Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria

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Draft Guidance for Industry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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Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria

Draft Guidance for Industry

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I. INTRODUCTION

This guidance document provides you, blood establishments that collect blood and blood components, with FDA's revised recommendations to reduce the risk of transfusion-transmitted malaria (TTM). Specifically, the guidance recommends selectively testing blood donations from donors at risk for malaria using an FDA-licensed donor screening nucleic acid test (NAT) for *Plasmodium species (spp.),* the causative agent of malaria.

The recommendations contained in this guidance apply to the collection of Whole Blood and blood components, except Source Plasma. We do not require blood establishments to screen Source Plasma donors for malaria risk factors because Source Plasma undergoes further manufacturing steps to effectively remove or inactivate pathogens such as *Plasmodia spp*. (see 21 CFR 630.15(b)(8)). Licensed plasma derivatives manufactured from Source Plasma have not transmitted malaria.

This guidance, when finalized, will supersede the guidance of the same title, dated December 2022 (December 2022 guidance) (Ref. 1).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances 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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Public Health Impact of Malaria Worldwide and in the United States (U.S.)

Malaria is primarily a mosquito-borne disease caused by infection with *Plasmodia* parasites. In 2022, malaria occurred in 85 countries, causing approximately 249 million cases and 608,000 deaths (Ref. 2). Five of the known species of *Plasmodium* parasites infect humans and can cause illness: *P. falciparum, P. malariae, P. ovale, P. vivax,* and *P. knowlesi*. Signs and symptoms of malaria typically include high fevers, shaking chills, anemia, thrombocytopenia (low blood platelets), and flu-like illness. However, asymptomatic, chronic infection can also occur. *P. falciparum* typically causes the most severe illness and is responsible for more than 90% of malaria-associated deaths (Ref. 2). *P. vivax*, the second most prevalent *Plasmodium* species, typically causes less severe disease and much lower mortality compared to *P. falciparum* malaria. People who live in malaria-endemic countries may develop partial immunity to malaria from frequent exposure to *Plasmodia spp.* Partial immunity does not protect these individuals from malaria after a new exposure but lessens symptoms and prolongs parasitemia, such that subclinical (asymptomatic) infection might persist for many years (Ref. 3).

In the U.S., malaria was eradicated in the 1950s and is no longer considered endemic. Currently, almost all individuals found to have malaria in the U.S. acquired the infection during travel to malaria-endemic countries or during a period of residence in such countries. Each year, approximately 28 million U.S. residents travel to parts of the world where malaria is endemic and about 2,000 imported cases of clinical malaria are reported annually in the U.S. (Ref. 4). Of all malaria cases where the country of origin was known, the majority (85%) were acquired in Africa (Ref. 4). CDC provides and periodically updates the list of malaria-endemic countries in their publication, *CDC Yellow Book: Health Information for International Travel* (commonly known as *The Yellow Book*) (Ref. 5).

Locally-acquired (autochthonous) mosquito-borne malaria is sporadically in the U.S. In 2003, 8 cases of autochthonous *P. vivax* malaria were identified in Palm Beach County, Florida (Ref. 6). No autochthonous cases were reported again until 2023, when 10 cases of locally-acquired, mosquito-borne malaria occurred in four geographically-diverse U.S. states – Florida (*P. vivax*, 7 cases), Texas (*P. vivax*, 1 case), Maryland (*P. falciparum*, 1 case) and Arkansas (*P. vivax*, 1 case) (Refs. 7-9). Consequently, mosquito-borne transmission may represent a new source of risk of malaria exposure among blood donors during local outbreaks in the U.S.

B. Transfusion-Transmitted Malaria in the U.S.

Although most cases of malaria worldwide result from mosquito-borne transmission, malaria can also be transmitted through transfusion of blood and blood components or less commonly through organ transplantation or congenital transmission from a mother to fetus (Refs. 10-12).

