



September 28, 2018

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Re: Docket No. FDA-2018-D-2478, “Recommendations for Reducing the Risk of Transfusion-Transmitted Babesiosis” draft guidance, July 27, 2018

Dear Dockets Manager:

AABB, America’s Blood Centers (ABC) and the American Red Cross (ARC) welcome the opportunity to provide comments on the Food and Drug Administration’s (FDA) July 2018 “Recommendations for Reducing the Risk of Transfusion-Transmitted Babesiosis; Draft Guidance for Industry (the draft guidance).” Members of the AABB’s Transfusion Transmitted Diseases Committee (TTD Committee) and representatives from ARC and ABC prepared these comments.

The blood community has long recognized the significant risk to recipients posed by transfusion transmission of *Babesia* (TTB) (most notably, *B. microti*) in areas of the US. In 1989 AABB initiated a recommendation for indefinite deferral of blood donors who provided a history of babesiosis and followed that in 1991 with a standard in the 14th edition of the *Standards for Blood Banks and Transfusion Services* that remains in effect today. This has been marginally effective. Members of our organizations have since worked to investigate and verify the performance characteristics of a variety of test methods and introduced testing under investigational protocols in areas of *B. microti* endemicity as early as 2010; such testing continues today with no transmissions reported from nucleic acid tested units. We last publicly urged FDA to support licensure of tests and to issue guidance to reduce/prevent *Babesia* transmission at the [May 2015 FDA Blood Products Advisory Committee meeting](#), and suggested specific strategies for implementation.

Below, we have reproduced some of the text from that statement along with updated comments/recommendations (the latter in italics):

1. Year-round regional testing of all donations of transfusable red cell products – specifically in the 9 states (MN, WI, ME, NH, MA, CT, RI, NY and NJ) with the highest rates of recognized infections, with inclusion of additional states based on scientific data, and exclusion of specific areas within a state with low rates. *We recognize the need to expand testing now beyond the 9*

states in their entirety to the 14 states plus DC, based on the expanding range of the tick vector and increasing numbers of clinical and TTB cases.

2. We acknowledge and support FDA's approval of donor screening assays earlier this year and the agency's forward movement on reviews of additional BLAs for sensitive and specific tests.

*3. As the agency develops its current thinking around the use of *B. microti* testing, it should consider testing algorithms that have high sensitivity and specificity to maximize safety and minimize deferral of uninfected donors. We believe that this can be accomplished using nucleic acid tests (NAT) alone with assays in development.*

*4. We encourage the development and approval of a supplemental test and/or reentry algorithms to allow for donor re-entry (including those deferred with IND tests) as expeditiously as possible. It is important that the number of donors who are not infected with *B. microti*, yet who are deferred due to false positive reactions, remains low. We thank FDA for including reentry in the draft guidance; however, depending on tests used, a 1-year deferral should be considered (see comments below).*

We also have newly developed specific comments to the draft guidance.

COMMENTS

Comment 1: As mentioned, we support regional testing, and with expansion to be considered in consultation with public health agencies and the blood collectors.

Comment 2: Scope of the draft recommendations.

The Introduction states:

“The draft recommendations contained in this guidance apply to the collection of blood and blood components, except Source Plasma.”

We support testing of red blood cell containing products, whole blood, red cell apheresis and granulocyte collections only.

Rationale: There have been no reports of TTB from plasma (frozen or not), nor from apheresis platelets. Licensed plateletpheresis and plasmapheresis platforms have submitted extensive data quantifying very low levels of RBC contamination and, critically, these blood products have never been associated with recognized transmission. We suspect that the absence of any documented cases from apheresis platelets and plasma relates to red cell contamination below the infectious dose. There are a few published cases of TTB from whole-blood derived platelets (Herwaldt et al.); the concentration of contaminating red cells in these platelet products is higher than in apheresis platelets. All whole-blood derived platelets will be tested based on the requirement to test the associated red cell component.

Comment 3: Reconsidering the currently licensed tests referenced in the draft guidance.

In the section, Licensed Screening Tests, FDA describes *“two independent assays for screening donors for *B. microti*: the Imugen Babesia microti Arrayed Fluorescent Immunoassay (AFIA) for the detection of *B. microti*-specific antibodies and the Imugen Babesia microti Nucleic Acid Test (NAT) for the detection of DNA of *B. microti*.”*

We are concerned that the availability of the licensed assays is insufficient to meet the intent of the guidance, and that tests in development will render the requirement for antibody testing redundant and wasteful of resources.

