



April 6, 2018

Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted via <http://www.regulations.gov>

Re: Docket No. FDA-2012-D-307, Amendment to “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry;” Draft Guidance for Industry, 22 December 2017.

Dear Dockets Manager:

AABB, America’s Blood Centers (ABC) and the American Red Cross (ARC) appreciate the opportunity to provide comments to the Food and Drug Administration (FDA) on the December 2017 draft guidance titled “Amendment to ‘Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry;’ Draft Guidance for Industry.” These comments on the draft guidance were prepared by a working group comprised of member experts, including members of AABB’s Regulatory Affairs Committee, the Transfusion Transmitted Diseases Committee, and interested parties from ABC and the ARC.

Our organizations support the FDA’s draft recommendations to amend the document entitled “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry” updated January 2016 (the January 2016 guidance) by revising and removing certain recommended deferrals for geographic risk of bovine spongiform encephalopathy (BSE) exposure and recommending deferral for individuals with a history of blood transfusion in Ireland from 1980 to the present. As noted in AABB’s October 2017 letter to Scott Gottlieb, Commissioner, FDA, we agree that FDA’s evidence-based approach will safely reduce outdated recommendations that have resulted in the unnecessary deferral of a substantial number of

potential blood donors each year. We believe FDA should continue to monitor the risk of transfusion-transmitted variant Creutzfeldt-Jakob Disease (vCJD) and Creutzfeldt-Jakob Disease (CJD) with the intention of using this risk-based approach to further reduce overly restrictive deferral requirements.

We have provided recommendations for changes intended to improve the clarity and operational feasibility of the recommendations. We have also requested corrections for a recurring error that is addressed in multiple comments.

COMMENT 1

We commend FDA for proposing to update the recommendations in the January 2016 guidance by moving to a risk-based approach that would limit deferrals to U.K., France and Ireland, and remove the current deferral for a long list of countries in Europe. We are pleased to note that FDA estimates deferrals using model 2 in Table 1 (Results from Risk Assessment Model) could safely remove the long-standing deferral of approximately 100,000 individuals.

COMMENT 2

New Data Support Re-evaluation of CJD Transfusion-Transmission Risk

The theoretical risk of the transfusion-transmission of classic CJD is not re-evaluated in this draft guidance. We request that you review the new information prior to finalizing the guidance.

Our recommendations and rationale: We request that the agency follow the same risk-based approach to re-evaluate and update the CJD and vCJD policy based on the new data on blood safety that was recently published. The August 2017 Transfusion article, “Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk”, by Crowder et al, (linked below) finds no evidence to support deferral for the theoretical risk of CJD transfusion-transmission based on this study’s lookback findings dating back to 1985, which is consistent with other epidemiologic studies. The article states:

“The additional years of data presented in this US study update combined with the published UK study data on the transfusion transmission risk associated with classic forms of CJD include 94 donors, 1037 recipients, and 5128 person-years of observation, with no reported cases of CJD in the traced recipients. We believe that these findings further support our conclusion that the risk of transfusion transmission of classic CJD remains theoretical. However, due to ongoing concern that CJD may be transmitted by blood, study enrollment and follow-up will continue.”

COMMENT 3

Regulatory Reform – Deferral of U.S. Military and Department of Defense Personnel

AABB sent the October 19, 2017 letter to Commissioner Gottlieb on behalf of our stakeholders, requesting that FDA consider reevaluating certain regulations and recommendations that are considered outdated, duplicative, overly burdensome and unnecessary to protect the public health. We believe our request is consistent with the CBER Interim Strategic Plan FY 2017-19 and the agency's efforts to identify future needs and direction. We have identified regulations and recommendations that (1) do not increase safety; (2) are outdated, duplicative, unnecessary or overly burdensome; (3) unnecessarily restrict access to products and technology; or (4) stifle innovation.

We recommend reviewing the information in this letter prior to finalizing the guidance. The letter characterized the current donor deferral policy related to the risk of transmission of CJD and vCJD as outdated, overly burdensome and unnecessary, stating:

“The 2016 donor deferral recommendations for potential exposure to Creutzfeldt-Jakob Disease (CJD) and variant Creutzfeldt-Jakob Disease (vCJD) do not reflect current science. The overly restrictive donor deferral recommendations have a substantial negative impact on the military blood system due to the travel of military members throughout the United Kingdom. Despite the absence of vCJD cases in the U.S. military and Department of Defense personnel over many years, these personnel continue to be ineligible for donation. This negative impact is also felt outside the Armed Services Blood Program because veterans and active duty personnel would be motivated to respond to the needs of community blood centers but remain deferred. Additionally, the policy is confusing, and difficult to interpret and enforce due to donors’ and their families’ non-consecutive travel.”

