March 24, 2023

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

Submitted via http://www.regulations.gov

Re: Docket No. FDA-2015-D-1211, Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products; Draft Guidance for Industry

Dear Dockets Manager:

The Association for the Advancement of Blood and Biotherapies (AABB), America's Blood Centers (ABC), and the American Red Cross (ARC) are pleased to submit joint comments to the U. S. Food and Drug Administration (FDA) in response to the recently released draft guidance, *Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products* (the draft guidance) recommending an evidence-based approach for determining donor eligibility based on each individual's behavior and risks, regardless of gender or sexual orientation.

Our organizations appreciate the opportunity to submit comments on this policy change, critical considerations, and strategies for a safe and effective implementation, as well as comments specific to new and revised recommendations in the draft guidance. As you develop the final guidance, please consider our comments and requests representing feedback from our organizations, member experts from our committees, and collective membership.

COMMENT 1 – Support for evidence-based decision-making to update donor eligibility requirements.

AABB, ABC, and ARC commend FDA for the extensive work conducted over many years to support this landmark policy change resulting in new, evidence-based recommendations, incorporating individual donor assessment to determine blood donor eligibility and remove unnecessary deferrals.

We applaud FDA's stated commitment to evolve policies:

- based on the best available science and data driving updated recommendations for donor eligibility criteria while maintaining appropriate safeguards to protect patients receiving blood transfusions.
- based on the analysis of new information from numerous data sources, including:
    - international data on similar changes implemented by the United Kingdom and Canada with post-implementation data,
    - surveillance information obtained from the Transfusion Transmissible Infections Monitoring System (launched by FDA and NHLBI in 2015 to monitor US blood safety and rates of transfusion-transmitted infections),
    - data assessing performance characteristics of nucleic acid testing for HIV, and
    - results from the FDA-funded Assessing Donor Variability And New Concepts in Eligibility (ADVANCE) study.
- using an effective, updated approach to assess donor eligibility for each individual, including risk for transfusion-transmitted infections:
    - moving away from outdated MSM deferral policies and the resulting unnecessary deferrals associated with gender or sexual orientation.
    - using the same set of evidence-based donor eligibility criteria and questions for all individuals.

Our organizations look forward to the publication of the data supporting this decision for a full understanding of the new information supporting FDA's determination that this approach will support our mutual commitment to both patients and donors by providing for appropriate and effective donor eligibility assessment while maintaining the safety of the blood supply. We received feedback asking that the agency consider replacing the phrase "Individual Risk Assessment" with "Individual Donor Assessment" in the final guidance, where appropriate, to remove the negative connotation perceived by donors and the public.

COMMENT 2 – Recommendations to address donor use of PrEP/PEP/ART

Background: These comments are directed to new recommendations in Section III.B. 2, 3 and 4, page 8.

We agree with FDA's first steps to address the impact of donor use of PrEP/PEP/ART, and the new recommendations that are consistent with AABB's Association Bulletin 22-03, *Updated Recommendations on Donor Deferral for Use of Antiretroviral Medications for HIV Prevention and Treatment including Long-Acting Injectable PrEP and the Impact on Blood Safety*.

- We strongly support FDA's plans to continue to monitor the impact of these new medications on blood donor testing for HIV and the agency's stated intention to make evidence-based adjustments in the deferral criteria for donor use of PrEP and PEP as new information becomes available.
- We appreciate the early public clarifications and ask the agency to continue those efforts to clarify that this is a medication deferral solely focused on the potential impact of PrEP/PEP on donor testing that could result in an undetected HIV infection, and is not

intended to target any subset of individuals based on their informed decision to use HIV prevention medications, as provided in:
    - FDA's Jan. 27 news release stating that the "available data demonstrate that the use of PrEP and PEP may delay detection of HIV by licensed screening tests for blood donations, potentially resulting in false negative results."
    - a February 2 briefing by Dr. Peter Marks, Director of CBER, where he explained that this decision was:
        - the first step to address the impact of PrEP medications on donor testing that could lead to an undetected HIV infection.
        - driven by science, after evaluation of the data available to date, and will be updated in the future when new evidence becomes available.
- Based on persistent misinformation and the resulting misconceptions about PrEP/PEP use and blood donation, we are requesting that our federal government partners join FDA in protecting the safety of the blood supply by actively promoting consistent messaging at every opportunity to tell the public that:
    - no one should stop taking HIV prevention medications, or any other medication, simply to donate blood,
    - every donor must pay attention to instructions at the top of the Medication Deferral List, developed by AABB's Donor History Task Force (DHTF), to ensure donors receive this instruction every time they visit a donor center: **"DO NOT STOP taking medications prescribed by your doctor in order to donate blood."**
    - PrEP/PEP medications are highly effective in preventing sexual transmission of HIV but that does not hold true for HIV transmission by blood transfusion where the "volume administered is relevant as transfusion involves volumes 100 to 1000 times greater than previously associated with HIV transmission" through sexual contact.
    - this medication deferral applies to all donors taking PrEP/PEP/ART without regard to gender or sexual orientation for the reasons described in the next bullet.
    - this medication deferral is completely unrelated to the reason a person decides to take HIV prevention medications and is solely based on the highly effective pharmacokinetics of these drugs:
        - to suppress the levels of HIV in an infected person to undetectable levels,
        - to increase the chances of a false negative HIV test, which means a donor using PrEP/PEP could unknowingly transmit HIV to a patient because the donor was infected but had undetectable levels of HIV when tested using the best donor testing methods available today.
        - Undetectable=Untransmittable does NOT apply to blood donation.

