

Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

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 <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (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 <https://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
Center for Biologics Evaluation and Research
July 2018**

Contains Nonbinding Recommendations

Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	DISCUSSION	5
IV.	RECOMMENDATIONS.....	8
V.	IMPLEMENTATION	13
VI.	REFERENCES.....	14

Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

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 revised recommendations to reduce the risk of transmission of Zika virus (ZIKV) by Whole Blood and blood components. In August 2016, FDA recognized ZIKV as a relevant transfusion-transmitted infection (RTTI) under Title 21 of the Code of Federal Regulations (CFR) Part 630. The recommendations contained in this guidance apply to the collection of Whole Blood and blood components. This guidance does not apply to the collection of Source Plasma.¹

This guidance document supersedes the guidance document of the same title dated August 2016.

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

A. ZIKV Epidemiology and Clinical Features

ZIKV is an enveloped, single-stranded RNA arbovirus in the *Flaviviridae* family (genus *Flavivirus*), closely related to dengue virus (DENV) and West Nile virus (WNV). Like DENV and chikungunya virus (CHIKV), ZIKV is primarily transmitted by *Aedes*

¹ Source Plasma is used for further manufacture of plasma-derived products. Viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of ZIKV.

Contains Nonbinding Recommendations

mosquitoes, most commonly *Aedes aegypti* (Ref. 1). In recent years, ZIKV has caused outbreaks on Yap Island, Micronesia in 2007, French Polynesia in 2013-2014, and the Americas in 2015, causing the largest outbreaks in Brazil and Colombia in 2016 and expanding to affect at least 91 countries in 2018 (Refs. 1-3). The first local mosquito-borne transmission of ZIKV in the United States (U.S.) was reported from Puerto Rico in December 2015, and soon thereafter local mosquito-borne transmission was also reported in American Samoa and the U.S. Virgin Islands (Refs. 2-4). Subsequently, in the continental U.S., local mosquito-borne transmission of ZIKV was reported in Florida in July 2016 and in Texas in November 2016 (Refs. 5, 6). Although there are currently no areas of increased risk for ZIKV transmission in the U.S. states (as of June 2018), the possibility of reintroduction or geographic spread of ZIKV by infected individuals exists in states and territories where *Aedes aegypti*, and possibly *Aedes albopictus* mosquitoes are present (Refs. 7, 8). Puerto Rico is still an area of ZIKV transmission risk in 2018, according to the Centers for Disease Control and Prevention (CDC) at the time of this writing (Ref. 3). An estimated 13% of the population of Puerto Rico was infected during the 2016 outbreak (Ref. 9). In addition to vector-borne disease, ZIKV infection was documented during the outbreaks to occur through other routes of exposure, including perinatal, intrauterine, sexual, laboratory-acquired and blood-borne transmission (Refs. 6, 10-17).

Most people infected with ZIKV are asymptomatic or have only mild symptoms such as fever, maculopapular rash, headache, arthralgia, and conjunctivitis that last up to a week (Ref. 1). However, ZIKV infection can occasionally be associated with Guillain-Barré syndrome and severe neurological complications (Ref. 18). ZIKV infection during pregnancy can cause microcephaly, severe congenital defects, and infant death (Refs. 1, 19, 20). ZIKV may be detected in serum or plasma for 1-2 weeks after infection and has been detected for longer periods of time in Whole Blood, red blood cells (RBCs), semen, and urine (Refs. 21-23). In a study of 150 ZIKV infected individuals in Puerto Rico, the median values for ZIKV RNA persistence were 11-17 days in serum; 6-10 days in urine; and 28-41 days in semen (Ref. 21). More than 60% of men with symptomatic ZIKV infection had detectable ZIKV RNA in their semen during the first 30 days of onset of illness, with the longest recorded duration of 281 days in one man; however, infectious virus appears to only be present for a few weeks after the onset of illness (Ref. 22). ZIKV RNA persists in RBCs and Whole Blood for several months following clearance in plasma and other body fluids (Ref. 23).

ZIKV Epidemiology Since the 2016 Outbreaks in the U.S.

The number of ZIKV disease cases in the U.S. has decreased considerably compared to 2016, the year during which ArboNET recorded over 5,000 cases in the states and over 36,500 cases in the U.S. territories (Ref. 6). In 2017, U.S. states reported 451 symptomatic ZIKV disease cases (436 cases in travelers returning from affected areas; 7 cases acquired through presumed local mosquito-borne transmission in Florida (n=2) and Texas (n=5); and 8 cases through other routes, including sexual transmission (n=7) and laboratory transmission (n=1), based on provisional data as of June 6, 2018). New York, Florida, Texas and California have had the highest number of ZIKV cases related to

Contains Nonbinding Recommendations

travel each year, accounting for over half of all symptomatic clinical cases in U.S. states. In 2017, U.S. territories reported 666 ZIKV disease cases (665 cases acquired through presumed local mosquito-borne transmission; 1 case in a traveler returning from an affected area) based on provisional data as of June 6, 2018. (Ref. 6).