Our recommendations and rationale: Our organizations do not agree with FDA's decision to retain the outdated and unnecessary recommendations found in Section IV. A. 5. of the January 2016 guidance:

“You should indefinitely defer former or current U.S. military personnel, civilian military personnel, and their dependents as follows:

- a. *Individuals who resided at U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or*
- b. *Individuals who resided at U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996.”*

We believe this decision to retain the military deferral is a missed opportunity for FDA to apply the same evidence-based approach to re-evaluate the deferral policies for the military employees and their dependents, none of whom have been diagnosed with vCJD to our knowledge. We request that FDA revisit this deferral requirement based current scientific information, including the absence of vCJD cases in the U.S. military and Department of Defense personnel (and their

family members) over many years, as described in Comment 2. Failing to amend these deferrals, we request that the agency address in the final guidance the circumstances under which they will be re-evaluated.

COMMENT 4

Clarification of this Complex Issue

The October 2017 Regulatory Reform letter also provided our observation that the current “policy is confusing, and difficult to interpret and enforce due to donors’ and their families’ non-consecutive travel” in the U.S. military and Department of Defense personnel over many years. The recommendations are difficult to follow in the December 2017 draft guidance. Explanations in the guidance are not sufficient to guide centers to the agency’s current thinking and interpretation.

Our recommendations and rationale: Evidence of the confusion and difficulty in understanding the recommendations is abundantly documented in the high proportion of biological product deviation reports for post-donation information reported to the agency resulting from the CJD/vCJD guidances.

Because it is critical to the work of our members, we recommend FDA improve clarity by:

- Using a clear and specific definition for “family member” and the rationale for the definition.
- Using examples to clarify commonly misunderstood deferral criteria that are known to FDA.
- Using plain language and phrasing to diminish confusion and variations in interpretation.
- Consolidating all information in the recommendation to ensure the reader fully understands the scope and intent rather than relying on a footnote to clarify information.
- Continuing to use Tables as a tool to present the changes.
- Including a clear “crosswalk” in tables to tightly link current recommendations to new recommendations in the Appendix Tables 1 and 2. For example, linking the current section for recommendation IV. D. 2. (page 28, January 2016 guidance) to proposed recommendation III. B. 4 in the December 2017 draft guidance. Currently, the proposed recommendations are not numbered in the various tables.

More detailed comments follow in Comment 6 with specific suggestions for improving clarity.

COMMENT 5

As part of the Introduction, FDA explains its plans to incorporate into an updated final guidance any new recommendations that are adopted from the December 2017 draft guidance and that “All other recommendations in the 2016 vCJD Guidance will remain unchanged.” This decision to present only the proposed revisions contributes to a lack of clarity in the December 2017 draft guidance that is further compounded by a series of random errors in the content, and inconsistencies between sections and tables, addressed later in comments 6-0 to 6-4.

Our recommendations and rationale: We strongly recommend presenting all recommendations that will be issued in the final guidance, including those that will remain unchanged.

When portions of the recommendations are not presented, the reader must move back and forth between the two lengthy, complex guidance documents to achieve a full understanding of the proposed changes that form FDA's new policy. The public health is best served when the guidance includes a complete explanation of all recommendations that will serve as a clear record of FDA's intent.

FDA identifies some recommendations that will be revised and some that remain unchanged in Appendix Tables 1 and 2. However, the tables contain the discrepancies and random errors related to the deferral for time spent in France and Ireland that make it difficult to determine FDA's intent.

COMMENT 6

We have observed discrepancies and recurring errors in the draft guidance:

- The revisions to recommendations related to deferral for time spent in France or Ireland.
- Related to proposed recommendation III. B. 4., primarily, and
- Repeated in some but not all related areas.

Our comments follow in 6-1 to 6-4, provide our observations related to this series of inconsistencies, and our recommendations related to time spent in France or Ireland.