COMMENT 3 – Implementation: Consistent updates to cellular therapy requirements where appropriate

Background:

This comment is offered in support of the important work of our members who provide

lifesaving cellular, tissue and biotherapy products. Our organizations believe that updated requirements for biotherapy and cellular therapy products, consistent with updated requirements for blood products *wherever possible,* are critical to ensure effective donor screening processes to support patient and donor safety. Equally as important, updated requirements to prevent outdated and unnecessary deferrals are critical to ensuring these lifesaving products are available to meet the critical needs of patients.

Request:

Our organizations are requesting timely evaluation of evidence-based decisions to update requirements for blood products to determine where similar updates can be appropriately applied to requirements for biotherapy products.

COMMENT 4 – Implementation: Importance of consistent public messaging at all levels

Background: This general comment is directed to Section IV. Implementation, page 12.

Our organizations know that consistent communication to the public and across our vein-to-vein community directly supports a successful transition to individual donor assessment and continued transfusion safety for patients who must rely on blood as an essential medicine. We know that consistent communication must:

- include blood donor centers, hospitals, and the associations and organizations who support them, as well as our federal government partners, as noted above.
- include relevant information for public messaging, to earn trust with accurate explanations of the goals for this change, the science influencing these decisions, and the importance of blood as an essential medicine for patients.
- demonstrate our mutual commitment to patients and donors who are at the heart of all we do, with strong relationships between federal regulators and partners in regulated industry as evidence of our commitment.
- demonstrate the federal government's commitment to supporting this landmark change with public messaging to underscore the scope of these complex changes at blood donor centers – changes so important that they must be executed perfectly to meet all FDA and AABB requirements.
- acknowledge that each regulated facility must determine an appropriate timeline for implementation based on the unique needs and challenges of that facility – recognizing the heavy responsibilities facing blood donor centers that are committed to providing the high level of blood safety we enjoy in the United States.
- actively encourage public patience during the transition and promote increased support for donation and the remarkable work of blood donor centers and transfusion services that are committed to serving donors and patients.

Request for important messaging on implementation and timelines

With the above comments in mind, please establish public messaging noting FDA's landmark decision and emphasizing our collective commitment to sustaining the high level of safety for our blood supply.

Please clarify whenever possible that these landmark changes in regulatory policies:

- are the first of many steps that must be executed very carefully by donor centers.
- require intense focus for successful implementation of changes to highly complex safety systems that must be updated, tested, and validated for performance, including changes to blood establishment computer systems which are FDA-regulated devices responsible for multiple safeguards.
- require extensive staff training and education.
- must be implemented with a **commitment to safety over speed** to maintain the public's trust in the blood supply.
- require patience and public support for blood donor centers supplying transfusion services to meet the needs of patients across the country.

COMMENT 5 – Implementation: Recognizing challenges and extended implementation timelines based on the collection of plasma for further manufacture.

Background: This comment is based on the background information in Section II of the draft guidance, page 5.

We noted that the following statement from the August 2020 HIV Guidance supporting the important work of blood centers collecting plasma for further manufacture was omitted in the draft guidance:

From page 4 of the August 2020 HIV Guidance:

> *To comply with global regulatory requirements on deferral policies, it is acknowledged that manufacturers of blood and blood components, including Source Plasma, collected in the U.S. and intended for further manufacturing use in other countries,* ***may not be able to implement all of FDA's recommended shortening of deferral policies noted in this guidance, and instead may elect to maintain longer deferral policies****.*

The draft guidance does not address the information, stating only this on page 5:

> *In considering the available data and the feasibility of other approaches, we believe implementation of the gender-inclusive, individual risk-based approach recommended in this guidance will maintain the current high level of safety of blood and blood components, including Source Plasma in the U.S.*

We appreciate the agency's stated interest in future initiatives to harmonize regulatory requirements with international agencies and authorities regarding Source and Recovered Plasma distributed to other countries. We look forward to working with the agency to resolve some of the current challenges and limitations.

