March 13, 2025

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

Submitted via http://www.regulations.gov

Re: **Docket No. FDA-2000-D-0187,** Recommendations To Reduce the Risk of Transfusion-Transmitted Malaria; Draft Guidance for Industry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(FDA) in response to the recently released, Recommendations To Reduce the Risk of Transfusion-Transmitted Malaria; Draft Guidance for Industry (Guidance).

Our organizations appreciate FDA providing an opportunity to comment on the Guidance. We recognize that malaria is a relevant transfusion-transmitted infection (RTTI) under 21 CFR 630.3(h)(x) and that the recent approval of the Roche Cobas malaria test requires FDA to evaluate, pursuant to 21 CFR 610.40(a)(3), whether a testing strategy utilizing this newly approved test "is necessary to reduce adequately and appropriately the risk of transmission of the RTTI by blood, or blood component, or blood derivative product manufactured from the collected blood or blood component."

However, until FDA performs real world modeling studies to determine the sensitivity of available tests, including studies performed in malaria-endemic locations, and including data on semi-immune donor populations, an option to continue the present TTM risk reduction questioning without testing is necessary to ensure any testing burden is justified by a commensurate increase in safety. We note that the current deferral policy is extremely effective, and testing requirements add significant financial costs for blood centers without providing a significant increase in safety. Furthermore, there is currently only one malaria test approved for screening of the blood supply. Without an alternative, supply chain challenges could adversely

impact blood availability. Therefore, we believe that FDA should ensure multiple tests are available prior to creating any new testing requirements.

COMMENT 1 – Regulatory Requirements for Testing to Reduce the Risk of TTM

Background:

Guidance Section II. BACKGROUND

D. Regulatory Requirements for Testing to Reduce the Risk of TTM, page 4:

> *Malaria is a relevant transfusion-transmitted infection (RTTI) (21 CFR 630.3(h)(1)(x)). Under 21 CFR 610.40(a)(3)(i), blood establishments must test for certain RTTI, including malaria, when 1) a test is licensed, approved or cleared by FDA for use as a donor screening test and is available for such use; and 2) testing is necessary to reduce adequately and appropriately the risk of transmission of the RTTI by blood, or blood component, or blood derivative product manufactured from the collected blood or blood component.*

With an established <1/10M residual risk of transfusion-transmitted malaria (TTM) [December 2022 FDA Malaria Guidance], testing is not "necessary to reduce adequately and appropriately the risk of transmission." Without adding a significant new layer of safety, this testing schema will continue to require a complex questioning subject to donor recall / disclosure, an identified failure mode responsible for half of exceedingly rare TTM cases. The proposed testing schema will not reduce the present <1/10M TTM rate by more than half.

Further, testing recent travelers for malaria in lieu of deferral allows individuals co-exposed to arboviral and other viral/parasitic agents, previously deferred for 3 months, to donate without a waiting period for symptom development, potentially increasing TTD risk. Maintaining the current 3-month traveler deferrals while testing donors traveling 3-12 months ago or introducing a new arboviral travel deferral significantly offsets any potential deferral-reduction benefit associated with cost-ineffective testing.

Request:

Option to continue questioning - Our organizations request an option to continue the present TTM risk reduction questioning without testing as reasonable given little to no expected reduction of the already exceedingly low residual risk under the proposed testing schema and already low numbers of ethnically diverse donor deferrals in many blood centers. One large blood center recorded a 2023 deferral rate of <0.1% for donors with a history of residence in a malarial country or diagnosed with malaria under the present questioning schema. Additionally, our organizations request that FDA perform real world modeling studies to determine the sensitivity of available tests, including studies performed in malaria-endemic locations and including data on semi-immune donor populations, and ensure any testing burden, including costs, is justified by a commensurate increase in safety.

COMMENT 2 – Testing donations from donors who report travel to a malaria-endemic country in the past 12 months

Background:

Guidance Section II. BACKGROUND

F. Scientific Basis for Use of a Selective Testing Strategy to Reduce the Risk of TTM, page 8:

- *Testing donations from donors who report travel to a malaria-endemic country in the past 12 months:*

  "…This approach to identifying malaria risk differs in several ways from the current deferral recommendations for travelers to malaria-endemic areas (Ref. 1). For example, in this guidance, we have eliminated the term "malaria-endemic area" and simplified the questioning to instead identify donors who report travel to any "malaria-endemic country." Also, the selective testing strategy uses a 12-month risk period to identify donations for testing, rather than the 3-month risk period currently recommended to identify donors for deferral."

The proposed simplification of eliminating the term "malarial-endemic risk area" and use of "malarial-endemic country" would mandate unnecessary testing of significant volumes of US vacationers, particularly to resort areas in Mexico and other areas where malaria prophylaxis may not be recommended, not just within the past 3 months, but within the past 12 months. Further reducing current <1/10M residual risk and expanding donor diversity can be accomplished without changes to current processes for the vast majority of travelers and would maintain safeguards against collections of donors from areas also experiencing arboviral outbreaks.

