with the most attributed vCJD cases and BSE-related risk, contributed 95% of the total risk exposure in the U.S." Please clarify whether French territories are included in this model and if "total risk exposure" actually means "total donor risk exposure."

The last paragraph of this section states that FDA recommends "that donors previously deferred for geographic risk for time spent in other European countries can be assessed for requalification using the revised recommendations for vCJD geographic deferrals and may be eligible for reentry." We recommend that an algorithm for such re-classification be provided.

Comment 9: Section III. Discussion, B. Rationale for Revised vCJD Recommendations, 2. Donor Deferral for Potential Exposure to U.K.- Sourced Beef on U.S. Military Bases.

The last paragraph of this section states that FDA recommends "that donors previously deferred for time spent on military base in Europe can be assessed for requalification and may be eligible for reentry." We recommend that FDA provides additional advice for this re-assessment.

Comment 10: Section III. Discussion, B. Rationale for Revised vCJD Recommendations, 3. Donor Deferral for Injection of Bovine Insulin Since 1980.

The first paragraph states that "no cases of transmission of vCJD have been reported in recipients of bovine insulin, or other injectable products manufactured in BSE-affected countries." Please clarify on what these "injectable products" are.

The last paragraph of this section states that FDA recommends "that donors previously deferred for injecting bovine insulin can be assessed for requalification and may be eligible for reentry." We recommend that FDA provide additional advice for this re-assessment.

Comment 11: Section IV. A. Blood Donor Screening Management.
In this section, there are multiple references to France and date intervals (e.g. 1980 to 2001 and 1980 to present). Please clarify if French territories are also included in these recommendations and what is the rationale for these time frames. In the 2016 Guideline it states, "deferral of donors for any cumulative travel or residence for a period of five years or more in any European country except the U.K. from 1980 through the present," so it is unclear why there is a change in the date ranges.

Comment 12: Section IV. Recommendations, A. Blood Donor Screening and Management, 2. Donor Deferral.

In subpart a, it states "Defer permanently a donor who has been diagnosed with vCJD, CJD or any other TSE or who has a blood relative diagnosed with genetic CJD (e.g. fCJD, GSS, or FFI)." With the new guidance, the question related to asking donors about having blood relatives to CJD may be stopped. However, if a potential donor volunteers that they have blood relatives known to have genetic CJD, then they should be deferred, and in-date blood and blood components quarantined upon post donation information about CJD family history. This is also restated in the Donor Deferral and Product Retrieval and Quarantine recommendations. It seems misleading to remove the question, yet still must manage donors with CJD family risk. Without having a preventative measure, such as initially asking this question, numerous donations could be potentially destroyed after the fact, i.e. post donation information. It does not seem feasible to rely on donors to voluntarily state "that they have blood relatives known to have genetic CJD." We suggest keeping the recommendation from the 2016 Guidance which better addressed the issue with donors from families with genetic form of TSE. This recommendation about not asking donor about their CJD history, but takes measures if the donor provides information voluntarily, is very confusing in respect to logistics of operations and reporting and removal of implicated product.

Additionally, donors with a family history placing them at risk of developing a TSE still need to be managed per European requirements. Please see above our request that regulators continue to seek convergence in policies when possible or provide a rationale as to why differences remain.

In subpart d, it states "Defer indefinitely a donor who has spent five years or more cumulatively in France or Ireland from 1980 to 2001. Note that this assessment does not include time spent in the U.K, which is evaluated separately in section IV.A.1.b. of this guidance." Please confirm that no action is needed for past donors or donations.

Comment 13: Section IV. Recommendations, A. Blood Donor Screening and Management, 3. Donor Requalification.

In the second paragraph, subpoint 2, it states that "donor previously deferred for receiving hGH are not eligible for reentry." Please provide the rationale behind CBER's risk-based decision to remove hGH as a reason for donor deferral without permitting reentry options. We can make the same query regarding other potential iatrogenic exposures to sCJD, considering the absence of evidence of its transfusion transmission. We recognize that the number of affected donors in both cohorts is very small.

Comment 14: Section IV. Recommendations, B. Product Retrieval and Quarantine; Notification of Consignees of Blood and Blood Components, 1. Blood and Blood

Components Collected from Donors with CJD, Risk Factors Related to CJD, or Geographical Risk Factors for vCJD and 2. Blood and Blood Components Collected from Donors with vCJD, Donors Suspected of Having vCJD or Under Investigation for vCJD.

In this section, there are a couple references to laboratory research and qualified laboratories. Please clarify the purpose for maintaining this blood for research as it should be part of the donor's consent to use blood or blood products for research. Additionally, please provide a list of these qualified laboratories in the Draft Guidance.

Comment 15: Section IV. Recommendations, B. Product Retrieval and Quarantine; Notification of Consignees of Blood and Blood Components, 2. Blood and Blood Components Collected from Donors with vCJD, Donors suspected of Having vCJD or Under Investigation for vCJD.

In the first paragraph, it states that "we recommend you contact FDA as soon as possible upon learning that you collected blood or blood components from a donor later determined to have vCJD, a donor suspected of having vCJD or under investigation for vCJD (i.e. CJD diagnosis and age younger than 55 years)." As a diagnosis for vCJD includes other factors besides a CJD diagnosis and age younger than 55 years (as listed on pages 2 – 3 of the Draft Guidance), we suggest changing the "i.e." to "e.g."

The last sentence of the first paragraph states that "you should consider identifying state and local public health authorities." Please clarify as to why these authorities should be identified.

Continuing, in line b, it states that "you should immediately retrieve and quarantine plasma components that have been pooled for further manufacture and plasma derivatives manufactured from such donors. . . will depend upon results of the investigation." We recommend that guidance provide more explicit recommendations with respect to risk factors and clinical signs and/or diagnostic findings before products are quarantined because younger age alone should not be a justification for quarantine if person does not have a relevant travel history, transfusion history, dura matter, hGH history or relevant clinical signs and/or diagnostic findings. This would create logistical problems and may not justifiable in terms of patient access to PDMPs. Alternatively, the recommendation to contact FDA in subsection "b" could be removed as it is redundant to the recommendation above subsection "a."

In conclusion, PPTA appreciates the opportunity to comment on the Draft Guidance. PPTA welcomes from FDA any questions regarding these comments. Should you have any questions or require additional information please do not hesitate to contact me at: mgustafson@pptaglobal.org.

Respectfully submitted,

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