Request for additional information

We are requesting that the final guidance include additional information on these important considerations, some of which were captured in the August 2020 guidance, to:

(1) demonstrate FDA's support of the important work of blood centers collecting plasma which will be further manufactured into lifesaving products.
(2) acknowledge most blood centers send excess plasma inventory to be manufactured into life-saving products to ensure the entire donation is used for patients in need. The receiving manufacturers who further process the excess plasma products may be located in other countries with additional regulatory requirements. As such, we are requesting the final guidance include the following information:

To comply with international regulatory requirements ***and*** *deferral policies, manufacturers of blood and blood components collected in the U.S, including Source Plasma, it is acknowledged that* ***blood centers providing plasma for further processing may need to add certain questions to the end of the donor history questionnaire, an option provided in the Instructions for Use of the AABB DHQ, to ensure the collection of plasma complies with additional requirements*** *established by other countries.* ***Complying with these additional international regulations may require blood centers to retain certain more restrictive donor deferral criteria, delaying full implementation of FDA's new recommendations.***

COMMENT 6 - Implementation: Requirement for an FDA Prior Approval Supplement (PAS) for changes to the AABB DHQ formally recognized by FDA

Background: This comment is directed to recommendation 2 under Section IV, Implementation, page 12.

The impact of this landmark policy change affects all areas of operations. Section II, Background, of the draft guidance provides an extensive discussion of the technical issues supporting this significant policy change but does not provide a discussion to support this *major* change and significant regulatory considerations that are critical for compliance. An explanation of reporting requirements in 21 CFR 601.12 is important given the unique circumstances that demand intensive focus on preparing to achieve compliance with these new recommendations and the range of complex implementation options. Provision of detailed regulatory information, including examples demonstrating major and minor changes that must be considered to determine if a PAS is or is not required, will support compliance efforts, as well as timely and effective implementation.

The recommendations in Section IV copied below address some but not all reporting requirements for implementation of the AABB DHQ with or without revisions. The narrow scope of that information, in the absence of background information for regulatory reporting, introduces the opportunity for misinterpretation because significant regulatory considerations are not included. Recommendation 2 is confusing as it does not include the reporting requirements for "major" and "minor" revisions when referring to the implementation of a "revised version of

the DHQ… prepared by the AABB Donor History Task Force … and found acceptable by FDA", as shown below. FDA's clarification of reporting requirements with an explanation of circumstances that qualify as a major or minor change is particularly important to support compliance efforts by our members collecting plasma for further manufacture. Our members are requesting clarification on reporting requirements to confirm that a PAS is not required when using the AABB DHQ formally accepted by FDA, inserting additional questions required by plasma fractionators in the designated area (at the end of the DHQ), and reporting implementation on the annual report as a minor change.

> *IV. IMPLEMENTATION*
>
> *Licensed blood establishments must report changes to their approved application to FDA in accordance with 21 CFR 601.12.*
>
> 1. *Licensed blood establishments that revise their own DHQs and accompanying materials must report the change to FDA in a Prior Approval Supplement (PAS) Supplement under 21 CFR 601.12(b). Include the following information in your PAS Supplement:*
>   a. *Form FDA 356h "Application to Market a New or Abbreviated New Drug, or Biologic for Human Use."*
>   b. *Cover letter describing the request and contents of the supplement.*
>   c. *The DHQ and accompanying document(s). Please highlight the modifications.*
> 2. *Licensed blood establishments that implement a revised version of the DHQ and accompanying materials prepared by the AABB Donor History Task Force or the Plasma Proteins Therapeutic Association (PPTA) and found acceptable by FDA must report the changes to FDA in an annual report under 21 CFR 601.12(d), noting the date the process was implemented (21 CFR 601.12(a)(3)).*
>
> *Unlicensed establishments are not required to report this change to FDA.*

Recommendation and request for additional information

We are suggesting revisions in two areas of the final guidance.

(1) The phrase "*a revised version of*" introduces confusion because it is unclear which DHQ is referenced. We suggest the following revisions to recommendation 2 in Section IV, below, to clarify that this refers to the DHQ that is updated to reflect the new requirements in the guidance, formally accepted by FDA:

> *Licensed blood establishments that implement ~~a revised version of~~ the DHQ and accompanying materials prepared by the AABB Donor History Task Force or the Plasma Proteins Therapeutic Association (PPTA) based on the recommendations in this guidance, and found acceptable by FDA must report the changes to FDA in an annual*

report under 21 CFR 601.12(d), noting the date the process was implemented (21 CFR 601.12(a)(3)).