B. ZIKV Transfusion Transmission

During recent epidemics, asymptomatic infection of blood donors has been documented, and transfusion-transmission of ZIKV has occurred. In the ZIKV outbreak in French Polynesia in 2013-2014, 2.8% of blood donors tested RNA positive by nucleic acid testing (NAT) (Refs. 16, 17). Media outlets reported the first cases of transfusion-transmitted ZIKV in Brazil in December 2015; subsequently, peer-reviewed articles described three cases of probable ZIKV transfusion transmission in Brazil from two donors who reported symptoms a few days after donating blood and whose retained serum samples subsequently were tested and found positive for ZIKV RNA (Refs. 13-16). During the French Polynesian outbreak, a retrospective study identified 30 ZIKV RNA-reactive blood components that were transfused to 26 recipients, with follow-up completed on 12 of the patients (Ref. 17). None of the transfusion recipients in this report or other published cases to date developed ZIKV-related symptoms after transfusion. However, the risk of transfusion-transmitted ZIKV is still relevant, considering the potential serious risk to fetuses and neonates. Additionally, there is concern about potential secondary exposure of the sexual partners of transfusion recipients if ZIKV enters the blood supply.

C. FDA Policies to Address ZIKV Transfusion Risk in 2016

Because of the rapid spread of ZIKV in the Americas and reports of transfusion transmission, FDA issued guidance in February 2016, with recommendations specific to areas with or without active (local, mosquito-borne) transmission of ZIKV (Ref. 24). For areas without active transmission, FDA recommended deferral of donors who reported a diagnosis of ZIKV infection, traveled to areas with active ZIKV transmission, or had sexual contact with men diagnosed with ZIKV or with men at risk through travel or residence. For areas with active transmission, FDA recommended discontinuing local blood collections and obtaining blood components from unaffected areas of the U.S., unless the establishment implemented investigational individual donation nucleic acid testing (ID NAT) or FDA-approved pathogen reduction technology for indicated components (i.e., platelets and plasma). Beginning in March 2016, Puerto Rico obtained blood and blood components from unaffected areas of the continental U.S. Subsequently, in April 2016, blood establishments in Puerto Rico initiated testing under an Investigational New Drug Application (IND) using the cobas ID NAT Zika test (Roche Molecular Systems, Inc.) (Refs. 25, 26).

With the possibility of sexual transmission of ZIKV over a prolonged period, and the first local mosquito-borne cases of ZIKV reported in Florida in July 2016, FDA recognized the potential for rapid spread of ZIKV in the U.S. Moreover, the significant delays in reporting ZIKV symptomatic disease cases rendered travel deferrals ineffective and impractical. Therefore, in August 2016, FDA recognized ZIKV as a transfusion-

Contains Nonbinding Recommendations

transmitted infection (TTI) under 21 CFR 630.3(l) and as an RTTI under 21 CFR 630.3(h) (Ref. 27). This determination was based on the severity of the disease, risk of transfusion-transmission by blood and blood components, the availability of appropriate screening measures including investigational screening tests for ZIKV and significant incidence and prevalence affecting the potential donor population. At that time, there were over 8,000 cases of locally-acquired ZIKV infection in Puerto Rico and other U.S. territories; 2,245 travel-associated cases in U.S. states; and 14 local mosquito-borne cases in Florida (Ref. 27). In the face of this urgent and evolving situation, the uncertain course of the epidemic, and the potentially severe consequences of ZIKV infection, FDA issued revised guidance in August 2016 recommending nationwide and territorial implementation of ID NAT on all blood donations (universal ID NAT) or pathogen reduction for indicated blood components (i.e., platelets and plasma) using a risk-based phased approach for implementation in the U.S. and its territories (Ref. 27).

