Recommendations for Reducing the Risk of Transfusion-Transmitted Babesiosis

Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft—Not for Implementation

Recommendations for Reducing the Risk of Transfusion-Transmitted Babesiosis

Draft Guidance for Industry

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I. INTRODUCTION

We, the Food and Drug Administration (FDA), are notifying you, blood establishments that collect blood and blood components, that we have determined babesiosis to be a relevant transfusion-transmitted infection (RTTI) under 21 CFR 630.3(h)(2)[1] and we are providing you with FDA's assessment. We are providing recommendations for donor screening, donation testing, donor deferral and product management to reduce the risk of transfusion-transmitted babesiosis (TTB). The recommendations contained in this guidance apply to the collection of blood and blood components, except Source Plasma.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Human babesiosis is a tick-borne zoonosis caused by infections of humans with intra-erythrocytic protozoa of the genus *Babesia*. Babesiosis can also be transmitted by transfusion of blood and blood components (Refs. 1, 2) and by transplantation of solid organs (Ref. 3) collected from an infected donor. Babesiosis is transmitted in many parts of the world but the highest prevalence is reported in the United States (U.S.). The first documented human case of

[1] See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015). The rule became effective May 23, 2016.

[2] Source Plasma is used for further manufacture of plasma-derived products. Pathogen inactivation and removal methods that are currently used in the manufacturing process for plasma-derived products are sufficient to reduce the risk of transmission of babesiosis.

babesiosis in the U.S. was identified in 1968 (Ref. 4). The majority of U.S. babesiosis cases are caused by *B. microti*, the species that is prevalent in the Northeast and upper Midwest (Ref. 5). Other *Babesia* species such as *B. duncani* (Refs. 6, 7) and related organisms are implicated in transmission of *Babesia* in several western U.S. states, while transmission of *Babesia* by "*B. divergens*-like" agents (Ref. 8) have been reported in multiple U.S. states.

The vast majority of *B. microti* infections are asymptomatic and never diagnosed (Ref. 9). While the precise duration of *B. microti* infections in healthy adults is not clearly known, in limited studies, the parasitemic period is reported to last from 2 to 7 months (Ref. 10), but parasitemia may persist for more than 2 years (Ref. 11). Although *Babesia* transmission is seasonal and coincides with tick activity (traditionally May-September), both tick-borne (Refs. 12-17) and transfusion-transmitted infections are reported year-round (Refs. 5, 10). There are insufficient data regarding the proportion of *Babesia* infections that persist as asymptomatic, chronic infections. In one study on Block Island, Rhode Island one third of *Babesia* infections were asymptomatic (Ref. 9), although the sample size was too small to draw firm conclusions. Transfusion of blood and blood components collected from asymptomatic donors may result in TTB, leading to potentially fatal clinical illness in blood transfusion recipients.

III. DISCUSSION

FDA has determined, as discussed below, that babesiosis is a transfusion-transmitted infection (TTI) under 21 CFR 630.3(1) and an RTTI under 21 CFR 630.3(h)(2). This determination is based on the severity of the disease, confirmed transfusion-transmission by blood and blood components, the availability of appropriate screening measures and donor screening tests and significant incidence and prevalence affecting the potential donor population.

A. Transfusion-Transmitted Infection

A transfusion-transmitted infection (21 CFR 630.3(1)) means a disease or agent:

> (1) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and
>
> (2) For which there may be a risk of transmission by blood or blood components, or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component, or blood derivative product.