Rationale: As background, the licensed IMUGEN assays (AFIA and real-time PCR), while licensed as separate BLAs, were qualified and validated as a single “system.” Their combined performance characteristics determined their application in prospective clinical studies including the ability to reduce the incidence of TTB. We consider the NAT assay provided by IMUGEN as “first generation” in that it amplifies the parasite’s single genomic DNA template, limiting analytic sensitivity, and thus requires concurrent use of the companion antibody assay to detect donors with low-level parasitemia. The IMUGEN PCR assay has a reported 95% limit of detection (LOD) of 66 parasites/mL; even at this level, it correlates well with hamster infectivity (Moritz et al. 2016). NAT assays in development for donor screening have materially improved analytic sensitivity; they amplify ribosomal RNA (rRNA) present at thousands of copies per parasite. Each manufacturer’s NAT assay should be considered on its own merit without assuming the need for concomitant antibody testing; i.e., NAT is the correlate of infectivity and antibody is a surrogate to compensate for lesser analytic sensitivity of some NAT assays. Importantly, the currently licensed assays, including the antibody test, are not commercially available and have operational features not conducive to the scope of testing proposed in the draft guidance.

Blood centers that are testing currently in endemic areas are using “next generation” rRNA NAT assays that have reported analytic sensitivity at their 95% LODs of 1-4 parasites/mL (Bres et al. 2017, and Bakkour et al. 2018). Thus, if even one infected red cell is sampled, it will be detected. In addition, these assays are not limited to the detection of *B. microti* and are able to detect multiple *Babesia* species that are human pathogens. We believe that these next generation rRNA NATs will provide the same level of clinical efficacy as the combination of the licensed IMUGEN assays, and through on-going clinical studies, data are being collected to support this statement. As these studies are on-going, the publication and implementation of final guidance should await the agency’s consideration of their performance.

NAT assays have been reported to have very low rates of false positivity and thus few donors would be deferred (and should only require a 1-year deferral based on published studies; Moritz et al. 2016, 2017). In contrast, antibody tests have variable specificity; that is, performance is manufacturer dependent (both based on antigen selection and assay format) and would (as demonstrated in IND studies) defer many more donors, both uninfected antibody-confirmed positive and false-positive donors.

Thus, we urge FDA to reconsider the assays to be used in favor of ultra-sensitive rRNA NAT assays currently in use under IND. The use of ultra-sensitive rRNA NAT assays is also consistent with the first formal use of risk-based decision making in the US, as conducted by the AABB (Ward et al. 2018). The abstract from the manuscript accepted for publication in *Transfusion* is included below:

Abstract

Recognizing the increasing threat of transfusion-transmitted babesiosis to the U.S. blood supply, the AABB Board of Directors tasked an Ad-Hoc Babesia Policy Working Group (the Working Group) to use the Alliance of Blood Operators’ risk-based decision-making (RBDM) framework to assess the risks and benefits of introducing babesia donation testing in the U.S. The regional nature of the *Babesia microti* risk added complexity to the RBDM assessment because of the unique operational and financial considerations for operators and hospitals located in endemic states. Therefore, the assessment considered safety, product availability, sector sustainability and technology availability.

After assessing safety risk, economic and operational impact, reimbursement equity, ethical considerations, and stakeholder feedback from two consultations, the Working Group concluded that a regional approach to donor screening in endemic states was appropriate because it applied the intervention where the risk was highest and appropriately allocated cost to the risk. Nucleic

acid testing using a ribosomal RNA template was the recommended intervention because it was the most cost-effective, resulted in no wasted units, and captured similar numbers of infections as antibody plus DNA-based PCR. The current model for blood reimbursement was maintained but AABB was encouraged to facilitate collection of data to identify threats to sector sustainability in endemic states. Babesia expansion was acknowledged with a mechanism to regularly re-evaluate what are “endemic states”. Finally, given that public awareness of the babesia threat is the first line of defense, AABB should work with appropriate agencies for general education about the health risk from *B. microti*.

Comment 4: Timeframe for deferral based on use of other tests.

Draft recommendation V.A.2.a. states:

*You must defer donors with a reactive screening test (NAT or antibody test) for B. microti (21 CFR 610.41(a)) **for at least 2 years** (21 CFR 630.35(a)).*

We believe that donor deferral should be for 1 year rather than 2 years, based on the use of ultra-sensitive rRNA NATs, and rapid clearance of DNA in NAT-positive donors enrolled in follow-up studies (Moritz et al. 2016). In addition, all other actions for donors and products including retrievals should correspondingly be changed to 1 year.

Comment 5: Important information in footnote 4.

Footnote 4 includes information clarifying that “*FDA is not recommending assessing donors for risk factors for babesiosis, in particular travel to or residence in an area endemic or at high-risk for babesiosis. Assessing donors for travel to or residence within the United States and deferring donors for time spent in areas endemic or at high-risk for babesiosis is not feasible because of the anticipated detrimental effect on the blood supply.*”

The information in footnote 4, regarding the agency’s opinions about travel to “testing states” is important enough to be included in the body of the guidance and should be moved.

Comment 6: Pathogen Inactivation.

The final guidance should mention technologies in development for pathogen inactivation. This will be an important option for mitigating *Babesia*.

Comment 7: Use of multiple versions of the Donor History Questionnaire (DHQ).