TTM remains a serious concern in transfusion medicine and *Plasmodium spp.* is defined as a relevant transfusion-transmitted infection under 21 CFR 630.3(h)(1)(x). The transfusion risk stems from asymptomatic blood donors with dormant liver-stage or chronic, asymptomatic blood-stage parasitic infection which can be indolent and persist for years. In 2001, the Centers for Disease Control and Prevention (CDC) published a comprehensive study on the number and characteristics of TTM cases in the U.S. from 1963 through 1999 (Ref. 10). A total of 93 TTM cases were reported in 28 states, of which 10 TTM cases were fatal (11%). The fatality rate associated with TTM is higher than the fatality rate among imported clinical cases (less than 1%) in the U.S., likely reflecting underlying morbidity or weakened immune status among recipients of blood transfusions compared to the general population. More recently, a total of 13 cases of TTM (average 0.62/year) were reported in literature between 2000 to 2020. Ten of the 13 cases were caused by *P. falciparum* (76.9%); 2 of the cases were caused by *P. malariae* (15.4%); and 1 of the cases was caused by *P. ovale* (7.7%) (Refs. 4, 13-16). Since 2000, all blood components implicated in causing TTM in the U.S. were donated by prior residents of sub-Saharan Africa.

Malaria is transmitted to transfusion recipients by parasite-infected red blood cells (RBC); consequently, Whole Blood or RBC components cause almost all TTM cases, including all cases in the last 2 decades in the U.S. There are rare reports of TTM associated with platelet components (Ref. 10) or never-frozen plasma components (Ref. 17) containing infected RBCs. Although there have been no reported cases of TTM associated with plasma components stored frozen and subsequently transfused, there are limited data on the viability of malaria parasites in plasma. Unlike Source Plasma, which is used to manufacture plasma derivatives, plasma intended for transfusion typically does not undergo further manufacturing steps to remove or inactivate pathogens.

C. Limitations of Current Approach to Screening Donors for Malaria Risk

In the absence of a licensed, approved, or cleared donor screening test for malaria, FDA has recommended time-limited deferrals for malaria risk based on self-reported donor history on the day of donation. Currently, FDA recommends either a 3-month or 3-year deferral period for individuals with different risk factors (i.e., travel to a malaria endemic area, prior residency in a malaria endemic country or a history of malaria) for exposure and infection. The scientific rationale for these deferrals was provided in the December 2022 guidance (Ref. 1).

Although these deferrals likely reduce the risk of TTM, TTM continues to occur because of the inherent limitations of donor history screening, in particular with respect to assessing the risk of exposure among prior residents of malaria-endemic countries. These screening procedures are complicated and error-prone for the collection staff and prospective donors, primarily because they involve recalling and assessing travel itineraries, determining the amount of time spent in malaria-endemic countries, and applying the appropriate deferral period. Donors may not disclose recent travel to

malaria-endemic areas or prior residence in malaria-endemic countries and collection staff may incorrectly interpret the information donors do provide.

A review of recent TTM cases identified the likely reasons that the current approach did not prevent transmission to patients. Seven of the 13 TTM cases reported between 2000 to 2020 implicated blood components collected from former residents of a malaria-endemic country. Because these former residents had been exposed to malaria more than three years prior to donating, it was consistent with FDA guidance recommendations to determine them eligible to donate. They still had asymptomatic parasitemia, however, and the infection was transmitted to the transfusion recipients. The remaining 6 of the 13 cases involved blood components collected from former residents of a malaria-endemic country, who might not have disclosed this malaria risk factor on the day of donation or might not have been evaluated by staff in accordance with FDA guidance recommendations (Refs. 13-15).

Another disadvantage of the current donor screening measures for malaria is the deferral of large numbers of otherwise healthy individuals based on travel risk and prior residence in malaria-endemic countries. According to some estimates, about 1% of all individuals who present to donate blood report malaria risk factors, amounting to an estimated 150,000 donations that are deferred for this reason (Ref. 13). Moreover, the deferral of travelers and prior residents of malaria-endemic countries in Africa, Asia and South America limits the genetic diversity of the blood supply. Having a predominantly Caucasian donor base with other ethnic groups underrepresented in the U.S. blood supply makes it difficult to find compatible blood for some patients. For example, rare or matched blood types needed by transfusion-dependent patients with diseases such as sickle cell disease and thalassemia are more prevalent among individuals from malaria-endemic countries (Refs. 18-19).