COMMENT 6-1

Upon close review, FDA's proposed strategy to move away from the deferral based on risk for time spent in Europe to deferral for time spent in France and/or Ireland is achieved in 3 steps:

- These 3 steps are not consistently presented throughout the document.
- The key phrasing related to the inconsistencies are shown in bold and underlined to assist you in linking the information that relates to the error, as described here and in comments 6-2 to 6-4.

Our recommendations and rationale: We find the first two steps (below) in this approach to be consistent with the detailed explanations in the background information and FDA's stated intent. We do not recommend any changes to the following:

FIRST STEP: The agency plans to update to the January 2016 guidance by **deleting, in its entirety, recommendation IV. A. 8.** (on page 25).

As shown in the December 2017 draft guidance, Appendix Table 1 (page 13), the agency plans to DELETE Recommendation IV. A. 8:

*“You should indefinitely defer donors of Whole Blood, blood components for transfusion, and Source Leukocytes, who have lived cumulatively for five years or more in Europe from the beginning of 1980 until the present. **(Note this criterion includes time spent in the U.K. from 1980 through 1996 and time spent in France from 1980 to the present.)** Unless otherwise unsuitable (for example, because they lived in the U.K. or France or on U.S. military bases for the periods of time noted previously), these donors remain eligible for Source Plasma donation.”*

We also see in Appendix Table 2, (page 14), that FDA plans to delete the corresponding recommendations related to the Donor History Questionnaire (DHQ) as would be expected.

SECOND STEP: The agency plans to update the recommendations in the January 2016 guidance by:

Revising recommendation IV. A. 4., (January 2016 guidance, page 24), *“You should indefinitely defer donors who have spent five years or more cumulatively in France from the beginning of 1980 to the present.”*, **by adding “or Ireland”** (December 2017 draft guidance, page 7) to read:

Defer indefinitely a donor who has spent five years or more cumulatively in France or Ireland² from 1980 to 2001.

Footnote 2 specifies: Note that Northern Ireland is part of the U.K.

However, these proposed changes are not consistent with the third step (Refer to comment 6-2).

COMMENT 6-2

THIRD STEP: As presented in Appendix Table 1 (page 13), the agency plans to revise the recommendations to update the DHQ to assess the donor’s history for risks defined in the deferral criteria by:

Revising the following deferral for France in question 4 (January 2016 guidance, page 28) to include Ireland:

“To identify donors of Source Plasma who have additional geographic risk of BSE exposure, you should ask the following questions:

4) Since 1980, have you spent time that adds up to five years or more in France?”

AND DELETING the following content (shown in Appendix Table 2, page 14):

“For donors of Whole Blood, components intended for transfusion, and Source Leukocytes, you should substitute the following for question 4):

Question 4 (alternative): *Since 1980, have you spent time that adds up to five years or more in Europe (including time spent in the U.K. from 1980 through 1996)?*

Donors deferred from donating Whole Blood based on this question remain eligible to donate Source Plasma in a CBER-approved program, unless they are otherwise unsuitable.

For Donors of Source Plasma, however, you should continue to ask the original version of Question 4, as described above, rather than the alternative.

European countries with BSE risk that FDA has identified as a basis for donor deferral are listed in the Appendix to this document. We will periodically issue new guidance to update the list of countries with BSE risk, to be used as a basis for donor deferral. FDA does not currently consider those European and non-European countries that are not listed in the Appendix to this document to pose a BSE-exposure risk warranting deferral of donors who have spent any period of time there, even if these countries have reported cases of BSE to the OIE.”

To read (December 2017 guidance, page 8):

“We recommend that blood collection establishments update their donor history questionnaires (DHQ), including full-length and abbreviated DHQs and accompanying materials (e.g., flow charts) and processes to incorporate the recommendations provided in this guidance.

We recommend that the updated DHQ and accompanying materials include the following elements to assess donors for geographic risk of BSE exposure:

...

4. A history of travel or residence that adds up to five years or more in France or Ireland from 1980 through 2001 (including time spent in the U.K. from 1980 through 1996.)”

- Appendix Table 1 (pages 13) - FDA presents the change in deferral criteria in the proposed recommendation:

Current deferrals-January 2016 vCJD Guidance		Proposed deferrals
IV.A.4	You should indefinitely defer donors who have spent 5 years or more cumulatively in France from the beginning of 1980 to the present.	You should indefinitely defer donors who have spent 5 years or more cumulatively in France or Ireland (<u>but not Northern Ireland, which is part of the U.K.</u>) from 1980 through 2001.