Request:

Reinstatement of "malaria endemic area" and 3-month travel deferral - The safeguards that a 3-month malaria deferral have already demonstrated in the prevention of collections from travelers to areas with co-endemic arboviral or other viral and parasitic diseases, strongly suggest that testing of travelers in lieu of a short deferral may not be desirable. Our organizations request the reinstatement of the definition "malaria-endemic area" along with a 3-month travel deferral with no testing.

COMMENT 3 – Significant Blood Establishment Computer Changes and Operational Challenges

Background:

Guidance Section IV. RECOMMENDATIONS, pages 10 - 16

Significant BECS alterations will be needed for the complex change to selective testing based on multiple questions, as well as product release when only some collections require test results. Extensive training and competency evaluation will be required for a new Donor History Questionnaire (DHQ) and standard operational procedures (SOPs).

Testing represents a new cost. Selective filling of a 4th (lysis) tube will operationally challenge many centers from multiple perspectives (e.g., information technology, donor management, tube supply chain, testing contracts, product and test flow).

Contractually, costs for FDA-mandated testing and implementation will be immediately borne by hospitals, so facilities already economically challenged to implement proven-effective patient interventions are likely to perceive further lowering of a <1/10M residual TTM risk without a guarantee of enhanced blood supply adequacy as antithetical to good patient care.

Pathogen reduction technology (PRT) in lieu of testing (in the absence of universal platelet and plasma pathogen reduction protocols) is generally impractical since flagging testing becomes procedure-specific (which can change from original donor intent after DHQ completion) rather than keyed to DHQ responses (as with contemplated malaria testing, Chagas testing for first time donors, and geographic Babesia testing). Further, platelet/plasma PRT cannot be guaranteed even for platelet- or plasma-only apheresis collections which may or may not be needed by customers or even eligible for PRT, which only becomes apparent after testing is/is not ordered at the collection site. PRT thus represents a helpful option primarily for rare autochthonous transmission mitigation or for providers with unusually high PRT adoption.

Request:

Universal testing option - Difficulties associated with the complexity of DHQ algorithms, donor recall, and response interpretation, sample tube management, and test ordering may make universal testing operationally more feasible for some centers should substantial testing volume be mandated. Universal testing should be included as an option for such collectors. Collectors implementing universal testing should not be required to ask any malaria risk questions.

COMMENT 4 – Elicitation of symptoms of malaria

Background:

Guidance Section IV. RECOMMENDATIONS

B. Donor Deferral, Donation Testing, and Requalification

1. Donor Deferral, Donation Testing, and Requalification, page 11:

In accordance with 21 CFR 630.10(a) and (e)(1) and (h), you must defer a donor who is not in good health or who has clinical evidence of a relevant transfusion-transmitted infection, including malaria. Accordingly, if a donor reports symptoms of clinical malaria or is currently being treated for malaria, you must defer that donor. We recommend that you defer the donor for at least one year and until the donor is free of malaria.

How should symptoms of malaria be elicited? Would this be a reflex question from "Have you ever had malaria"? Would symptoms under "Are you feeling healthy and well today" require staff education regarding the symptoms of malaria (which can be non-specific) to trigger the recommended 1-year malaria deferral rather than a 1-day not healthy and well deferral?

Request:

Malaria symptoms - Our organizations request that FDA clarify the details on how information on malaria symptoms should be elicited from the donor.

COMMENT 5 – Testing of individuals who report a history of malaria, who are prior residents of a malaria-endemic country and who report travel to a malaria-endemic country in the past 12 months

Background:

Guidance Section IV. RECOMMENDATIONS

B. Donor Deferral, Donation Testing, and Requalification (2)(a)(i-iii), pages 11 – 13

i. Donations from donors who report a history of malaria
ii. Donations from donors who are prior residents of a malaria-endemic country
iii. Donations from donors who report travel to a malaria-endemic country in the past 12 months

Required testing only for individuals 1) ever residing in a malarial country and 2) those disclosing infection would address as much TTM risk as the proposed more extensive testing schema and provide almost the entire expected increment in ethnically diverse donations.

Requests:

1. **Retaining a 3-month deferral option -** A more effective counterproposal would be to maintain as-proposed testing of donors reporting a history of malaria at every presentation but continue to allow a 3-month deferral *without testing* after travel to malarial areas for donors never residing in an endemic country (i.e., those not at risk for partial immunity).

2. **Limited period of every presentation testing of prior residents -** Regarding individuals ever residing in a malarial country, the logical inconsistency of one-time testing for these donors (more than half of whom have had malaria in heavily affected locations), who may not have received a formal diagnosis or neglect to reveal past infection seems at odds with more aggressive management of those revealing their diagnosis. A limited period of every-presentation testing can identify whether intermittent hepatic reservoir parasitemia occurs in prior residents of endemic countries. This additional testing should be offset by removing the requirement to test travelers never residing in an endemic country, a large donor group from which only 1 TTM case has ever been reported. There is no evidence that amongst the 28 million US residents traveling annually to countries with malaria, changing the previous 12-month donor deferral to 3 months adversely affected TTM risk.