D. Regulatory Requirements for Testing to Reduce the Risk of TTM

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. The regulations require blood establishments to perform this testing on every donation unless an exception applies. Under 21 CFR 610.40(a)(3)(ii), when evidence related to the risk of transmission of the RTTI supports that testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood, blood component, or blood derivative product manufactured from the collected blood or blood component, blood establishments may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA (21 CFR 610.40(a)(3)(ii)(A)) or stop testing in accordance with procedures found acceptable for this purpose by FDA (21 CFR 610.40(a)(3)(ii)(B)).

E. FDA's Assessment of Testing Strategies and Use of Pathogen Reduction Technology to Reduce the Risk of TTM

FDA licensed the first donor screening test for malaria on March 19, 2024: cobas Malaria. The cobas Malaria test, which is manufactured by Roche Molecular Systems, is a qualitative in vitro nucleic acid screening test, intended for the direct detection of *Plasmodium* (*P. falciparum, P. malariae*, *P. vivax*, *P. ovale* and *P. knowlesi*) DNA and RNA in whole blood samples from individual human donors (Ref. 20). The availability of an FDA-licensed NAT for screening blood donations for malaria has prompted FDA to reevaluate our recommendations to reduce the risk of TTM.

On May 9, 2024, FDA sought the advice of the Blood Products Advisory Committee (BPAC) on strategies for selectively testing blood donations using a licensed NAT donor screening test to reduce the risk of TTM (Ref. 21). Specifically, the BPAC discussed the possible advantages and disadvantages of FDA's proposed selective testing strategies to test donations from donors who report a history of malaria, prior residence in a malaria-endemic country, or travel to a malaria-endemic area, as determined by the donor history questionnaire (DHQ). The BPAC also commented on the possible advantages and disadvantages of testing donations in areas in the U.S. when public health authorities identify local mosquito-borne malaria transmission. BPAC members and commenters in the Open Public Hearing generally supported a selective testing strategy if it could be simplified and more tailored to the risk groups. However, some members preferred to retain the donor deferral recommendations instead of testing, as consistent with the December 2022 guidance. Other members supported an option for blood establishments to choose to either selectively test some donations or to continue to defer all prospective donors who report malaria risk in accordance with the recommendations in the December 2022 guidance.

FDA has concluded that TTM is a public health concern and an ongoing risk to transfusion recipients, and that the current deferrals for risk of malaria negatively affect blood availability and genetic diversity of the blood supply. We have also concluded that there is sufficient scientific information, explained in section II.F below, to support the determination that testing is necessary to reduce adequately and appropriately the risk of TTM (see 21 CFR 610.40(a)(3)(i)(B)) and that selective testing using an FDA-licensed NAT for malaria will improve the safety and availability of blood and blood components for transfusion. Further, there is sufficient evidence relating to risk of TTM to support a determination that testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission, and FDA finds that the selective testing strategy described in section IV.A of this guidance is an acceptable alternative testing procedure to reduce such risk adequately and appropriately (see 21 CFR 610.40(a)(3)(ii)(A)).[1]

[1] In this draft guidance, FDA is proposing that testing for malaria is necessary, and that selective testing is an acceptable alternative testing procedure. FDA does not intend to consider these determinations final unless and until they are included in a final guidance.

We reached these determinations after carefully considering the current TTM risk, the advice of the BPAC, and the available evidence.[2] The selective testing strategy described in this guidance is intended to identify donations at greatest risk of transmitting malaria and reduce adequately and appropriately the risk of TTM, while also improving the genetic diversity and availability of the blood supply.