D. Blood Products Advisory Committee on ZIKV Blood Donor Screening Alternatives

Universal ID NAT effectively intercepted potentially infectious units from asymptomatic blood donors. From the outset, FDA acknowledged the need to continue to evaluate changes in ZIKV epidemiology and the ongoing experience with ID NAT blood donation screening to inform changes to policy. On December 1, 2017, the Blood Products Advisory Committee (BPAC or committee) reviewed the available data on ZIKV blood donor screening and the evolving epidemiology in the U.S., and discussed alternatives to universal ID NAT to provide an adequate and appropriate safeguard against the current and future risk of ZIKV transmission through blood transfusion (Ref. 28). The BPAC unanimously determined that the incidence and prevalence of ZIKV did not support continued universal ID NAT in the U.S. or its territories (Ref. 28). However, the committee was also unanimous in its recommendation that blood establishments should not stop testing for ZIKV in the U.S. and its territories. A majority of the committee members supported the use of MP NAT year-round in all U.S. states and territories, with defined criteria to switch to ID NAT when local mosquito-borne ZIKV transmission is suspected or documented in a state or defined geographic collection area. The committee generally agreed that other donor screening options were not feasible or acceptable, such as using ID NAT to test donors who report possible exposure to ZIKV through travel or sexual contact or providing ID NAT-negative blood components to selected patients based on clinical indications (e.g., pregnant women, intrauterine transfusion, neonates).

Experience with ZIKV ID NAT Blood Donation Screening in the U.S.

In April 2016, blood establishments in Puerto Rico implemented ID NAT under IND using the investigational cobas Zika test (Roche Molecular Systems, Inc.) (Refs. 25, 26, 29). The prevalence of donations reactive for ZIKV RNA peaked at 1.8% in July 2016 (Refs. 25, 26).

Contains Nonbinding Recommendations

- From April 3, 2016 to October 7, 2017, a total of 111,808 blood donations were tested with cobas Zika (Ref. 28). Overall, 356 of 369 initially reactive donations were confirmed positive ($356/111,808 = 0.32\%$ or ~ 1 in 314 donations), either on the index donation ($n=347$) or follow-up sample ($n=9$), based on ID NAT repeat reactivity, positive alternative NAT, or positive IgM results. (Ref. 28). All confirmed-positive donations were also tested after diluting the index sample 1:6 with Zika-negative plasma. Retesting these simulated minipools created by dilution using the investigational NAT detected 251 of the 356 (71%) confirmed-positive donations.

Blood centers in U.S. states implemented ID NAT under IND in phases in 2016, using the investigational cobas Zika (Roche Molecular Systems, Inc.) or the investigational Procleix Zika Virus Assay (Grifols Diagnostic Solutions, Inc.) (Refs. 29-33).

- From May 23, 2016 to October 7, 2017, a total of 4,341,770 blood donations were tested by investigational ID NAT with cobas Zika (Ref. 28). Overall, 29 of 100 initially reactive donations were confirmed positive ($29/4,341,770 = 0.0007\%$ or ~ 1 in 150,000 donations), either on the index donation ($n=28$) or follow-up testing ($n=1$) (Ref. 28). Confirmed-positive donations were also tested after diluting the index sample 1:6 with Zika-negative plasma. Retesting in simulated minipools (1:6) by the investigational NAT detected 11 of the 28 (39%) confirmed-positive donations.
- From June 20, 2016 to November 18, 2017, a total of 8,867,530 donations were tested by investigational ID NAT, and 392,256 donations were tested in 24,516 minipools comprising 16 donations each, with Procleix Zika Virus Assay (Ref. 28). Overall, 25 of 376 initially reactive ID NAT donations were confirmed positive by subsequent testing ($25/8,867,530 = 0.0003\%$ or ~ 1 in 355,000 donations). No reactive donations were identified by minipool (MP) NAT screening.

III. DISCUSSION

A. FDA's Risk Assessment of MP NAT Strategy for ZIKV

Taking into account the BPAC discussion and recommendations, FDA further evaluated the use of universal MP NAT screening as an alternative to universal ID NAT. An MP NAT strategy identifies certain conditions which, when present, would trigger the recommendation to convert to ID NAT when local mosquito-borne ZIKV transmission is presumed in the collection area, to provide an adequate and appropriate safeguard against the current and future risk of ZIKV transmission through blood transfusion. The results of FDA's computational model, described below, support the use of MP NAT as a strategy to adequately and appropriately detect early infections in an outbreak, while reducing the burden of ID NAT testing.

Contains Nonbinding Recommendations

An MP NAT screening strategy is feasible because ZIKV infections are characterized by high levels of viremia within hours of infection, which is still detectable after dilution in minipool testing of multiple donations (Refs. 34, 35). In the first month of blood donation testing in Puerto Rico at the outset of the 2016 outbreak, 11 of 12 (90%) ID NAT-reactive donations were positive upon 1:6 dilution to simulate minipools of 6 donations (MP6), with the first reactive MP6 donation detected on the first day of testing (Ref. 28).