In this regard, FDA examined:

Severity of Disease

Clinical symptoms of babesiosis, caused by *B. microti*, range from asymptomatic to mild to severe, and can result in death in certain high-risk populations. In the majority of individuals who develop illness, clinical symptoms appear 1 to 4 weeks after an infectious tick bite (Ref. 5). Following transfusion of blood components collected from an infected donor, symptoms in transfusion recipients have been observed anywhere from 1 week to 9 weeks, and as long as 6 months after transfusion (Ref. 2). Common symptoms include malaise, fatigue, fever, chills, headache, myalgia, anorexia, arthralgia and nausea (Refs. 5, 9, 18, 19). Severe disease caused by *B. microti* infection requiring hospitalization is generally seen in neonates, the elderly, asplenic patients, and those receiving immunosuppressive drugs for cancer therapy (Refs. 5, 19, 20). The most common severe clinical manifestations include acute respiratory distress syndrome and disseminated intravascular coagulopathy. Congestive heart failure, coma, liver failure and renal failure are also reported (Refs. 5, 19, 20). In tickborne cases, fatality rates range from 6 to 9% among hospitalized patients and up to 21% in immunosuppressed patients (Refs. 19, 20). In TTB cases, a fatality rate of about 20% has been reported in the literature (Ref. 21).

Transfusion Transmission

There is demonstrated evidence that babesiosis is transmitted by transfusion of blood and blood components (Refs. 1, 2). The first U.S. case of TTB was reported in 1980 (Ref. 1). Since then, 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. While *B. microti* remains the major causative agent of TTB, three cases of transfusion-transmitted infections attributed to *B. duncani* (Ref. 2) and one possible case caused by a *B. divergens*-like parasite were reported in the U.S. (Ref. 23).

Therefore, FDA has determined that babesiosis is a TTI because it is a disease agent that can be fatal or life-threatening and is transmissible by blood or blood components.

B. Relevant Transfusion-Transmitted Infection

Having determined that babesiosis is a TTI, we outline, below, the criteria establishing babesiosis as an RTTI under 21 CFR 630.3(h)(2)(i) and (ii).

A relevant transfusion-transmitted infection means:

> A transfusion-transmitted infection not listed in 21 CFR 630.3(h)(1) when the following conditions are met:
>
> (i) Appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by the FDA and is available; and
>
> (ii) The disease or disease agent: (A) May have significant incidence and/or prevalence to affect the potential donor population; or (B) May have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

Availability of Appropriate Screening Measures or Screening Tests

Donor History Questionnaire: Currently, prospective donors are asked if they have ever had babesiosis as part of the medical history interview. We do not find it necessary to continue to ask about a history of babesiosis when donations will be tested. Health history questions generally cannot prevent TTB because the donors implicated in these cases are typically unaware of their infection status and hence do not report a history of babesiosis (Ref. 24). As states begin testing for *B. microti* per our recommendations in this guidance, we expect that some asymptomatic blood donors will learn about their infection status when they are deferred, but the possibility exists that they might still present to donate blood in another state that does not perform testing. To address this concern, we have added a recommendation to assess donor history for a positive test result for babesiosis when donations will not be tested for *B. microti*.

Licensed Screening Tests: On March 6, 2018, FDA licensed 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*. These assays are intended to be used as donor screening tests on Whole Blood (NAT assay) or in plasma (AFIA test) samples from individual human donors, including volunteer donors of Whole Blood and blood components as well as living organ and tissue donors. Further discussion of the value of NAT and antibody-based tests for screening blood donors for *B. microti* is provided in the Appendix of this document.

Significant Incidence and Prevalence

In 2011, national surveillance for babesiosis began in 25 jurisdictions in 24 states and New York City (Refs. 12-17). Between 2011 and 2017, an average of 1628 (range 937-2100) babesiosis cases per year was observed in 26 states which excluded several *Babesia*-risk states because disease reporting was not required in those states (Refs. 12-17). According to data from the Centers for Medicare and Medicaid Services, babesiosis cases were reported among elderly Medicare beneficiaries in all states and Washington,

D.C., except for Wyoming (Refs. 25, 26). About 99% of the clinical babesiosis cases reported are from Connecticut, Massachusetts, Rhode Island, New York, New Jersey, Minnesota, Wisconsin, New Hampshire, Maine, Maryland, Virginia, Vermont, Pennsylvania, Delaware, and Washington, D.C. (Refs. 12-17, 26).