In addition, based on the available evidence relating to risk of TTM and evidence of effectiveness of FDA-approved pathogen reduction devices indicated for use against *Plasmodium falciparum*[3], FDA finds that it is acceptable for blood establishments to use such devices to reduce adequately and appropriately the risk of TTM for platelets and plasma in lieu of testing (see 21 CFR 610.40(a)(3)(ii)(B)).

To provide for appropriate donor screening and testing for malaria, the Director of the Center for Biologics Evaluation and Research is providing an alternative procedure (testing or pathogen reduction) under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10 (a) and (h) that require, among other things, that blood establishments defer donors for risk factors for malaria. Specifically, as set forth in detail in section IV.B of this guidance, FDA is not requiring deferral of donors for a history of malaria, prior residence in a malaria endemic country, and/or travel to a malaria-endemic country if such testing or pathogen reduction is performed. FDA is also not requiring deferral of donors in regions of the U.S. with local, mosquito-borne malaria transmission if such testing or pathogen reduction is performed. FDA is recommending testing or pathogen-reducing donations, in place of deferrals, because these alternatives to deferrals reduce adequately and appropriately the risk of TTM and increase the availability of blood and blood components.

Use of pathogen reduction under this alternative procedure would encompass donations from donors with a history of malaria or prior residence in a malaria endemic country and donations collected in regions of the U.S. with local, mosquito-borne malaria transmission, in addition to donors who have traveled to a malaria-endemic country. We are expanding the scope of the pathogen reduction technology alternative procedure as provided in the December 2022 guidance because pathogen reduction is expected to be effective against *Plasmodium falciparum* regardless of the donor's risk category.

[2] See Section II.F of this guidance. In addition, we note that the Canadian Blood Services conducted a risk-based decision analysis for TTM, and their findings are aligned with this guidance (Ref. 22). Specifically, their report recommends the use of a malaria NAT for risk groups when a test becomes available in Canada.

[3] See additional information on FDA-approved pathogen reduction devices at https://wayback.archive-it.org/7993/20190207203516/https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm427488.htm and https://wayback.archive-it.org/7993/20190207203517/https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm427204.htm.

FDA does not recommend maintaining the currently recommended deferrals for malaria risk instead of implementing the testing or pathogen reduction approaches in this guidance.

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

The scientific basis for selectively testing donations from donors with malaria risk as described in section IV of this guidance is as follows:

- *Testing each donation from donors who report a history of malaria or a positive test for malaria*

  Individuals with a history of malaria can have prolonged periods of dormant liver stage infection, and asymptomatic chronic or intermittent parasitemia, which can last for many years. Consequently, testing every donation from individuals who report ever having had malaria or a positive test for malaria is necessary to reduce adequately and appropriately the risk of TTM. We expect that this will be a small number of donations each year. Further, the donation loss from falsely positive screening test results is likely to be very low, based on the demonstrated specificity of the licensed donor screening NAT.

- *One-time testing of donors who report prior residence in a malaria-endemic country*

  Blood components collected from prior residents of malaria-endemic countries accounted for all reported TTM cases in the U.S. in the last two decades and represent the most relevant risk which has proven difficult to mitigate with donor history screening alone (Refs. 4, 13-15). For purposes of this guidance, residence is defined as a continuous stay of 5 years or more in a country or countries having any malaria-endemic area (see section III of this guidance).

  The incidence and prevalence of individuals with asymptomatic parasitemia in the potential donor population, as well as the concentration of circulating parasites among such individuals, is unknown. The available data from investigations of TTM cases, however, support that molecular testing with the licensed donor screening NAT for malaria will identify these individuals. In a detailed review of published TTM cases in the U.S. and Canada since 2010, eight TTM cases were identified in which molecular testing had been performed as part of the investigation to identify the implicated donors with malaria (Ref 16). All the implicated donors associated with the TTM cases had asymptomatic malaria and were prior residents of Africa. Half of the implicated donors were likely exposed more than 3 years prior to the time of their donation and so it was consistent with FDA guidance recommendations to determine them eligible to donate. The other half were likely exposed within the 3 years prior to the date of their donation and

so FDA guidance would recommend they be deferred, but they were accepted, either because of nondisclosure of information by the donor or because FDA's recommendations were not followed. In the eight TTM cases, investigators conducted molecular testing with PCR tests for *Plasmodia* DNA. The PCR tests used were reported to have a lower sensitivity than the currently licensed NAT for malaria, which detects *Plasmodia* RNA in addition to DNA. A follow-up sample from the implicated donor was positive in the PCR tests in seven of eight cases; in the eighth case, the test was performed on a retained sample which had been stored for weeks and was suboptimal for PCR (Ref. 16).