FDA's computational model simulated a future outbreak and mathematically determined the likelihood of detecting or missing ZIKV-reactive donations by MP NAT compared to ID NAT. The model used data on screened donations in Puerto Rico in 2016 and included only ID NAT reactive donations having negative IgM and IgG results, which reflect infections at the beginning of the outbreak in a susceptible donor population. The model calculated the time (since infection) to be detected by antibody tests, candidate MP NAT assays and ID NAT, based on the analytical lower detection limit of the assays and the reported doubling time of ZIKV RNA in the blood of infected macaques (Refs. 34-36). The differential sensitivity of MP NAT tests was estimated based on sensitivity of an ID NAT and dilution factors of ZIKV RNA in minipools of 6 (MP6) or 16 (MP16) donations. We assumed the infection times of reported ID NAT positive/IgG negative/IgM negative cases were evenly distributed within a range detectable by ID NAT but not by antibody tests. In each simulation, the model randomly selected the infection time for each reactive donation from that range and determined whether it is detectable by MP6 or MP16. The model estimated about 8.5% (2.5-95 percentile, 0.01, 26.67) and 13% (2.5-95 percentile, 0.01, 32.49) ID NAT positive cases reported in Puerto Rico would be missed by MP6 and MP16, respectively. The model determined that, at the beginning of an outbreak, the overall probability that a candidate MP NAT would detect the first ID NAT reactive unit in an outbreak is about 90%. Specifically, MP6 yields a probability of detecting the first ID NAT-reactive unit of 92% (2.5-95 percentile, 73%-99%); MP16 screening predicted a probability of 87% (2.5-95 percentile, 68%-99%).

B. Public Health ZIKV Surveillance and Other Considerations

During a potential future outbreak, CDC or state or local health departments might identify the first case of Zika infection before MP NAT screening identifies a ZIKV-reactive, asymptomatic blood donor in the community (Ref. 37). Consequently, we are also recommending switching from MP NAT to ID NAT, even in the absence of ZIKV-reactive donations, when CDC or state or local health departments identify an area at increased risk for ZIKV transmission that affects a defined geographic collection area.

Contains Nonbinding Recommendations

For example, CDC has previously identified the following areas to be at increased risk for ZIKV transmission during defined periods in 2016-18

(<https://www.cdc.gov/zika/areasatrisk.html>):

- Hidalgo County, Texas – From September 1, 2017 – February 7, 2018.
- Cameron County, Texas – From December 9, 2016 – August 29, 2017.
- Miami-Dade County, Florida – From July 29, 2016 – June 2, 2017.
- Palm Beach County, Florida – From August 24, 2016 – November 2, 2016.

FDA recognizes that blood establishments, CDC, and state or local health departments work collaboratively to assess the potential for increased risk of ZIKV transmission in a county based on blood donation screening, public health surveillance and other epidemiologic information (<https://www.cdc.gov/zika/areasatrisk.html>). A known limitation in designating risk areas based on ZIKV case reporting, or other surveillance data, is that it is subject to unavoidable delays, such that a transmission risk may be present for many weeks in a geographic area before complete information is available and a notification posted. The use of MP NAT screening of blood donations in conjunction with available surveillance data from other sources likely mitigates the risk of such delayed recognition of increased risk for ZIKV transmission in areas that potentially affect blood donors.

As an alternative to testing, blood establishments may use FDA-approved pathogen reduction technology for indicated blood components (i.e. platelets and plasma) to reduce the risk of ZIKV transmission by blood and blood components (21 CFR 610.40(a)(3)(ii)(B)). Published studies support the effectiveness of pathogen reduction methods against ZIKV for plasma (Refs. 38, 39) and platelets (Refs. 40, 41).

FDA is not recommending predonation assessment for ZIKV risk factors, such as possible exposure to ZIKV through travel or sexual contact, because:

- This approach is inherently inadequate in this situation when sensitive testing strategies are available to protect the blood supply.
- Most infected persons and their sexual partners are unaware of their risk, because the infection is usually asymptomatic (Ref. 1).
- Geographic-based criteria to identify at-risk donors for ID NAT may not be effective given the unavoidable delays in ZIKV case reporting and designation of risk areas.
- Extensive and dynamic travel deferrals are complicated to track and result in large numbers of deferred donors that could disrupt the supply and potentially cause local shortages.

Therefore, 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 (i.e., testing, as described in section IV of this document) under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10 that require blood establishments to

Contains Nonbinding Recommendations

assess donors for risk factors of ZIKV, in particular travel to or residence in an area endemic or at risk for ZIKV, to allow blood establishments to collect blood or blood components without first assessing donors for specific risk factors for ZIKV.²

IV. RECOMMENDATIONS

The following recommendations are intended to reduce the risk of ZIKV transmission through the transfusion of blood and blood components. The recommendations apply to the collection of all Whole Blood and blood components³ in the U.S. and its territories. If, based upon the available scientific evidence, the risk of ZIKV transmission by blood and blood components significantly changes, FDA may update these recommendations as warranted. In making this determination, FDA intends to consider available epidemiologic and other scientific evidence.

