Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance when appropriate.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus

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Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are providing you, blood establishments that collect Whole Blood and blood components, with recommendations for donor screening, donor deferral and product management to reduce the risk of transfusion-transmitted Zika virus (ZIKV). The recommendations contained in this guidance apply to the collection of Whole Blood and blood components intended for transfusion. This guidance does not apply to the collection of Source Plasma.[1]

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

II. BACKGROUND

ZIKV is an arbovirus from the *Flaviviridae* family, genus *Flavivirus*. It is transmitted to humans primarily by the *Aedes aegypti* mosquito, but it may also be transmitted by the *Aedes albopictus* mosquito (Refs. 1, 2). In addition, intrauterine, perinatal and sexual transmission of ZIKV has been reported (Refs. 3, 4, 5). It was first isolated in 1947 from a rhesus monkey in the Zika Forest of Uganda, and isolated from a human in 1968 in Nigeria (Ref. 2). Epidemiological studies showed that the virus has circulated in humans between 1951 and 1981 in African and Asian countries (Ref. 6). ZIKV illness was first recognized outside of Africa and Asia in 2007

[1] This guidance does not apply to the collection of Source Plasma, which is used for further manufacture of plasma-derived products. Viral inactivation and removal methods are currently used to clear viruses in the manufacturing process for plasma-derived products.

during an outbreak on Yap Island, Micronesia (Refs. 7, 8). An outbreak of ZIKV was next reported in French Polynesia from October 2013 to February 2014, when about 11% of the population had symptomatic infection (Refs. 9, 10).

Recent outbreaks of arboviral disease in the Americas have included large dengue and chikungunya virus outbreaks. ZIKV reached the region of the Americas in early 2015 with local transmission first reported in Brazil (Refs. 11, 12) and as of February 10, 2016, there are 30 countries and territories worldwide with active local transmission of the virus (Refs. 13, 14). Outside of the Americas, local transmission of ZIKV has been reported in the Pacific Islands of Samoa, American Samoa and Tonga, and Cape Verde in Africa. As of February 10, 2016, local mosquito-borne transmission of ZIKV has not been reported in the continental United States, but cases have been reported in travelers returning to the United States from areas with local transmission (Ref. 14).

In February 2016, the World Health Organization (WHO) Director Dr. Margaret Chan declared that "the recent cluster of microcephaly cases and other neurological disorders reported in Brazil constitutes a Public Health Emergency of International Concern." In January 2016, Zika virus disease was added to the list of nationally notifiable conditions in the U.S. as a subtype of Arboviral diseases (Ref. 15).

ZIKV disease symptoms include: fever, arthralgia, maculopapular rash, and conjunctivitis. Less frequently, observed symptoms include digestive problems (abdominal pain, diarrhea and constipation), mucous membrane ulcerations (aphthae), and pruritus (Refs. 16, 17). In addition, neurological manifestations and congenital anomalies have been temporally and spatially associated with ZIKV disease outbreaks (Ref. 17). Association of ZIKV infection with Guillain-Barré syndrome cases has been reported during outbreaks in Polynesia (Ref. 18) and in Brazil (Ref. 19). In Brazil, there has also been a marked increase in the incidence of microcephaly in regions most affected by the ZIKV epidemic (Refs. 19, 20).

Sexual transmission of ZIKV has been reported (Refs. 4, 5). The two reported cases involved transmission of the virus through sexual contact. In a separate report, ZIKV was isolated from semen at least two weeks and possibly up to 10 weeks after illness onset (Ref. 21). The duration of persistence of ZIKV in semen remains unknown. Data are currently not available regarding the presence of ZIKV in vaginal fluids. Sexual transmission of ZIKV from infected women to their sexual partners has not been reported.

Two instances of possible transfusion-transmission have been described in media announcements in Campinas, Brazil (Refs. 20, 22). In French Polynesia, 3% of samples from asymptomatic blood donors contained detectable ZIKV RNA during the outbreak in French Polynesia in 2013-14, indicating the likelihood of transmission by blood transfusion (Refs. 9, 23, 24). For these reasons, measures should be taken to prevent transfusion-transmission.

Regarding measures to help prevent ZIKV transmission through blood products, ZIKV is likely cleared by the existing viral inactivation and removal methods that are currently used to clear viruses in the manufacturing processes for plasma-derived products. For example, these viral clearance steps for various products may include pasteurization, solvent/detergent (S/D) treatment and incubation at low pH (Refs. 25, 26, 27). These methods are highly effective in

clearing lipid-enveloped viruses in plasma-derived products, but are not generally applicable for use in blood and blood components intended for transfusion. However, an S/D treated pooled plasma product has been FDA-licensed and is commercially available.