We anticipate that prior residents of malaria-endemic countries who have subsequently had at least one negative result using an FDA-licensed donor screening NAT for malaria likely do not have a chronic parasitemia, and we consider them to pose the same risk as travelers from nonendemic countries. This selective testing strategy does not involve assessing the number of consecutive years that a prior resident spends in a nonendemic country prior to donation, as is the case under the FDA's current deferral policy.

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

  Among 4,156 imported, clinical malaria cases reported between 2016-2018 for which the date of arrival in the U.S. and the onset of illness was known, >99% (4,127) developed clinical symptoms within 12 months of return to the U.S., and >94 % (3,908), within 3 months (Refs. 4, 23-24). The selective testing strategy described in this guidance therefore includes testing donations from donors who report travel to a malaria-endemic country in the last 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. In contrast to time-based deferrals, a testing strategy can assess for a longer risk period without an excessive reduction in the number of donations. Finally, based on the demonstrated specificity of the licensed donor screening NAT for malaria, we expect that the rate of false positive screening tests associated with this testing strategy will be very low.

- *Testing all donations collected in regions of the U.S. with local, mosquito-borne malaria transmission*

  Local mosquito-borne malaria outbreaks in the U.S. occur unpredictably but are an increasing public health concern as well as a serious risk to transfusion safety.

We expect that testing will be more effective in preventing TTM than managing post-donation information and component retrieval when an outbreak is identified in a local area, given the difficulty in recognizing cases and the inherent delays in post-donation actions. Consequently, the selective testing strategy includes testing all donations collected in regions of the U.S. when FDA determines, in consultation with CDC and state and local health authorities, as appropriate, that it is necessary to address the risk of TTM because of local mosquito-borne malaria transmission.

Based on the scientific evidence summarized above, FDA considers the following potential benefits of selectively testing, or using an FDA-approved pathogen reduction device indicated for use against *Plasmodium falciparum* on, donations from donors at risk for malaria in place of donor deferrals:

- Improves the safety of the blood supply and adequately and appropriately reduces the risk of TTM;
- Encourages recruitment of a genetically diverse donor base that includes those individuals who have lived in malaria-endemic countries to support transfusion therapy for underrepresented patient groups with complex transfusion requirements (e.g., genetically-matched blood types, rare blood types)
- Increases blood availability by reducing the loss of donations from individuals who are deferred for malaria risk;
- Limiting testing to individuals at risk for malaria poses less burden than universally testing all donations;
- Reduces the complexity of donor questioning and minimizes the potential for donor errors in reporting risk and staff errors in assessing donor eligibility; and
- Supports timely implementation with an operationally feasible approach.

In conclusion, FDA has determined that testing blood and blood components (except Source Plasma) for evidence of malaria is necessary to reduce adequately and appropriately the risk of TTM. However, as described above, we have determined, in accordance with 21 CFR 610.40(a)(3)(ii), that testing *each donation* is not necessary. We have determined that, as an alternative to testing each donation, blood establishments may implement one of the following procedures, as described in more detail in section IV of this guidance:

- A selective testing strategy to 1) test donations from donors who have had malaria or resided in or traveled to a malaria-endemic country, and 2) test donations collected in regions of the U.S. that FDA identifies as having local, mosquito-borne malaria transmission; or

- Implementation of pathogen reduction technology for platelets and plasma donations using an FDA-approved pathogen reduction device indicated for use against *P. falciparum*, according to the manufacturer's instructions for use, when

collected from donors who have had malaria or resided in or traveled to a malaria-endemic country or collected in regions of the U.S. that FDA identifies as having local, mosquito-borne malaria transmission.