A. Testing or Pathogen Reduction

To comply with the requirements in 21 CFR 610.40(a)(3), you must:

1. Test all donations collected in the U.S. and its territories with a licensed NAT for ZIKV, using either MP NAT or ID NAT⁴ according to the manufacturer's instructions in the package insert. In general, you may use either MP NAT or ID NAT for screening, but we recommend that you use ID NAT when certain threshold conditions are present based on: (a) detection or notification of a ZIKV-reactive donation in a defined geographic collection area, or (b) notification by CDC or other public health authority, such as a state or local health department, of areas at increased risk for ZIKV transmission in a collection area, even in the absence of ZIKV-reactive donations (See section IV.B.1. of this document);

OR

2. Collect and prepare blood components using pathogen reduction technology with an FDA-approved pathogen reduction device according to the manufacturer's instructions for the device. Currently pathogen reduction technology is approved for use with platelets and plasma. If an FDA-approved pathogen reduction device

² Although predonation assessment of donors for ZIKV risk factors is not recommended for donation of blood and blood components because appropriate testing strategies are available, it is recommended for donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps) (Ref.42). This is because Zika virus persists in HCT/Ps, in particular, semen, umbilical cord blood or other gestational tissues, for longer periods of time when ZIKV RNA is no longer detectable in plasma (Refs. 21, 22, 42).

³ The recommendations do not apply to the collection of Source Plasma. Viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of ZIKV.

⁴ Blood establishments must use a licensed donor screening test for ZIKV (21 CFR 610.40(b)). Blood establishments that are participating in a clinical trial and testing for ZIKV using an unlicensed test may continue in the clinical trial but must also begin to test for ZIKV using FDA-licensed tests (21 CFR 610.40(b)).

Contains Nonbinding Recommendations

becomes available for Whole Blood or RBCs, you may implement pathogen reduction technology for such products rather than testing the donations as described in section IV.A.1. of this document (21 CFR 610.40(a)(3)(ii)(B)).

You do not need to provide donor educational material and screen donors for ZIKV risk factors, such as travel history, because of the alternative procedure under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10, which is provided for in this document.

Under 21 CFR 630.10(a), if a donor volunteers a recent history of ZIKV infection, you must not collect blood or blood components from that individual. We recommend that you defer such a donor for 120 days after a positive viral test or the resolution of symptoms, whichever timeframe is longer (21 CFR 630.35(a)).

B. Recommendations Regarding Switch between MP NAT and ID NAT when Threshold Conditions to Trigger or Detrigger are Present

If you perform MP NAT for ZIKV, we recommend that you convert from MP NAT to ID NAT when certain threshold conditions are present in a defined geographic collection area. A geographic collection area could be defined as a zip code, county or county equivalent (e.g., parish, borough), or group of counties, among other possibilities.

1. Determine if the following threshold conditions are present for ID NAT triggering: (a) blood donor screening and detection or notification of a ZIKV-reactive donation in a defined geographic collection area; or (b) CDC or other public health authority (such as a state or local health department) notification of an increased risk for ZIKV transmission in a county or county equivalent, even in the absence of ZIKV-reactive donations.
 - a. Threshold conditions for triggering ID NAT are present when blood donor screening identifies one ZIKV-reactive donation in a geographic collection area, and local mosquito-borne transmission is possible. A ZIKV-reactive donation is based on:
 - A donation in a reactive MP that is reactive following MP resolution testing by ID NAT, or
 - A donation that is reactive by ID NAT.

We recommend that blood establishments that collect in the same geographic area develop a standard operating procedure (SOP) to communicate such ZIKV-reactive results with other blood establishments in that same geographic area and public health jurisdictions within 24 hours.

- i. If the ZIKV-reactive donation was collected in a county previously listed by CDC as being at increased risk for ZIKV transmission (e.g., Miami-Dade County, Florida; Hidalgo County, Texas)

Contains Nonbinding Recommendations

(<https://www.cdc.gov/zika/areasatrisk.html>), then local mosquito-borne transmission is presumed and the screening test result alone triggers the recommendation to switch to ID NAT.

- ii. If the ZIKV-reactive donation was collected in a geographic area that has not been listed as an area at increased risk for ZIKV transmission (<https://www.cdc.gov/zika/areasatrisk.html>), you may further assess the donor for possible ZIKV exposure outside the collection area within the 30 days prior to the ZIKV-reactive donation. Threshold conditions to trigger ID NAT are present if there is a ZIKV-reactive donation, unless it can be determined within 24 hours of the reactive test that the donor was exposed to ZIKV through an alternative ZIKV exposure rather than through local mosquito-borne ZIKV transmission within the geographic collection area.