Draft recommendations in Section V.A. with test requirements specific to a location / state, and a DHQ that is different depending upon location / state, are problematic for some blood establishments that operate in testing and non-testing states. AABB recommends a flexible approach that accommodates blood centers that operate in multiple states, some of which may be endemic for *Babesia*. The approach should be nimble enough to allow for one line of questioning that works for all geographies so as to avoid challenges of managing and maintaining multiple DHQs.

Comment 8: Indefinite deferral of donors.

Draft recommendations in Section V.A.3.b. requires blood centers to “...*indefinitely defer donors who report a history of a positive test result for Babesia (21 CFR 630.10(h)).*”

We disagree with the “indefinite” deferral of donors who report a history of a positive test in states that do not test for *Babesia*. Such donors should be deferred for the same period as mentioned in recommendation V.2.a (either 2 years, or a modification to 1 year). These donors should be cleared for continued donation based on a follow-up sample that tests negative by the required tests, as would occur in recommendation 2.a. for a donation sample obtained following the deferral period.

Comment 9: Updates to the DHQ.

Draft recommendations in Section V.A.3.a. require blood centers to update the “...donor history questionnaire to assess prospective donors for a positive test result for *Babesia*” (obtained from either a medical diagnosis, or a reactive donor screening test result).

The AABB Donor History Task Force will be responsible for the decisions on how best to implement these new recommendations. We noted the following areas that need clarification to support the decisions of the Task Force:

- Unlike the recommendation for areas where testing is performed, the guidance *does not* expressly state that non-testing states “may discontinue asking donors about a history of babesiosis.” The draft guidance does not discuss an option to replace or revise, but instead to “update” the current question “Have you ever had Babesiosis?”

Please clarify:

- 1) For areas where testing is not performed, is it FDA’s intent to allow the question “Have you ever had babesiosis?” to be removed?
- 2) If the question, “Have you ever had babesiosis?” is required to be retained, what risk factors are identified by this as compared to “Have you had a positive test for *Babesia*?”
- 3) Is the question, “Have you had a positive test for *Babesia*?” only applicable to the segment of donors where testing is not performed, or should the original question for history of babesiosis continue to be included in this questionnaire?

Comment 10: Update Sections II and III.A. to include relevant information.

Relevant information should be added to the final guidance in the following sections:

In Section II, *Background*, the last paragraph (page 2) should include information on symptomatic infection in blood donors found in Moritz et al (draft guidance reference 10), Supplementary Appendix. Specifically, the final guidance should include the information found in Figure S1a. (page 5 of the Supplementary Appendix) on donor follow-up and the development of symptoms; “68/160 (42.5%) donors reported one or more symptoms.”

In Section III.A., the first paragraph under “*Transfusion Transmission*” (page 3) references “*more than 200 cases of transfusion-associated infections have been documented (Refs. 2, 22); about 25% of all cases were recorded during the period of 2010-2016.*” This statement should be corrected to reflect the following:

- The Red Cross alone published 62 cases during the period of 2010-2016 (from draft guidance reference 10).
- Moritz et al. 2016 report 29 cases during the investigational testing phase but a total of 62 for the period 2010-2016.

- These should be added to the 55 reported for NY from 2004-2015 (from draft guidance reference 22), two of which overlap with the 62 Red Cross cases, and the 162 cases reported by Herwaldt et al. 2011 (from draft guidance reference 2).

References used in our comments:

Herwaldt BL, Linden JV, Bosserman E, et al. Transfusion associated babesiosis in the United States: a description of cases. *Ann Intern Med* 2011;155:509-19.

Moritz ED, Winton CS, Tonnetti L, et al. Screening for *Babesia microti* in the U.S. blood supply. *N Engl J Med* 2016;375:2236-45.

Moritz ED, Tonnetti L, ME Hewins, et al. Description of 15 DNA-positive and antibody-negative “window-period” blood donations identified during prospective screening for *Babesia microti*. *Transfusion* 2017;57:1781–6.

Bres V, Proctor M, Self D, et al. Preliminary performance characteristics of a *Babesia* nucleic acid test on a fully automated system, and results from screening donated blood from endemic regions of the United States. Abstract 5A-S33-05. 2017. 27th Regional Congress of the ISBT, Copenhagen Denmark.

Bakkour S, Chafets DM, Wen L, et al. Minimal infectious dose and dynamics of *Babesia microti* parasitemia in a murine model. 2018. Accepted *Transfusion*.

Ward SJ, Stramer SL, Szczepiorkowski ZM. Assessing the risk of *Babesia* to the U.S. blood supply using a Risk-Based Decision-Making Approach (RBDM). Report of AABB’s Ad Hoc *Babesia* Policy Working Group (original report). *Transfusion* 2018. doi.org/10.1111/trf.14912.

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,

A handwritten signature in cursive script that reads "Sharon Carayiannis".

Sharon Carayiannis
AABB
Director, Regulatory Affairs