A pathogen reduction device (amotosalen + UV illumination) for plasma and platelets has recently been approved by the Center for Biologics Evaluation and Research (CBER), FDA (Refs. 28, 29) and demonstrated effective reduction of a panel of viruses, including flaviviruses, such as dengue and West Nile virus. A recent publication showed that the same pathogen reduction technology (PRT) can effectively reduce ZIKV in plasma (Ref. 24). These devices have been used to reduce the risk of ZIKV infection by plasma or apheresis platelet components that are collected in areas experiencing ZIKV outbreaks (Ref. 9).

Risk of ZIKV Transmission by Blood Transfusion

The risk of transmission of ZIKV by blood transfusion is considered likely based on the following evidence:

(a) two possible cases of transfusion-transmission in Campinas, Brazil (Refs. 20, 22);

(b) there have been documented transfusion-transmissions of other flaviviruses such as West Nile virus, dengue virus and Yellow Fever vaccine virus (Refs. 30, 31, 32), all of which have been shown to produce detectable viremia (the presence of virus in the blood) during asymptomatic and symptomatic infections;

(c) ZIKV infection produces viremia with up to 8.1×10^6 copies/ml that may last up to (and possibly beyond) 14 days, with varying reports of viremia from 2 days before to 11 days after onset of symptoms (Refs. 3, 7, 23, 33);

(d) the pre-symptomatic period for ZIKV infection varies (if symptoms develop) from 3 to 12 days, during which viremia may occur (Refs. 34, 35);

(e) an estimated 80% of ZIKV infections remain asymptomatic (Refs. 8, 9);

(f) perinatal transmission of ZIKV, most likely by transplacental transmission or during delivery, has been reported (Ref. 3); and,

(g) blood donations positive for ZIKV viral RNA by nucleic acid testing (NAT) were detected during the French Polynesia outbreak in 2013-2014 (Refs. 9, 23).

III. RECOMMENDATIONS

Consistent with existing regulations and applicable guidance, donors must be in good health at the time of donation (21 CFR 640.3(b)) as indicated by, among other things, freedom from any disease transmissible by blood transfusion, as can be determined by history and examination (21 CFR 640.3(b)(6))[2]. Standard operating procedures that are already in place should result in the deferral of individuals who have symptoms consistent with ZIKV at the time of donation. The following recommendations are intended to reduce the risk of collecting blood and blood components from at-risk donors who could be potentially infected with ZIKV and do not display clinical symptoms during the incubation period or have an asymptomatic infection.

For the purpose of this guidance, an area with "*active transmission of ZIKV*" is an area included on the CDC website listing of countries and U.S. states and territories with local vector-borne (i.e., mosquito-acquired) transmission of ZIKV: http://www.cdc.gov/zika/geo/index.html.[3]

A. Recommendations for Areas without Active Transmission of ZIKV

1. Donor Educational Material and Donor History Questionnaire

   a. Donor Educational Material

      i. We recommend that you update your donor educational material to include the risk factors for and signs and symptoms of ZIKV infection so that donors can self-defer. Relevant information on the signs and symptoms of ZIKV infection can be found on CDC's website at: http://www.cdc.gov/zika/symptoms/index.html.

      ii. The educational material should instruct donors as follows:

         a. A donor with a history of ZIKV infection should self-defer for 4 weeks after the resolution of symptoms.

         b. A donor who exhibits signs and symptoms of ZIKV infection within 2 weeks of departure from an area with active transmission of ZIKV should self-defer for 4 weeks after the resolution of symptoms.

[2] Under 21 CFR 630.10(a), which will replace 21 CFR 640.3 and will be effective May 23, 2016, (80 FR 29842, May 22, 2015), a donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes set out in the new rule. Additionally, under 21 CFR 630.10(a) a donor is not eligible if you identify any factor(s) that may cause the donation to adversely affect the safety, purity, or potency of the blood or blood component. Such factors include travel to, or residence in, an area endemic for a transfusion-transmitted infection (21 CFR 630.10(e)(2)(iii)). Accordingly, the recommendations in this guidance will continue to apply under the new rule when it becomes effective.

[3] In general, an area is considered to have active transmission of ZIKV when locally transmitted, mosquito-borne ZIKV has been reported.

c. In addition to the above instructions, a donor should self-defer for 4 weeks after the last sexual contact with a man who has been diagnosed with ZIKV or who traveled to or resided in an area with active transmission of ZIKV in the 3 months prior to that instance of sexual contact.[4]

iii. In addition, we recommend that the educational material instruct donors with a history of recent travel to or residence in an area with active ZIKV transmission to inform the blood collection establishment promptly if they are diagnosed with ZIKV infection or if they develop symptoms suggestive of ZIKV infection within 2 weeks following donation.