COMMENT 6 – Elicitation of information leading to additional testing for residents of malaria-endemic countries

Background:

Guidance Section IV. RECOMMENDATIONS

B. Donor Deferral, Donation Testing, and Requalification, (2)(a)(ii)(bullet 3), page 12:

ii. Donations from donors who are prior residents of a malaria endemic country

- *A donor who is a prior resident of a malaria-endemic country whose donation tests non-reactive may present for future donation without subsequent testing for malaria, provided the donor does not report other risk factors for malaria (i.e., a history of malaria, another period of residency in a malaria-endemic country or travel to a malaria-endemic country in the past 12 months) as described in section IV.A.2 of this guidance.*

As written, this provision is unclear in the context of one-time testing.

1) How would a one-time tested donor who had previously disclosed residency in a malaria-endemic country now report another subsequent period of residency which should trigger a second test as required herein?

2) Why would significant time spent in an endemic country >12 months before presentation not require re-testing in a potentially partially immune person?

There is no question to capture the former situation, and FDA does not require retesting in the latter circumstance.

Request:

Determination of a second period of residence - Our organizations have suggested that residents of malaria-endemic countries be tested at each donation in lieu of testing travelers never residing in an endemic country. Should FDA feel one-time testing is sufficient for residents of malaria-endemic countries, the Agency should clarify how a second period of residence in a malaria-endemic country triggering subsequent testing should be elicited from the donor. FDA should also address the logical inconsistency of only considering endemic area travel within the past 12 months as a reinfection risk in populations likely to be partially immune.

COMMENT 7 – Clarification of details on FDA's oversite in regions of the U.S. with local, mosquito-borne malaria transmission

Background:

Guidance Section IV. RECOMMENDATIONS

B. Donor Deferral, Donation Testing, and Requalification (2)(a)(iv), page 13

iv. Donations collected in regions of the U.S. with local, mosquito-borne transmission

FDA oversight of testing zones to avoid autochthonous TTM risk relieves blood centers from monitoring nationwide public health sources, but the Agency's lack of detail around this process makes it difficult for collectors to gauge impact and selectively implement platelet PRT.

Request:

Number of cases and geographic rules - Our organizations request that FDA better describe the number of cases required and geographical rules to be employed (how donors' home/work/travel zones impact the size of affected collection zones).

COMMENT 8 – Request to reduce the lookback/notification period when testing is triggered due to travel or a local outbreak

Background:

Guidance Section IV. RECOMMENDATIONS

C. Product Management, Retrieval and Quarantine, Notification of Consignees of Blood and Blood Components (3)(a), (3)(b), (3)(c), pages 14-15:

3. *We recommend that you take the following actions when a donation tests reactive for malaria by a licensed donor screening NAT:*

    a. *Identify all cellular blood components previously collected from that donor in the 12 months prior to the date of the reactive index donation…*

    b. *Quarantine the identified in-date cellular components held at your establishment; and*

    c. *Notify consignees of all identified cellular blood components collected from the donor in the 12 months prior to the date of the reactive index donation that have been distributed, and:*
        1. *Retrieve the identified in-date cellular blood components.*
        2. *If components were transfused, encourage consignees to have a discussion with the recipient's physician of record about a possible risk of TTM, particularly if the involved component(s) had not been tested or pathogen reduced.*

As written, this provision would require a 12-month lookback period when a donation tests reactive for malaria, and the testing was triggered due to travel or a local outbreak. This 12-month lookback period is required regardless of the timeframe of the travel or local outbreak that triggered testing. The result is that, for local outbreaks or travel, the lookback period extends well beyond the time of increased risk of malaria infection that justifies any concern about the donor harboring malaria.

Request:

Shortened lookback - Our organizations request that, when a donation tests reactive for malaria, and the testing was triggered due to travel or a local outbreak, that FDA shorten the lookback period to no longer than the time between the date on which the travel or local outbreak commenced, and the donation occurred.

COMMENT 9 – Request for an extended implementation period

Background:

Guidance Section V. IMPLEMENTATION AND REPORTING CHANGES TO AN APPROVED APPLICATION, pages 16 - 17

You may implement the approaches described in this guidance, when finalized, as soon as feasible. However, FDA recognizes that it may take blood establishments time to implement these approaches, including careful revision of relevant procedures. Therefore, FDA intends to include in the final guidance an appropriate implementation period (e.g., 12 months) before the Agency would expect compliance with the underlying requirements for testing to reduce risk of TTM.

Request:

Extended implementation period - After final guidance, many centers will require a long horizon (≥12 months) for implementation. FDA should commit to ≥12 months, currently listed as only one potential choice in the Guidance.

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*]

Sharon Carayiannis
Vice President Science and Practice
AABB

Kate Fry
Chief Executive Officer
America's Blood Centers

J. Chris Hrouda
President, Biomedical Services
American Red Cross