Risk factors that would support the determination of an alternative ZIKV exposure within the 30 days prior to the ZIKV-reactive donation include:

- Travel outside the collection area to an area at risk for ZIKV transmission (<https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika>).
- Sexual contact with a partner with a travel-related ZIKV diagnosis or with a partner with a history of travel to or residence in an area at risk for ZIKV transmission (<https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika>) in the 3 months prior to the last sexual contact.

You should also contact state or local health departments or other public health authorities, as appropriate, to determine whether there is an increased risk for ZIKV transmission in the collection area that has not yet been announced.

- b. Threshold conditions for triggering ID NAT are present even if there have been no ZIKV-reactive donations in the area when CDC or other public health authority announce that there is an increased risk for ZIKV transmission in a county, based on symptomatic disease cases, the presence of competent vectors, the likelihood of local mosquito-borne transmission, and other epidemiological information. CDC provides information for blood and tissue collection centers on a dedicated webpage (<https://www.cdc.gov/zika/areasatrisk.html>).
2. Convert from MP NAT to ID NAT screening as soon as feasible, but within 24 hours of detection or notification of a ZIKV-reactive donation, or a public health notification that meets threshold conditions for triggering (see section IV.B.1 of this document).

Contains Nonbinding Recommendations

In the event of a ZIKV-reactive donation, you should convert to ID NAT within 24 hours of obtaining the test result, or being notified of a test result by a different blood establishment, unless you have obtained adequate information to reasonably conclude that the donor's infection may not have resulted from local mosquito-borne transmission within the geographic collection area, because both of the following apply:

- a. The donor interview determines that infection most likely resulted from identified travel to areas at risk of ZIKV transmission, according to CDC (<https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika>), or through sexual contact with an individual with ZIKV or at risk for ZIKV infection because of travel or residence in an area at risk for ZIKV transmission; and
 - b. The collection area has not been previously listed as an area with increased risk for ZIKV transmission, according to CDC (<https://www.cdc.gov/zika/areasatrisk.html>).
3. Continue ID NAT until defined conditions are present to resume MP NAT (i.e., detrieger), as follows:
- a. If triggering is based on a ZIKV-reactive donation only, and you have obtained adequate information to reasonably conclude that the donor's infection may not have resulted from local mosquito-borne transmission within the geographic collection area (see section IV.B.2. of this document), then ID NAT can be discontinued upon completion of the investigation and you may resume MP NAT.
 - b. If triggering is based on ZIKV-reactive donation(s), and an alternative ZIKV exposure is not identified, or if local mosquito-borne ZIKV transmission is presumed in the geographic collection area, then continue ID NAT for at least 14 days. If there are no additional ZIKV-reactive donations in 14 days, and the CDC or state health department does not identify the collection area as an area at increased risk for ZIKV transmission, you may resume MP NAT.
 - c. If CDC or other public health authority, such as a state or local health department, determines that a county or county equivalent is at increased risk for ZIKV transmission, you should continue ID NAT for as long as the area is identified by the CDC or other public health authority as being at increased risk. You may resume MP NAT when CDC or other public health authority makes the determination that the area is no longer considered at increased risk, as long as there have been no reactive donations in the defined geographic collection areas for at least 14 consecutive days.

Contains Nonbinding Recommendations

C. Donor and Product Management

1. If you perform screening using MP NAT, you may release all units whose test samples comprise a non-reactive minipool, provided all other donation suitability requirements are met (21 CFR 630.30).
2. We recommend that you resolve a NAT-reactive minipool using ID NAT to test each specimen in the minipool to identify the unit(s) that led to the reactivity of the minipool, according to manufacturer's instructions in the package insert (21 CFR 606.65(e)). You should manage the donor and the individual donation based on the ID NAT results, as further described below.
 - a. You may release ID NAT non-reactive donations provided all other donation suitability requirements are met (21 CFR 630.30).
 - b. If an individual donation tests ID NAT reactive for ZIKV, you must not distribute or use the donation unless an exception exists (21 CFR 610.40(h)).⁵

Note: Laboratory controls procedures must make adequate provision for “monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments” (21 CFR 606.140(b)). You must conduct and record a thorough investigation of any unexplained testing discrepancy (21 CFR 606.100(c)), for example, when the frequency of unresolved minipools exceeds the threshold defined in your laboratory control procedures, when possible laboratory contamination of negative donor samples with positive samples is suspected, or when discrepant test results suggest the possibility of low-level ZIKV viremia in donor sample(s). The investigation should attempt to determine the cause of the initial reactivity of the unresolved minipool. If all individual donations comprising a NAT-reactive minipool are non-reactive by ID NAT, you may release all individual donations based on the ID NAT result, after conducting an appropriate investigation of an unexplained discrepancy.