As stated in section III.A. of this document, the first U.S. case of TTB was reported in 1980 (Ref. 1). Since then more than 200 cases of transfusion-associated infections have been documented by the Centers for Disease Control and Prevention (CDC) and FDA (Refs. 2, 27). According to the CDC, between 1979-2009, 19 states reported TTB cases with 87% occurring in the seven highest *B. microti* endemic states (Ref. 2). TTB risk outside of the endemic states is mostly attributed to travel to endemic areas and movement of blood components from endemic states to non-endemic states. About 95% of TTB cases are reported from Connecticut, Massachusetts, Rhode Island, New York, New Jersey, Minnesota, Wisconsin, New Hampshire, Maine, Maryland, Virginia, Vermont, Pennsylvania, Delaware, and Washington, D.C. (Ref. 25).

Therefore, we have determined that babesiosis meets the criteria in 21 CFR 630.3(h)(2) for an RTTI because of the availability of appropriate screening measures and screening tests, and because of the sufficient incidence and prevalence of *Babesia* to affect the potential donor population in the U.S.

IV. MITIGATING THE RISK OF TRANSFUSION-TRANSMITTED BABESIOSIS

FDA has solicited public input on how best to mitigate the risk of TTB in the U.S. and support the development of donor screening tests for *Babesia*. On September 12, 2008, FDA convened a public workshop entitled "Approaches to Reduce the Risk of Transfusion-Transmitted Babesiosis in the United States" (Refs. 28, 29). The focus of this workshop was to discuss various aspects of TTB in the U.S. including the status of detection technologies and possible strategies to identify and defer blood donors who might have been exposed to *Babesia* parasites. Experts emphasized the need for better understanding of the epidemiology of babesiosis in the U.S. and efforts to develop highly sensitive and specific laboratory tests to identify *Babesia*-infected blood donors, especially tests to distinguish between current infections and resolved infections. Discussions also focused on the biology, pathogenesis and epidemiology of babesiosis. A detailed summary of this workshop has been published in *Transfusion* and the meeting transcript is available on the FDA website (Refs. 28, 29).

On July 26, 2010, FDA discussed "Risk of *Babesia* Infection by Blood Transfusion and Potential Strategies for Donor Testing" at a Blood Products Advisory Committee (BPAC or Committee) meeting (Ref. 30). Based on the information available at that time, the Committee recommended regional testing of blood donors for *Babesia*. The Committee did not provide advice on the question of the most suitable technologies for donor screening for *Babesia*, noting that additional information on the performance of different testing technologies was needed. A complete transcript of the meeting and the presentations delivered at this BPAC meeting are available on the FDA website (Refs. 30-34).

On May 13, 2015, FDA again sought advice from the BPAC on strategies to test blood donors for evidence of *B. microti* infection using licensed tests, when such tests become available (Ref. 25). In recent years, limited testing of blood donations using the available investigational tests has provided additional information on the magnitude of *B. microti* prevalence in endemic areas and on the relative value of NAT and antibody-based tests in identifying *Babesia* exposed versus parasitemic donors. The sponsors of the investigational *B. microti* tests presented the results of their clinical studies (Refs. 35, 36). The Committee advised that the scientific data and FDA analysis support the concept of nationwide, year-round testing of blood donations for *Babesia*-risk by an antibody-based test. The Committee also unanimously recommended that NAT-based testing should be performed on blood donations in certain high-risk states, and the majority supported NAT testing in the nine states considered endemic at that time (Connecticut, Maine, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Rhode Island, and Wisconsin). The Committee also recommended including the bordering state of Pennsylvania in the year-round NAT-based testing program. Since the meeting, Pennsylvania has been identified as a *B. microti* endemic state. Additionally, the Committee supported a deferral period of at least 2 years for donors with reactive test results, after which time, donor eligibility may be assessed based on testing by both antibody and NAT-based testing.