FDA will continue to monitor clinical cases of malaria and reported TTM cases in the U.S. and worldwide and may revise this document in the future, as appropriate, to reflect available scientific evidence.

III. DEFINITIONS

The following definitions, which are offered for the purpose of this guidance only, provide explanations of terms used in section IV of this guidance, below:

History of Malaria - Malaria is an infectious disease caused by a parasitic protozoan of the genus *Plasmodium*. A malaria diagnosis or a history of malaria in a prospective donor is based on a positive diagnostic test indicating *Plasmodium* infection, or a determination of a history of malaria made by the blood establishment's responsible physician. A prospective donor who had a reactive donor screening test for *Plasmodia spp*. nucleic acid is also considered to have a history of malaria.

Malaria-endemic country - Any country having an area or areas with malaria where CDC recommends anti-malarial chemoprophylaxis for travelers in the *CDC Yellow Book: Health Information for International Travel* commonly known as (*The Yellow Book*) at the time the donor is screened. A country that has any malaria-endemic areas should be considered to be malaria-endemic in its entirety.

Residence in a malaria-endemic country - For purposes of this guidance, residence is defined as a continuous stay of 5 years or more in a malaria-endemic country or countries.

Travel to a malaria-endemic country - Any travel to or through a malaria-endemic country. The duration of travel to a malaria-endemic country is defined as more than 24 hours to less than 5 years.

IV. RECOMMENDATIONS

The approaches described in this guidance for selectively testing blood donations from donors with malaria risk, or for implementing pathogen reduction of platelets and plasma, are based on the current epidemiological data on malaria and the risk of TTM, and on the availability of an FDA-licensed donor screening test for malaria and approved pathogen reduction devices. FDA may modify this guidance in the future based on scientific evidence as it becomes available, for example, if we determine that the selective testing approach described in this guidance is no

longer adequate and appropriate to reduce the risk of TTM. In addition, we may modify this guidance in the future based on the availability of additional licensed, approved, or cleared donor screening or supplemental tests and approved pathogen reduction devices.

A. Donor History Questionnaire

1. We recommend that you update your donor history questionnaire, including the full-length and abbreviated donor history questionnaires, and accompanying materials to incorporate the recommendations provided in this document and, in particular, to include the elements listed below in section IV.A.2 of this guidance. You must update your standard operating procedures to reflect any changes (21 CFR 606.100(b)).

2. You must conduct a medical history interview at each donation to determine if a donor is in good health and to assess donors for risk factors closely associated with exposure to or clinical evidence of relevant transfusion-transmitted infections (21 CFR 630.10(e)). We recommend that the donor history questionnaire include the following elements to assess prospective donors for malaria risk at each donation (note definitions in section III of this guidance):

    a. A history ever of malaria;

    b. A history ever of prior residence in a malaria-endemic country; and

    c. A history in the past twelve months of travel to a malaria-endemic country.

B. Donor Deferral, Donation Testing, and Requalification

1. 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.[4] We recommend that you defer the donor for at least one year and until the donor is free of malaria.

2. To comply with the requirements in 21 CFR 610.40(a)(3) and 610.40(b), you must test each donation using an FDA-licensed donor screening NAT for malaria in accordance with the manufacturer's instructions or implement one of the following alternative testing procedures described in section IV.B.2.a.-b:

[4] Note that the Director of CBER has not authorized testing or pathogen reduction as an alternative to the requirement to defer such donors.

a. Test donations from donors with malaria risk as described in section IV.B.2.a.i-iv of this document for evidence of malaria using an FDA-licensed donor screening NAT (21 CFR 610.40(a)(3)(ii)(A)).

   i. Donations from donors who report a history of malaria

      - You must test each donation collected from a donor who reports a history ever of malaria.

      - You must test donations collected from a donor with a history of malaria at each subsequent donation, even if the donor does not report other risk factors for malaria (i.e., residence 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.