(2) We recommend (a) expanding Section II. Background of the final guidance to address important regulatory considerations specific to this landmark policy change, including examples of "major" and "minor" changes to clarify requirements for use of a PAS versus annual report, and (b) two additional recommendations to Section IV. Implementation for the examples below which are not currently addressed in the guidance:

EXAMPLE OF A MINOR CHANGE:
For the blood collection establishment that collects plasma for fractionators based outside of the United States:

When the fractionator continues to require additional or more restrictive donor eligibility criteria, the addition of question(s) to the "area for additional questions" at the end of the DHQ would qualify as a "minor change".

We propose adding a recommendation as number 3 under Section IV to address the above example of a minor change:

Licensed establishments that implement the DHQ and accompanying materials as prepared by the AABB Donor History Task Force and found acceptable by FDA in their entirety, but modified by the addition of more restrictive criteria using the area for additional questions at the end of the DHQ, as described in the Instructions for Use of the DHQ, must report the changes to FDA in your annual report under 21 CFR 601.12(d), noting the date the process was implemented (21 CFR 601.12(a)(3)).

EXAMPLE OF A MAJOR CHANGE:
For the blood collection establishment that adds questions to the AABB DHQ formally accepted by FDA without using the area for additional questions at the end of the DHQ:

The blood establishment is making a major change requiring a PAS if:

- the language of questions on the DHQ submitted by AABB and accepted by FDA is changed, and/or
- the order of questions on the DHQ submitted by AABB and accepted by FDA is changed, including inserting additional questions into the body of the questionnaire.

We propose the following recommendation as number 4 under Section IV to address the above example of a major change:

Licensed establishments that implement the DHQ and accompanying materials as prepared by the AABB Donor History Task Force and found acceptable by FDA but modified by changing the language and/or order of the questions, including inserting

additional questions into the body of the DHQ must report the change to FDA in a Prior Approval Supplement (PAS) Supplement under 21 CFR 601.12(b). Include the following information in your PAS Supplement:

a. Form FDA 356h "Application to Market a New or Abbreviated New Drug, or Biologic for Human Use."
b. Cover letter describing the request and contents of the supplement.
c. The DHQ and accompanying document(s). Please highlight the modifications.

COMMENT 7 – Clarification on reference to "positive test" verses "confirmed positive test"

Background: This comment is directed to the recommendations in Section III.B.1.

We noted that clarifying details were not included in recommendation III.B.1 to support compliance similar to III.A.3.a which provides context in footnote 2 regarding what constitutes a "positive test" clarifying that:

> *[2]In this context, "positive" includes reactive test results on an HIV diagnostic assay and repeatedly reactive or reactive results on antibody or NAT blood donor screening assays, respectively.*

Recommendation III.B.1, page 8, refers to a "confirmed positive" test for HIV that results in a permanent deferral. Footnote 5 in this recommendation provides context to clarify the agency's expectations for the combination of HIV test results which "may be considered for re-entry by a requalification" but does not provide clarifying details for what constitutes a "confirmed positive test result" for HIV that is the basis for this permanent deferral:

> *III. B Donor Deferral*
> *We recommend that you defer as follows:*
> *1. Defer permanently an individual who has ever had a confirmed positive test result for HIV infection.[5]*
>
> *[5] A donor deferred indefinitely because of a repeatedly reactive or reactive result on an antibody or a NAT blood donor screening assay, respectively, may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 610.41(b)). Under 21 CFR 630.35(b), deferred donors with a previously false-positive result on an HIV diagnostic test may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 630.35(b)). We recommend that you contact FDA for recommendations on a case-by-case basis for an acceptable requalification method or process.*

Request for additional information

Based on member comments, we are requesting additional information in the final guidance to clarify the combination of test results that constitutes a "confirmed positive test result for HIV" that is the basis for the permanent deferral of an individual who has ever had a confirmed positive test result for HIV infection.

COMMENT 8 – Sexual contact with a person who has "ever had a positive test for HIV" versus a "confirmed positive test for HIV"

Background: This applies to recommendation III.B.9, page 8

We noted the use of the word "ever" to establish the timeframe creates inconsistencies in recommendation III.B.9 which requires the deferral of a donor based on "sexual contact with a person who has EVER had a positive test for HIV" yet the donor's sexual partner with a false positive test for HIV could be requalified for donation following the reentry pathway provided in recommendation III.B.1, footnote 5. The use of the word "ever" to set the timeframe for the sexual partner's risk creates more restrictive criteria for the donor than the sexual partner who put the donor at risk for HIV, as illustrated in this example:

- The donor is deferred for 3 months following sexual contact with a partner who **ever** tested positive for HIV,
- On the same day the donor is deferred, the donor's sexual partner (who had a false-positive test for HIV years ago) could be actively donating after requalifying via the reentry process as described in recommendation III.B.1, footnote 5 on page 8, *yet the donor described in the first bullet remains deferred*.