3. You must defer a donor who tests ID NAT reactive for ZIKV and notify the donor of the deferral (21 CFR 610.41(a) and 630.40). You must defer the donor for 120 days⁶ from the date of the reactive test or from the date of resolution of ZIKV symptoms, whichever timeframe is longer (21 CFR 630.35(a)). Deferred donors must be counseled about the possible medical significance of the results (21 CFR 630.40(b)).

⁵ This requirement applies to all donations that test ID NAT reactive for ZIKV, including those that have been pathogen-reduced.

⁶ A deferral period of 120 days is required until more data become available on the duration of the viremic period and virus transmissibility.

Contains Nonbinding Recommendations

4. Further testing to obtain additional information about the donor's infection status or as part of the epidemiological investigation should be considered by the responsible physician. Additional testing on the index donation using the same or different FDA-licensed ZIKV NAT screening assay, an investigational ZIKV NAT test, or serological tests for ZIKV antibodies may be of value in donor counseling.
5. We recommend that you quarantine and retrieve in-date blood and blood components collected from a donor in the 120 days prior to the donation that is ID NAT reactive. Additionally, if such blood components were transfused, we recommend that you encourage consignees to have a discussion with the recipient's physician of record about possible transfusion-transmitted ZIKV.
6. Blood establishments may exercise discretion concerning disposition of blood components that were tested by MP NAT and were collected in a geographic area that is later identified with increased risk for ZIKV transmission. The responsible physician should determine whether to quarantine undistributed, in-date blood components tested by MP NAT or take other corrective actions and whether to retrieve and quarantine such distributed blood products so that they will not be transfused.

D. Labeling of Whole Blood and Blood Components Intended for Transfusion

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. You must update your circular of information to include the non-reactive test result using a FDA-licensed test for ZIKV (21 CFR 606.122(h)).

V. IMPLEMENTATION

1. We consider the implementation of the recommendations in this guidance without modification and in their entirety to be a minor change. Licensed blood establishments must report this change to FDA in the annual report under 21 CFR 601.12(d), noting the date the method or process was implemented.
2. We consider the implementation of an MP NAT screening strategy different from the one described in this guidance to be a major change. Therefore, licensed blood establishments must submit a Prior Approval Supplement (PAS) to FDA under 21 CFR 601.12(b). We recommend the supplement include the following:
 - a. Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" which may be obtained at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.
 - b. A cover letter describing the request and the contents of the submission.
 - c. A written SOP describing the testing algorithm or process.

Contains Nonbinding Recommendations

VI. REFERENCES

1. Petersen, L.R., et al., “Zika virus.” *N Engl J Med* 2016; 374(16):1552-63.
2. Pan American Health Organization and the World Health Organization, Regional Zika Epidemiological Update (Americas), August 25, 2017, (updated monthly).
http://www.paho.org/hq/index.php?option=com_content&view=article&id=11599%3Aregional-zika-epidemiological-update-americas&catid=8424%3Acontents&Itemid=41691&lang=en.
3. CDC, Travelers’ Health, Zika Travel Information, World Map,
<https://wwwnc.cdc.gov/travel/page/zika-information>.
4. Thomas, D.L., et al., “Local transmission of Zika virus - Puerto Rico, November 23, 2015-January 28, 2016.” *MMWR Morb Mortal Wkly Rep* 2016; 65:154-8.
5. Likos, A., et al., “Local mosquito-borne transmission of Zika virus-Miami-Dade and Broward Counties, Florida June-August 2016.” *MMWR Morb Mortal Wkly Rep* 2016; 65:1032-8.
6. CDC, Zika cases in the United States, <https://www.cdc.gov/zika/reporting/case-counts.html>.
7. Hahn, M.B., et al., “Updated reported distribution of *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* (Diptera Culicidae) in the United States, 1995-2016.” *J Med Entomol* 2017; 1-5 doi: 10.1093/jme/tjx088.
8. CDC, Surveillance and control of *Aedes aegypti* and *Aedes albopictus* in the United States. Updated September 2017. <https://www.cdc.gov/chikungunya/pdfs/surveillance-and-control-of-aedes-aegypti-and-aedes-albopictus-us.pdf>.
9. Chevalier, M.S., et al., “Use of blood donor screening data to estimate Zika virus incidence, Puerto Rico, April – August 2016.” *Emerg Inf Dis* 2017; 23:790-795.
10. Besnard, M., et al., “Evidence of perinatal transmission of Zika Virus, French Polynesia, December 2013 and February 2014.” *Euro Surveill* 2014; 19(13):pii=20751.
11. Deckard, D.T., et al., “Male-to-Male Sexual Transmission of Zika Virus, Texas, January 2016.” *MMWR Morb Mortal Wkly Rep*. 2016; 65(14).
12. Davidson, A., et al., “Suspected Female-to-Male Sexual Transmission of Zika Virus – New York City, 2016.” *MMWR Morb Mortal Wkly Rep*. 2016; 65(28):716-7.
13. Boadle, A., “Brazil reports Zika infection from blood transfusions.” February 4, 2016; Reuters website; <http://www.reuters.com/article/us-health-zika-brazil-blood-idUSKCN0VD22N>.
14. Barjas-Castro, M.L., et al., “Probable transfusion-transmitted Zika virus in Brazil.” *Transfusion*. 2016; 56:1684-8.
15. Motta, I.J.F., et al., “Evidence for transmission of Zika virus by platelet transfusion.” *N Engl J Med* 2016; 375:1101-3.
16. Musso, D., et al., “Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014.” *Euro Surveill* 2014 April 10;19(14). pii: 20761.
17. Berlaire, D., et al., “Zika virus and blood transfusion: the experience of French Polynesia.” *Transfusion* 2017; 57:729-733.
18. Cao-Lormeau, V.M., et al., “Guillain-Barre syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study.” *Lancet* 2016; 387:1531-9.
19. Johansson, M.A., et al., “Zika and the risk of microcephaly.” *New Eng J Med* 2016; 375(1):104.