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

      - You must test at least one time, a donor of blood or blood components who reports that they are a prior resident of a malaria-endemic country (i.e., a continuous stay of 5 years or more in a country or countries having any malaria-endemic area).

      - Each blood establishment should review its records to determine the history of testing for malaria in donations from a prospective donor who reports a history of prior residence in a malaria-endemic country to determine whether testing must be performed.

      - 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.

iii. Donations from donors who report travel to a malaria-endemic country in the past 12 months

- You must test each donation from a donor who reports travel to a malaria-endemic country in the past 12 months.

- After this 12-month period, you are not required to test subsequent donations from the donor, unless the donor reports risk factors for malaria (i.e., a history of malaria, prior residence 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.

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

- Upon notification by FDA via a posting on the agency's website, you must test each donation collected in a region of the U.S. with local, mosquito-borne malaria transmission.

- FDA will make such a notification, in consultation with CDC and other public health authorities, as appropriate, based on the identification of mosquito-borne malaria transmission in a localized, geographic area in the U.S. and the available evidence regarding the likelihood of continued transmission or a sustained outbreak. In making this determination, FDA will consider the number of local, mosquito-borne malaria cases reported and under investigation, environmental conditions, and likelihood of ongoing local transmission.

- FDA intends to identify the geographic region(s) for which testing of each donation must be implemented by zip code(s)or larger area(s), as appropriate, depending on the cases reported. FDA will notify blood establishments via a posting on the agency's website when the identified region(s) no longer have local, mosquito-borne malaria transmission that necessitates testing of donations collected in the region(s) to reduce adequately and appropriately the risk of TTM (e.g., when no new case is identified within a rolling 8-week period in a geographic location).

b. For platelets and plasma donations, implement pathogen reduction technology using an FDA-approved pathogen reduction device

indicated for use against *Plasmodium falciparum,* according to the manufacturer's instructions for use (21 CFR 606.65(e)), when collected from donors who have had malaria or resided in or traveled to a malaria-endemic country or collected in regions of the U.S. that FDA identifies as having local, mosquito-borne malaria transmission.

3. You must defer donors with a reactive NAT result for malaria (21 CFR 610.41(a)). We recommend you defer the donor for at least 1 year from the date of the reactive donation. You must make reasonable attempts to notify any donor whose donation tests reactive for malaria of their deferral and of their test results, within 8 weeks after determining that the donor is deferred (21 CFR 630.40). Where appropriate, deferred donors must be provided information concerning medical follow up and counseling (21 CFR 630.40(b)).

   Following the deferral period, the donor may be found to be eligible to donate under 21 CFR 610.41(b), provided all other donor eligibility criteria are met. Subsequent donations from donors with a reactive NAT result for malaria must either be tested for malaria at each donation, or, for platelet and plasma donations, you can instead implement pathogen reduction technology, consistent with section IV.B.2 of this guidance (21 CFR 610.40(a)(3)).

4. Requalification of previously deferred donors: A donor who was previously deferred for a history of malaria, prior residence in a malaria-endemic country or travel to a malaria-endemic area as determined by donor questioning may be eligible to donate under 21 CFR 630.35(b) provided the following conditions are met: 1) On the day of donation, the donor has not had a positive test for malaria in the past 1 year and they meet all other eligibility criteria and 2) the donations from the donor must either be tested for malaria, or, for platelet and plasma donations, you may implement pathogen reduction technology, consistent with section IV.B.2 of this guidance.

C. Product Management, Retrieval and Quarantine, Notification of Consignees of Blood and Blood Components

1. You may release donations that are nonreactive for malaria by a licensed donor screening NAT provided all other donation suitability requirements are met (21 CFR 630.30).

2. You must not ship or use a donation that is reactive for malaria, unless an exception for shipment or use is applicable (21 CFR 610.40(h) and 21 CFR 630.30(b)(1)).

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. The responsible physician should also consider the disposition of in-date cellular components (e.g., frozen RBC components) collected more than 12 months prior to the reactive index donation, especially those that were not tested; and

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.