Our recommendations and rationale:

- It is important to note that when similar recommendations were issued in the January 2016 guidance to update the DHQ, the recommendations named the specific deferral criteria for time spent in Europe with a reference to include time spent in the U.K. In the December 2017

guidance, we do not see the expected correlation between deferral criteria and instructions to update the DHQ.

- As written, Recommendation III. B. 4. introduces the unexpected phrase “**including time spent in the U.K. from 1980 through 1996**” and creates new deferral criteria.
- If the phrase regarding the U.K. risk is retained in III. B. 4., we request an explanation of the revisions to transition from the current recommendations for question 4 and alternative question 4 to the proposed recommendation in III. B. 4.
- We request clarification on this issue because we cannot interpret the current recommendations with confidence based on the inconsistencies. Refer to comment 6-4.

We recommend the agency more clearly communicate the revisions and establish a clear and consistent approach.

COMMENT 6-3

- It is FDA’s long-standing practice to present all deferral criteria in one section, followed by recommendations for updating the DHQ, which mirror the deferral criteria.
- In the past, we have *not* seen FDA introduce new deferral criteria when addressing updates to the DHQ.
 - We believe FDA intended to continue the standard practice, with Section III. B. (December 2017 guidance, page 7) providing recommendations for updates to the DHQ to capture the proposed deferral criteria defined in Section III. A.
 - We cannot conclude FDA intended to propose new deferral criteria in recommendation III. B. 4. that would be established based on the unexpected phrase, “**including time spent in the U.K. from 1980 through 1996**”.

Our recommendations and rationale: We cannot conclude that FDA intended to add the unexpected phrase, as written, because:

- Section B does not mirror the deferral criteria in Section III. A. (a departure from established FDA practice) and introduces the unexpected phrase “**including time spent in the U.K. from 1980 through 1996**”.
- Footnote 2, “**Note that Northern Ireland is part of the U.K.**”, clarifies that Northern Ireland is not part of Ireland. This clarification indicates that risks associated with Northern Ireland are assessed independently of Ireland and as part of the U.K. The proposed recommendation in III. A. 2. states:

Defer indefinitely a donor who has spent five years or more cumulatively in France or Ireland² from 1980 to 2001.

- The unexpected phrase would recommend an update to the DHQ to capture a risk that does not exist in the deferral criteria recommended by FDA in III.A. 2. and conflicts with footnote 2.
- This unexpected phrase is not reflected in the background information. All deferral criteria and time periods clearly laid out in Section A., “Recommendations for Donor Deferral”, are

based on geographic risk of BSE exposure unique to the U.K. or to France and Ireland, as described in the background information.

- The background does not describe the basis for providing a threshold for risk associated with overlapping geographical risks for deferral recommendations listed in both III. A. 1. and A. 2. that would capture all three areas (U.K., Ireland, and France).

We recommend:

- FDA more clearly communicate the revisions and establish a clear and consistent approach. We found that in other recommendations, areas of risk are defined within the recommendations. This approach is more effective but is not a consistent practice. A footnote can be easily overlooked.
- Based on the recommendation to “defer indefinitely a donor who has spent five years or more cumulatively in France or Ireland² from 1980 to 2001”, the corresponding recommendation in Section III. B. 4. (page 8) should be revised to include the information in footnote 2 and read:

4. A history of travel or residence that adds up to five years or more in France or Ireland from 1980 through 2001 (**but not Northern Ireland, which is subject to the U.K. deferrals**).

- Using a direct statement within the recommendation to clearly define the areas of risk, ensures the information is noted and understood. We believe FDA determined that a clarification regarding Ireland and Northern Ireland is needed. We agree that this information is useful and recommend it be revised to state more clearly that this donor assessment does not include Northern Ireland because Northern Ireland is subject to U.K. deferrals.

COMMENT 6-4

As noted above, the unexpected phrase regarding risk associated with the U.K. is not seen in key areas of the document, such as Table 2 (December 2017 guidance, page 6) and Appendix Tables 1 and 2, (pages 13-14).

Throughout the background information, FDA consistently addresses the risk associated with the U.K. completely independently from the risks associated with France and Ireland.