Recommendation III.B.9 states:

B. Donor Deferral

We recommend that you defer as follows:

9. Defer for 3 months from the most recent sexual contact, an individual who has had sex with a person who has ever had a positive test for HIV.

Footnote 5 states:
[5]*A donor deferred indefinitely because of a repeatedly reactive or reactive result on an antibody or a NAT blood donor screening assay, respectively, may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 610.41(b)). Under 21 CFR 630.35(b), deferred donors with a previously false-positive result on an HIV diagnostic test may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 630.35(b)). We recommend that you contact FDA for recommendations on a case-by-case basis for an acceptable requalification method or process.*

Request for clarification of FDA's intent for this deferral:

We are requesting clarification regarding the intention of the recommendation to defer a donor for sexual contact with a person who has **ever** had a positive test for HIV, including deferral for all of the following:

- sexual contact with a partner who has had a false positive test result but qualifies for reentry or who has requalified to donate based on the reentry information provided in III.B.1, footnote 5,
- sexual contact with a partner who has a confirmed positive test for HIV,
- sexual contact with a partner who does not have the details of the partner's positive test for HIV.

COMMENT 9 – Definition of a "new partner"

Background: This comment is directed to recommendation III.A.3, page 7.

Recommendation III A.3.e. states:

> *A history in the past 3 months of sex[3] with a new partner. Individuals who report sex with a new partner in the past 3 months should be assessed for a history in the past 3 months of anal sex.*

Request for additional information

Our members are requesting that FDA provide a definition of "new partner". Our organizations do not have access to the current data which would support a proposed definition. As described by several member organizations, the lack of a definition for "new partner" will be problematic at the operational level. For example, would a military spouse deployed for a year be considered a "new partner" upon return? Blood collection establishments will use this definition or, in the absence of a definition, examples in the final guidance (such as the example above) to meet the intent of the new recommendations and support consistent donor screening.

COMMENT 10 - Calculating the donor deferral period.

Background: This comment is directed to recommendations III.B.5 and 6.

Use of the phrase "most recent sexual contact" rather than specifically referencing "most recent anal sexual contact" introduces confusion on the date that must be used to calculate the start of the deferral period.

We agree with and appreciate FDA's prompt response to an early inquiry from AABB's DHTF confirming a 3-month deferral from the most recent anal sexual contact based on "The intent of the individual risk questions is to determine if a donor who answers "yes" to having a new or multiple partners in the last three months had anal sex."

This clarification is necessary because the deferrals described in recommendations III.B.5 and 6 could be misinterpreted to defer for 3 months from the last date of any type of sexual contact, considering the clarification highlighted in footnote 3, page 7, which states:

> *Unless specified as "anal sex", throughout this guidance the term "sex" refers to having anal, oral, or vaginal sex, regardless of whether or not a condom or other protection is used.*

Request for clarification and suggested revision

Please include in the final guidance the clarifying information provided to AABB confirming that the deferrals for recommendations III.B.5 and 6 are calculated to defer a donor for 3 months from the last date of anal sexual contact.

We suggest the following revision:

> **Recommendation III.B Donor Deferral**
>
> *We recommend that you defer as follows:*
>
> 5. *Defer for 3 months from the most recent anal sexual contact, an individual who has had a new sexual partner in the past 3 months and who has had anal sex in the past 3 months.*
>
> 6. *Defer for 3 months from the most recent anal sexual contact, an individual who has had more than one sexual partner in the past 3 months and who has had anal sex in the past 3 months.*

In closing, our organizations recognize FDA's commitment to evidence-based donor eligibility recommendations to support the safety and availability of the blood supply. The blood community appreciates the agency's willingness to work with us as we review the published data supporting the recommendations in the final guidance, and prepare for the complex implementation process which will follow.

AABB (Association for the Advancement of Blood & Biotherapies) is an international, not-for-profit organization representing individuals and institutions involved in the fields of transfusion medicine and biotherapies. The Association works collaboratively to advance the field through the development and delivery of standards, accreditation and education programs. AABB is dedicated to its mission of improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide.

Founded in 1962, America's Blood Centers 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 American Red Cross 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.

Sincerely,

[*signatures on file*]

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