The recommendation for consignee notification and retrieval does not apply to previously distributed cellular blood components that were pathogen reduced using an FDA-approved device according to its instructions for use.

d. Identify all acellular blood components (i.e., frozen plasma products intended for transfusion) previously collected from that donor in the 12 months prior to the date of the reactive index donation. Quarantine any in-date acellular blood components held at your establishment.

Note: Based on the very low risk of TTM associated with frozen acellular blood components, we are not recommending notification of consignees or product retrieval if you distributed frozen acellular blood components.

D. Product Disposition and Labeling

1. You must not ship or use blood and blood components that test reactive for malaria by a licensed donor screening NAT, except as provided in 21 CFR 610.40 (h)(2)(i) through (h)(2)(vii), such as for certain research or use as a component of, or to prepare, a medical device. (21 CFR 610.40(h)).

2. If you relabel reactive blood and blood components intended for shipment or use in accordance with 21 CFR 610.40(h)(2), 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 label the blood and blood components (21 CFR 606.121(c)(10) and (f) and 610.40(h)(2)(ii)(E)), as applicable:

a. "NOT FOR TRANSFUSION: Collected from a Donor Determined to Be Reactive for Malaria"

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"

E. 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.

1. When testing for malaria is performed as described in this guidance, you must update your circular of information to include the test and result (21 CFR 606.122(h)). We recommend the following statement:

   "A licensed NAT for Plasmodium RNA and DNA has been performed and found to be nonreactive for blood collected from donors at risk for malaria when testing is required by FDA."

V. IMPLEMENTATION AND REPORTING CHANGES TO AN APPROVED APPLICATION

This draft guidance is being issued for comment purposes only.

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.

As discussed below, licensed blood establishments must report changes to their approved applications to implement the approaches described in this guidance in accordance with 21 CFR 601.12. Unlicensed establishments do not need to report changes to FDA.

A. Donor History Questionnaire

Licensed blood establishments must report changes to their donor history questionnaire (DHQ) and accompanying materials under 21 CFR 601.12 as follows:

1. Licensed blood establishments that implement a version of the DHQ and accompanying materials prepared by the AABB Donor History Task Force 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. Licensed blood establishments that revise their own DHQs and accompanying materials to reflect the recommendations in this guidance must report the change to FDA in a Prior Approval Supplement under 21 CFR 601.12(b). We recommend that you include the following in the submission:

    a. FDA Form 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" which may be obtained at https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.
    b. A cover letter describing the request and the contents of the submission.
    c. A written standard operating procedure (SOP) describing the donor questions and process to identify donations for testing.
    d. The donor history questionnaires and accompanying document(s). Please highlight the modifications.

B. Testing and Pathogen Reduction Technology

Licensed blood establishments that implement testing for malaria with an FDA-licensed donor screening NAT or pathogen reduction technology using an FDA-approved pathogen reduction device indicated for use against *Plasmodium falciparum* consistent with section IV.B of this guidance, must report the change under 21 CFR 601.12 in an annual report under 21 CFR 601.12(d)[5], noting the date that the process was implemented.

Note that implementation of an alternative testing procedure that FDA has not found to be adequate and appropriate in accordance with 21 CFR

[5] See 21 CFR 601.12 (a)(3)

610.40(a)(3)(ii) would be a major change requiring submission of a prior approval supplement (21 CFR 601.12(b)(1)). As part of its review of the supplement, FDA would consider whether the proposed testing procedure is an adequate and appropriate alternative testing procedure that is acceptable to reduce risk of TTM under 21 CFR 610.40(a)(3)(ii).

C. Circular of Information

Licensed blood establishments that update their circular of information to include the test statement recommended in section IV.E of this guidance document must report this change under 21 CFR 601.12. You may include this change in your supplement reporting implementation of testing, or you may include it in your next annual report.

Licensed blood establishments must submit a Prior Approval Supplement under 21 CFR 601.12(f)(1) if you intend to update your circular of information to include a different test statement than recommended in section IV.E of this guidance.

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