FDA has considered the BPAC discussion and determined that limiting donation testing to states with *Babesia* risk, but requiring both NAT and antibody testing year-round in those states, is a preferred strategy that balances risk reduction with the scope of testing (see the Appendix of this document for discussion and scientific rationale for this strategy).

V. RECOMMENDATIONS

A. Donation Testing, Donor History Questionnaire, Donor Deferral and Requalification

1. We recommend that you update your donor history questionnaire, including full-length and abbreviated donor history questionnaires, and accompanying materials as necessary to incorporate the recommendations provided in this document. You must update your standard operating procedures to reflect any such changes (21 CFR 606.100(b)).

2. You must test each donation for evidence of *B. microti* infection using a licensed NAT and licensed antibody test[3] when collected in Connecticut, Delaware, Maine, Maryland, Minnesota, Massachusetts, New Hampshire, New Jersey, New

[3] When this guidance is finalized, blood establishments must use licensed donor screening tests for *B. microti* (21 CFR 610.40(b)). Blood establishments that are participating in a clinical trial and testing for *B. microti* using an unlicensed test may continue in the clinical trial but must also begin to test for *B. microti* using FDA licensed tests (21 CFR 610.40(b)).

York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin and Washington, D.C. Testing must be performed year-round (21 CFR 610.40(a)(3)(ii)(A) and 610.40(b)).

a. 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)). You must make reasonable attempts to notify any donor whose blood tests reactive for *B. microti* of their deferral and of their test results, within 8 weeks after determining that the donor is deferred (21 CFR 630.40). Deferred donors must be counseled about the possible medical significance of the results (21 CFR 630.40(b)).

b. When testing is performed, you may discontinue asking donors about a history of babesiosis.[4]

c. Donors who were previously deferred for a history of babesiosis based on their responses on the donor history questionnaire may be eligible to donate provided they have not had a positive test result for *Babesia* in the last 2 years and they meet all other donor eligibility criteria (21 CFR 630.35(b)). The donation must be tested for *B. microti* by both a licensed NAT and a licensed antibody test (21 CFR 610.40(a)(3) and 610.40(b)).

3. In states that do <u>not</u> test donations for *B. microti*, we recommend the following:

a. Update your 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.

b. You must indefinitely defer donors who report a history of a positive test result for *Babesia* (21 CFR 630.10(h)).

c. A deferred donor may be eligible to donate under 21 CFR 630.35(b) provided the following conditions are met:

i. On the day of donation, the donor has not had a positive test result for *Babesia* in the last 2 years and they meet all other eligibility criteria.

[4] To provide for appropriate donor screening and testing for this RTTI, the Director of the Center for Biologics Evaluation and Research is providing an alternative procedure (testing, as described in section V. of this document) under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10 that require blood establishments to assess donors for risk factors for babesiosis before collecting blood or blood components. Specifically, 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. Approximately one-quarter of the U.S. population resides in the states identified at risk for babesiosis in this guidance, and even more individuals may travel to the at-risk states.

ii. The donation must be tested for *B. microti* by both a licensed NAT and a licensed antibody test (21 CFR 610.40(a)(3)(ii)(A).

The donor's eligibility should be assessed at each subsequent donation by the donor history questionnaire (see section V.A.3.a. of this document). The donor's history of *Babesia* should be assessed for the time period after the date of the donor's last negative test result for *B. microti*.

B. Product Management

1. You may release donations that are nonreactive for *B. microti* by both a licensed nucleic acid test and antibody test provided all other donation suitability requirements are met (21 CFR 630.30).

2. If a donation tests reactive for *B. microti* by a licensed nucleic acid test or antibody test, you must not ship or use the donation, unless an exception for shipment or use is applicable (21 CFR 610.40(h) and 21 CFR 630.30(b)(1)).