b. Donor History Questionnaire

i. We recommend that you update your donor history questionnaire, including full length and abbreviated donor history questionnaires, and accompanying materials and standard operating procedures, as necessary, to incorporate the recommendations provided in this guidance.

ii. We recommend that your donor history questionnaire assess prospective donors for a history of residence in or travel to an area with active transmission of ZIKV in the past 4 weeks.

iii. We recommend that you refer to the CDC website for a listing of countries and territories with active transmission of ZIKV: http://www.cdc.gov/zika/geo/index.html.

iv. Blood collection establishments that use capture questions (e.g., "Have you traveled outside the United States within the past 3 years?") should review these questions to ensure they are adequate to identify travel to or residence in areas with active transmission of ZIKV, including U.S. territories. As necessary, capture questions may be revised or followed up with questions specific to areas with active transmission of ZIKV.

[4] Male donors with a history of sexual contact with another male would already be deferred for 12 months from last sexual contact consistent with the recommendations contained in the FDA Guidance, "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products," dated December 2015.

2. Donor Deferral

We recommend that you defer for 4 weeks[5] donors at risk for ZIKV infection as follows:

a. Defer for 4 weeks after the resolution of symptoms a donor with a history of ZIKV infection.

b. Defer for 4 weeks after the resolution of symptoms a donor who reports symptoms suggestive of ZIKV that arose within 2 weeks of departure from an area with active transmission of ZIKV.

c. Defer for 4 weeks after the last sexual contact a donor who has had sexual contact with a man who has been diagnosed with ZIKV or who traveled to or resided in an area with active transmission of ZIKV in the 3 months prior to that instance of sexual contact.[4]

d. Defer for 4 weeks from the date of his or her departure, a donor who has been a resident of or has traveled to an area with active transmission of ZIKV.

e. A deferred donor may be considered eligible after the deferral period has lapsed provided that all donor eligibility criteria are met.

B. Recommendations for Areas with Active Transmission of ZIKV

For areas with active transmission of ZIKV, we recommend the following strategies to reduce the risk of transfusion-transmitted ZIKV:

- Obtain Whole Blood and blood components for transfusion from areas of the U.S. without active transmission of ZIKV to fulfill orders, except that you may,
    - Collect and prepare platelets and plasma locally if you implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device as specified in the Instructions for Use of the device, or
    - Collect blood components locally and test blood donations with an FDA-licensed blood donor screening test for ZIKV, when available.[6]

Note: Use of an investigational donor screening test under an investigational new drug (IND) application or investigational pathogen reduction under an investigational device

[5] The deferral for 4 weeks provides a margin of safety in excess of the known incubation period of 3 to 12 days plus 14 days of viremia post symptom onset.
[6] Note: An FDA-licensed blood donor screening test for ZIKV is not currently available.

exemption (IDE) may be permitted in situations where approved technologies are unavailable.

Specifically, we recommend the following:

1. **Whole Blood and Red Blood Cells (RBCs)**

    - Obtain Whole Blood and blood components for transfusion from areas of the U.S. without active transmission of ZIKV to fulfill orders, except that you may,

        - Collect blood components locally and test blood donations with an FDA-licensed blood donor screening test for ZIKV, when available.[6]

2. **Platelets and Plasma**

    - Obtain Whole Blood and blood components for transfusion from areas of the U.S. without active transmission of ZIKV to fulfill orders, except that you may,

        - Collect and prepare platelets and plasma locally if you implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device as specified in the Instructions for Use of the device, or

        - Collect blood components locally and test blood donations with an FDA-licensed blood donor screening test for ZIKV, when available.[6]

    NOTE: Pathogen reduction may only be applied to products as specified in the Instructions for Use of the relevant device. At this time, PRT has only been approved by FDA for the treatment of plasma and certain apheresis platelets.

3. **Donor Educational Material, Donor History Questionnaire and Donor Deferral**

If you continue to collect blood components locally because you have implemented FDA-approved pathogen reduction technology or an FDA-licensed blood donor screening test (when available),[6] we recommend the following:

a. Donor Educational Material

i. We recommend that you update your donor educational material to include the signs and symptoms of ZIKV infection. Relevant information on the signs and symptoms of ZIKV infection can be found on CDC's website at: http://www.cdc.gov/zika/symptoms/index.html.

ii. The educational materials should instruct donors as follows:

a. A donor that exhibits signs and symptoms of ZIKV infection or has a history of ZIKV infection should self-defer for 4 weeks after the resolution of symptoms.

b. In addition to the above instructions, a donor should self-defer for 4 weeks after the last sexual contact with a man who has been diagnosed with or had symptoms suggestive of ZIKV infection in the 3 months prior to that instance of sexual contact.[4]

iii. In addition, we recommend that the donor educational material instruct donors to inform the blood collection establishment promptly if they are diagnosed with ZIKV infection or develop symptoms suggestive of ZIKV within 2 weeks following donation.