Our recommendations and rationale: Our understanding of FDA’s intended approach is consistent with Table 2 (below) which shows most clearly FDA’s plans to revise the recommendation in the January 2016 guidance to read “**Donors who spent cumulatively ≥ 5 years in France or Ireland from 1980 to 2001.**”

Table 2. Summary of Current Geographical vCJD Blood Donor Deferrals and the Proposed Deferrals

Current deferrals	Proposed deferrals
Donors who spent cumulatively ≥ 3 months in the U.K. from 1980 to 1996	Unchanged
Donors who spent cumulatively ≥ 5 years in France or other countries in Europe from 1980 to present	Donors who spent cumulatively ≥ 5 years in France or Ireland from 1980 to 2001
Donors with a history of blood transfusion in the U.K. and France from 1980 to the present	Donors with a history of blood transfusion in the U.K., France, or Ireland from 1980 to the present
Donors based on time and duration of exposure at military bases in Europe during periods in which commissaries and mess halls were supplied with beef products from the U.K.	Unchanged

- Further, the discussion of Table 2. (December 2017 guidance, page 5,) is consistent with our understanding of FDA’s intent and do not mention a “third category” for cumulative risk of deferral criteria III. A. 1. and A. 2.:

“Table 2 includes a summary of the proposed recommendations for geographical donor deferral changes...The risk assessment model also indicated that Ireland had a BSE risk similar to that of France. Therefore, we are recommending the same deferral period for time spent in France and Ireland and adding a deferral for individuals who had a blood transfusion in Ireland from 1980 to present. The risk period for BSE exposure in Ireland and France is limited to 1980-2001 based on implementation of safeguards to the food chain by 2001 within the European countries (Ref. 37).”

- Appendix Tables 1 and 2 (pages 13 -14) should reflect the same deferral criteria:

Current deferrals-January 2016 vCJD Guidance		Proposed deferrals
IV.A.4 <i>[copied from Appendix Table 1]</i>	You should indefinitely defer donors who have spent 5 years or more cumulatively in France from the beginning of 1980 to the present.	You should indefinitely defer donors who have spent 5 years or more cumulatively in France or Ireland <u>(but not Northern Ireland, which is part of the U.K.)</u> from 1980 through 2001.
IV.D.2. question 4 <i>[copied from Appendix Table 2]</i>	Since 1980, have you spent time that adds up to 5 years or more in France?	Assess donors for a history of travel or residence that adds up to 5 years or more in France or Ireland from 1980 through 2001 <u>(including time spent in the U.K. from 1980 through 1996).</u>

- Based on the discrepancies, we cannot conclude that the agency intended to introduce a “third category of risk” that would capture deferrals listed in recommendations in both III. A. 1. and A. 2.
- There is inadequate information and explanations in this draft to conclude that FDA intends to defer a subset of donors for the cumulative time of 2 months spent in Northern Ireland and 4 years, 10 months spent in Ireland.

We recommend the agency more clearly communicate the revisions and establish a clear and consistent approach.

COMMENT 7

We request that FDA correct and clarify the final guidance based on the following questions.

- Is it FDA's intent to defer donors based on the recommendation for cumulative time spent in France and Ireland, as stated in III. A. 2, **without including** time spent in the U.K. from 1980 through 1996?
- If so, there are discrepancies that must be revised for agreement with the recommendation in III. B. 4. Refer to comments 6-0 to 6-4, for examples of the recurring errors.
- If not, and FDA intends that the phrase "**including time spent in the U.K. from 1980 through 1996**" should apply, then the agency must clearly and specifically address this very significant element for donor deferral in Recommendation III. A. 2 and the related discrepancies throughout the draft guidance.

We believe any final guidance must be revised significantly to improve the background information:

- to clarify the basis for this donor assessment and deferral,
 - to correct the recommendations in III. A. 2. and/or III. B. 4. to capture the same deferral,
 - to consistently include this critical element of the deferral and discrepancies throughout the draft guidance.
-

About us:

AABB is an international, not-for-profit association representing individuals and institutions involved in the fields of transfusion medicine and cellular therapies. The association is committed to improving health through the development and delivery of standards, accreditation and educational programs that focus on optimizing patient and donor care and safety. AABB membership includes physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers. AABB members are located in more than 80 countries and AABB accredits institutions in over 50 countries.

Founded in 1962, ABC is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The ARC shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international

humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer these comments. We look forward to continuing to work with the FDA on patient and donor safety initiatives. Questions concerning these comments may be directed to SCarayiannis@aabb.org.

Sincerely,

Sharon Carayiannis, MT(ASCP)HP
Director, Regulatory Affairs
AABB