3. Within 3 calendar days after a donation tests reactive for *B. microti* by a licensed NAT or antibody test, you should:

   a. Identify and quarantine all in-date blood and blood components held at your establishment from the donor that were not tested for *B. microti* and were collected from that donor in the 2 years prior to the donation that was reactive for *B. microti*; and

   b. Notify consignees and retrieve and quarantine all distributed in-date blood and blood components collected in the 2 years prior to the donation that was reactive for *B. microti*; and

   c. If previously distributed blood components collected in the 2 years prior to the donation that was reactive for *B. microti* were transfused, encourage consignees to have a discussion with the recipient's physician of record about possible TTB.

   When there is information indicating risk of *Babesia* infection from blood components collected from a donor who was found to have a reactive NAT or antibody test for *B. microti*, in addition to the recommendations provided in section V.B.3.a. of this document, we recommend that the responsible physician determine any additional actions that should be taken on previously distributed products and the extent of additional consignee notification and recipient notification.

C. Product Disposition and Labeling

1. We recommend that you destroy or relabel blood and blood components that were collected from a donor who should have been deferred according to the recommendations in section V.A.3. of this document. If you relabel the blood and blood components, they may be released for research if labeled appropriately as described below.

   You must label the unit as required under 21 CFR 606.121. You must use the following statements to prominently relabel the blood and blood components (21 CFR 606.121(c)):

   a. "NOT FOR TRANSFUSION: Collected from a Donor with a History of Babesiosis"

      and

   b. "Caution: For Laboratory Research Only"

2. We recommend that you destroy or relabel blood and blood components that test reactive for *B. microti*. If you relabel the blood and blood components, they may be released for research or for further manufacture into non-injectable products or in vitro diagnostic reagents when no other suitable sources are available, if labeled appropriately as described below.

   You must label the reactive unit as required under 21 CFR 606.121 and with the "BIOHAZARD" legend (21 CFR 610.40(h)(2)(ii)(B)). You must use the following statements to prominently relabel the blood components (21 CFR 606.121(c)):

   a. "NOT FOR TRANSFUSION: Collected from a Donor Determined to be Reactive for *Babesia microti*"

      and

   b. "Caution: For Laboratory Research Only"

      or

      "Caution: For Further Manufacturing into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

      or

"Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources"

D. Circular of Information

Under 21 CFR 606.122(h), the circular of information must include the names and results of all tests performed when necessary for safe and effective use. When testing is performed, you must update your circular of information to state that licensed tests for nucleic acid and antibodies to *B. microti* were used to screen donors and that the results of testing were nonreactive (21 CFR 606.122(h)). We recommend the following statement:

"Blood donations found to be nonreactive by a licensed nucleic acid test and a licensed antibody test for *Babesia microti*"

VI. IMPLEMENTATION AND REPORTING

We propose that once the guidance is finalized, licensed blood establishments report implementation of the recommendations:

A. Donor History Questionnaire

Licensed blood establishments that modify the donor history questionnaire (DHQ) must report the change under 21 CFR 601.12 as follows:

1. If you implement testing of each donation for *B. microti* consistent with the recommendations in section V.A.2. of this document, you may remove the current question regarding a history of babesiosis from your DHQ. Report this change in your next annual report, noting the date the change was made (21 CFR 601.12(d)).

2. If you do not implement testing for *B. microti*, you should update your current DHQ consistent with the recommendations in section V.A.3. of this document. Adding an additional question to your DHQ or using a revised DHQ found acceptable to FDA is considered a minor change and must be reported in your next annual report, noting the date that the change was made (21 CFR 601.12(d)).

3. You must submit a Prior Approval Supplement if you wish to update your DHQ other than as recommended in section V.A.3. of this document. (21 CFR 601.12(b)(1)).