b. Donor History Questionnaire

i. We recommend that you update your donor history questionnaire, including full length and abbreviated donor history questionnaires, and accompanying materials and standard operating procedures, as necessary, to incorporate the recommendations provided in this guidance.

ii. We recommend that your donor history questionnaire assess prospective donors for:

a. A history of ZIKV infection or symptoms suggestive of ZIKV in the past 4 weeks;

b. A history of sexual contact in the past 4 weeks with a man who has been diagnosed with or had symptoms suggestive of ZIKV in 3 months prior to that instance of sexual contact.[4]

c. Donor Deferral

We recommend that you defer for 4 weeks donors at risk for ZIKV infection as follows:

i. Defer for 4 weeks after the resolution of symptoms a donor who reports a history of ZIKV infection.

ii. Defer for 4 weeks after the resolution of symptoms a donor who reports symptoms suggestive of ZIKV.

iii. Defer for 4 weeks after the last sexual contact a donor who has had sexual contact with a man diagnosed with or had symptoms suggestive of ZIKV infection in the 3 months prior to that instance of sexual contact.[4]

iv. A deferred donor may be considered eligible after the deferral period has lapsed provided that all donor eligibility criteria are met.

C. Post-Donation Information and Product Management

Except for blood components that have been pathogen-reduced, we recommend that you take the following actions if you determine that blood or blood components have been collected from a donor who should have been deferred according to the recommendations in Section III.A.2 or Section III.B.3.

1. If you collected blood or blood components from a donor who should have been deferred according to the recommendations in Section III.A.2 or Section III.B.3, or who has reported post-donation symptoms or diagnosis of ZIKV infection within 2 weeks of collection, we recommend that you quarantine and destroy any undistributed in-date blood or blood components collected from that donor.

2. If you distributed blood or blood components collected from a donor who should have been deferred according to the recommendations in Section III.A.2 or Section III.B.3, or who has reported post-donation symptoms or diagnosis of ZIKV infection within 2 weeks of collection, we recommend that you advise the transfusion service to quarantine and destroy any in-date blood or blood components collected from that donor.

3. Additionally, if blood components collected from a donor with a history of ZIKV in the past 4 weeks or from a donor who reports post-donation symptoms or ZIKV infection within 2 weeks of donation have been transfused, we recommend that you advise the transfusion service to inform the transfusion recipient's physician of record regarding the potential need for monitoring the recipient for a possible ZIKV infection.

D. Product Disposition and Labeling

1. We recommend that you destroy or re-label blood and blood components that were collected from a donor who should have been deferred according to the recommendations in Section III.A.2. or Section III.B.3. of this guidance document.

2. We recommend that you destroy or re-label blood and blood components that were collected from a donor who reports post-donation symptoms or diagnosis of ZIKV within 2 weeks of donation.

3. If you re-label such blood or blood components, they may be released for research, or for manufacture into non-injectable products or in vitro diagnostic reagents for which there is no alternative source, if labeled appropriately as described below.

4. You should use the following statements to prominently re-label the blood and blood components:

   a. "NOT FOR TRANSFUSION: Collected From A Donor Determined To Be At Risk For Infection With Zika Virus"

      and

   b. "Caution: For Laboratory Research Only"

      or

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

      You should not label these products with a U.S. license number unless FDA specifically approves such action.

IV. IMPLEMENTATION

A. Recommendations for Areas without Active Transmission of ZIKV

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than 4 weeks after the guidance issue date.

Consistent with 21 CFR 601.12, licensed establishments implementing these recommendations should update their annual reports indicating the date that the establishment revised and implemented their standard operating procedures consistent with these recommendations. These changes do not require our prior approval.

B. Recommendations for Areas with Active Transmission of ZIKV

We recommend that you implement the recommendations in this guidance as follows:

- For collections intended for intrauterine transfusion, transfusion in pregnant women, or transfusion in other at-risk recipients when requested by the prescribing physician, we recommend that you implement the recommendations in the guidance immediately, and use locally collected blood components only if blood components from an area without active transmission or pathogen-reduced blood components are unavailable and the urgent need for transfusion is judged by the prescribing physician to outweigh the risk.

- For all other collections, we recommend that you implement the recommendations in the guidance as soon as feasible, but not later than 2 weeks after the guidance issue date.

- We recommend that in-date blood components (e.g., red blood cells or frozen plasma) collected in areas with active transmission and remaining in inventory after you implement the recommendations be destroyed or re-labeled consistent with the recommendations in Section III.D. above.

Consistent with 21 CFR 601.12, licensed establishments implementing these recommendations should update their annual reports indicating the date that the establishment revised and implemented their standard operating procedures consistent with these recommendations. These changes do not require our prior approval.

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