B. Testing

Licensed blood establishments that implement testing for *B. microti* must report the change under 21 CFR 601.12 as follows:

Submit a supplement to your biologics license application adding testing for *B. microti*. Include the name, address and FDA registration number of the product testing laboratory and the effective date on which testing will be initiated in your supplement.

1. If testing will be performed by a laboratory that is FDA-registered and approved to perform donor/blood product testing, but does not currently perform testing for your blood establishment, submit the supplement as a Supplement-Changes Being Effected (21 CFR 601.12(c)(5)).

2. If the laboratory is not registered with the FDA, submit the supplement as a Prior Approval Supplement (21 CFR 601.12(b)). The testing laboratory must register (21 CFR 607.20(a)) and be inspected by FDA prior to performing testing on blood donation samples.

3. If testing will be performed by either your own FDA-registered laboratory or your current contract outside testing laboratory approved for use by the FDA, submit this change in your next annual report (21 CFR 601.12(d)).

C. Circular of Information

Licensed blood establishments that implement testing for *B. microti* must update their circular of information to include the test statement recommended in this document in accordance with 21 CFR 606.122(h). You may include this change in your supplement reporting implementation of testing or you may include it in your next annual report under 21 CFR 601.12(d).

Note: Unlicensed blood establishments are not required to report implementation of the recommendations in this document to FDA.

VII. TESTING PRIOR TO PUBLICATION OF THE FINAL GUIDANCE

We understand that some blood establishments may wish to implement testing for *B. microti* prior to publication of the final guidance. Such establishments must use the test consistent with the test kit's manufacturer's instructions (21 CFR 606.65(e)). In addition, licensed blood

establishments must report the change to FDA under 21 CFR 601.12.[5] Blood establishments that also wish to revise their DHQ to remove the question regarding a history of *Babesia* must submit a prior approval supplement prior to implementation (21 CFR 601.12(b)(1)).

[5] See "Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture; Guidance for Industry" dated December 2014.

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APPENDIX

SCIENTIFIC RATIONALE AND FURTHER EXPLANATION FOR THE RECOMMENDATIONS AND ADDITIONAL CONSIDERATIONS

Detection and Persistence of Antibodies to B. microti

Antibodies are a reliable marker of exposure to *B. microti*. Detectable antibodies emerge during acute infections, persist in chronic infections. and indicate potential presence of parasites in the host. However, antibodies to *B. microti* also may persist for an extended period after resolution of parasitemia. The question of how long antibodies persist after *B. microti* infection is poorly understood. While the *B. microti*-specific antibodies may persist for several years, in limited studies, clearance of parasitemia is often associated with decline in antibody titers. Ruebush et al., determined the development and persistence of *B. microti* antibodies in 16 patients who developed IFA titers of 1:1024 or 1:4096 between the first 3 to 4 weeks after onset of clinical symptoms. The antibody titers began to decline in the next 2 to 3 months and ranged between 1:16 to 1:256 at 5-7 months after onset of illness and were maintained at that level for up to 13 months (Ref. 37). In another prospective study, *B. microti*-infected individuals were followed for up to 27 months to detect the episodes of illness and evidence of parasitemia and sero-conversion. In 12 patients who were monitored for babesial DNA and persistence of antibody, the circulating DNA lasted for 3 months or more after the initial diagnosis which also paralleled the rise and decline of antibody titers. At 12 months after the initial diagnoses, antibody levels either returned to baseline or dropped from a peak reciprocal titer of 1:1400 to 1:200 (Ref. 11). In another longitudinal study, investigators assessed the course of *B. microti* infection in sero-positive donors; 6 donors had become sero-negative within 6-9 months of being parasitemic. On the other hand, 3 donors remained sero-positive over three years of follow up, despite having received anti-babesial treatment (Ref. 38). Lastly, in a comprehensive long-term follow up study, 62.1% (139/224) of all donor samples were negative for anti-*B. microti* antibody at 20 months and 94.6% (212/224) of all donor samples were antibody negative by 40 months after index samples were tested (Ref. 39). These results suggest that, while the antibody response to *B. microti* may persist for several years in a subset of individuals, generally there is a sharp decline in antibody titers after the initial infection. The prolonged antibody levels in some *B. microti* exposed individuals may be due to protracted asymptomatic infections, reinfections or recrudescence.

Nucleic Acid-based Assays for Detection of B. microti

Whereas antibodies are a reliable marker of exposure to *B. microti,* the presence of nucleic acid indicates an active infection. However, due to the intraerythrocytic nature of *Babesia* parasites and the sensitivity limitations of nucleic acid tests (NAT), it is difficult to ascertain the ability to transmit *B. microti* infections by sero-positive, but PCR-negative blood units. Studies in *Babesia*-endemic areas have shown the presence of antibody positive donors year round (Refs. 10, 40); in a longitudinal study of 83 sero-positive blood donors, 21% had evidence of parasitemia as determined by a PCR test, microscopy or hamster inoculation (Ref. 38). In a smaller study, of *B. microti* antibody positive blood donors from Connecticut, 10 of 19 (53%)

seropositive donors were also PCR positive (Ref. 41). NAT has been effective in detecting early infections (window period: WP) when antibody levels are below detection limit. In one study of prospective blood donors using the investigational NAT and antibody assays, 15 of 220,479 donations (about 1 in 15,000 donations) were NAT positive but antibody negative (Ref. 39) in index sample testing. Twelve of 13 WP donors seroconverted in follow up testing while one donor failed to seroconvert.

The scientific rationale and further explanation for the recommendations in section V. of this document are as follows:

- Due to the intra-erythrocytic nature of *Babesia* parasites, and the likelihood of low-grade parasitemia during the early phase of acute infection (window period), and low-grade, asymptomatic infections in chronic carriers, a NAT alone may not be effective to detect all infected donors (Ref. 5). On the other hand, antibody-based tests may be highly effective in detecting acute and chronic low-grade infections. However, antibody-based tests have limitations in detecting the early phase of infections prior to seroconversion (i.e., window period), lack of seroconversion or low antibody response in some donors, and inability to distinguish between active and previously resolved infections (Refs. 10, 38). Therefore, a combination of NAT and antibody-based tests was considered the most suitable option to detect *Babesia* infection during all phases of infection cycle.

- Although tick-borne *B. microti* transmission in endemic areas is seasonal and occurs primarily during the months of May-September (Refs. 12-17, 26), both clinical and TTB cases are reported in all months of the year (Refs. 10, 12-17). Likewise, results of investigational testing (Refs. 10, 42) and epidemiological (Refs. 40, 41) studies in endemic areas have reported the presence of sero-positive and parasitemic donors year-round. Therefore, year-round NAT and antibody testing has been recommended to detect asymptomatic chronic infections outside the main transmission season in *Babesia*-risk states.
- Due to donor travel to and from endemic areas and interstate commerce of blood and blood products, TTB risk is not limited to endemic areas only but extends nationwide (Refs. 2, 26). For example, although a vast majority of clinical cases and TTB cases are reported within the 7 highest endemic states (Refs. 2, 12-17), clinical babesiosis have been reported in 49 states (Ref. 26) and TTB cases have been reported in 22 states (Refs. 2). Therefore, to minimize the TTB risk, FDA is recommending that donor testing should not be limited only to endemic states, but should also be expanded to include the high-risk states, particularly in those states that are adjoining to those states where endemic *B. microti* transmission is reported.
- The May 13, 2015 BPAC recommended that antibody testing should be year-round and nationwide. The Committee also recommended that year-round NAT should be implemented in 9 endemic states and Pennsylvania. However, FDA's recommendation that the *B. microti* testing should be implemented in the 14 high risk states and Washington, D.C. is based on the following scientific rationale:

About 99% of clinical babesiosis cases (Refs. 12-17, 26) and 95% of TTB cases (Ref. 25) are reported from these 14 states - Connecticut, Massachusetts, Rhode Island, New York, New Jersey, Minnesota, Wisconsin, New Hampshire, Maine, Maryland, Virginia, Vermont, Pennsylvania, Delaware and Washington, D.C. Of these, endemic *B. microti* transmission is reported in following 10 states - Connecticut, Massachusetts, Rhode Island, New York, New Jersey, Minnesota, Wisconsin, New Hampshire, Maine and Pennsylvania. The states of Maryland, Virginia, Delaware, Vermont and Washington, D.C. are included because of the combination of estimated high babesiosis risk and proximity to an endemic state. About 26% of the U.S. population resides in these 14 states and Washington, D.C.

The FDA benefit-risk assessment model has indicated that NAT and antibody testing in the 14 states and Washington, D.C. would lead to 84.9% TTB risk reduction (Positive Predictive Value 43.9%) versus 96% risk reduction (Positive Predictive Value 19.3%) by nationwide testing. As shown in Table 1 of this document, although an incremental increase in TTB risk reduction is achieved with nationwide testing, the positive predictive value (the probability that donors with reactive testing results actually have babesiosis) decreases significantly under this testing scenario. The model estimated that nationwide testing could result in the discard of over 1,700 additional otherwise-suitable donations per year (compared to the selective testing strategy), the deferral of the falsely positive donors, and the loss of future donations from the deferred donors, all of which pose a risk to the blood supply. Alternatively, under the benefit-risk assessment model, the positive predictive value improves significantly when testing is performed only in the highest risk states.

In summary, FDA is adopting a selective testing strategy for *B. microti* in the 14 highest risk states and Washington, D.C. after considering the benefits and risks of the selective testing strategy under the model, as explained in the paragraph above, and the fact that approximately 99% of the clinical babesiosis cases and 95% of the TTB cases are reported in these states. However, FDA will continue to monitor the epidemiology of babesiosis, cases of TTB in the U.S., and other scientific information as it becomes available. If, based upon the available scientific information, the risk of transmission of babesiosis by blood and blood components changes significantly, we may update these recommendations as warranted.

- We have followed the Committee recommendation for a two-year deferral for *Babesia*-reactive blood donors in states that perform routine donation testing. Such donors may present for donation after a two-year deferral period when testing by NAT and antibody will be performed.

- Donors of Source Plasma are exempt from *Babesia* questioning and testing for *Babesia microti*. This recommendation is consistent with the regulation that donors of Source Plasma are excluded from deferral due to malaria risk under 21 CFR 630.15(b)(8).

Similar to *Plasmodium* parasites, *Babesia* parasites are also intra-erythrocytic in nature and subjected to killing during the manufacturing process.

Definitions:

Babesiosis – An infectious disease caused by the intraerythrocytic parasitic protozoans of the genus *Babesia*. For additional information regarding babesiosis and its associated symptoms, visit the CDC website at https://www.cdc.gov/parasites/babesiosis/.

***Babesia*-endemic state –** Any state where tick-borne transmission of babesiosis is reported to take place, as determined by the CDC or in the published literature.

***Babesia*-risk state –** Any *Babesia* endemic state, a state that is adjoining an endemic state, or a state where a high number of clinical or transfusion-transmitted cases of babesiosis are reported.

Table 1. Summary of Benefits and Risks Under Nucleic Acid and Antibody Testing Under the Nationwide and the 14 Testing Scenarios by the FDA Risk Model (Ref. 25)

Testing Scenario	Percent TTB Risk Reduction	Positive Predictive Value	Units From Positive Donors Interdicted	False Positive Donor Test Results
No Donor Testing	0	0	0	0
14 States + DC CT, MA, RI, NY, NJ, MD, NH, ME, DC, VA, MN, VT, PA, DE, WI	84.9	43.9	868	652
50 States + DC	96.0	19.3	985	2422