Contains Nonbinding Recommendations

20. Honein M.A., et al., “Birth defects among fetuses and infants of US women with evidence of possible Zika virus infection during pregnancy.” *JAMA* 2017;317:59-68.
21. Paz-Bailey, G., et al., “Persistence of Zika Virus in Body Fluids – Preliminary Report.” *N Engl J Med* 2017; Feb 14, [Epub Ahead of Print].
22. Mead PS, Duggal NK, Hook SA, Delorey M, et al., Zika virus shedding in semen of symptomatic infected men. *New Eng J Med* 2018;378:1377-1385.
23. Stone, M., et al. “Zika RNA persistence in blood and body fluids and clinical outcomes in infected blood donors.” *Transfusion* 2017; 57(Suppl. 3): 4A (abstract).
24. Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus, Guidance for Industry, (February 2016).
25. Kuehnert, M.J., et al., “Screening of blood donations for Zika virus infection — Puerto Rico, April 3–June 11, 2016.” *MMWR* 2016; 65. DOI: <http://dx.doi.org/10.15585/mmwr.mm6524e2>.
26. Adams, L., et al., “Update: ongoing Zika virus transmission – Puerto Rico. November 1, 2015–July 7, 2016.” *MMWR Morb Mortal Wkly Rep* 2016; 65:774-9.
27. Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components, Guidance for Industry, (August 2016).
28. FDA Blood Products Advisory Committee “116th meeting of the Blood Products Advisory Committee.” December 1, 2017. Transcript available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM590284.pdf>.
29. Pate, L.L., et al., “Detection of Zika virus RNA in Puerto Rico donations using cobas Zika on the cobas 6800/8800 Systems.” *Vox Sang* 2017; 112 (Suppl 1):185.
30. Galel, S.A., et al., “First Zika-positive donations in the continental United States.” *Transfusion* 2017; 57:762-769.
31. Pate, L.L., et al., “Detection of Zika virus RNA in United States blood donations using cobas Zika on the cobas 6800/8800 Systems.” *Transfusion* 2017; 57 (Suppl S3):26A (abstract).
32. Williamson, P.C., et al., “First cases of Zika virus-infected US blood donors outside states with areas of active transmission.” *Transfusion* 2017;57:770-778.
33. Saá, P.P., et al., “Investigational detection of Zika virus RNA in U.S. blood donors.” *Transfusion* 2017; 57 (Suppl S3):25A (abstract).
34. Osuna, C.E., et al., “Zika viral dynamics and shedding in rhesus and cynomolgus macaques.” *Nat Med*, 2016; 22:1448-1455.
35. Coffey, L.L., et al., “Zika virus tissue and blood compartmentalization in acute infection of Rhesus macaques.” *PLoS ONE* 12(1):e0171148. Doi:10.1371/journal.
36. Roche Molecular Systems, Inc. cobas Zika Nucleic Acid Test for use on the cobas 6800/8800 systems. <https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm579113.htm>.
37. Russell, S.P., et al., “Detecting local Zika virus transmission in the continental United States: a comparison of surveillance strategies *PLOS Currents Outbreaks*.” 2017 Nov 22. Edition 1. doi: 10.1371/currents.outbreaks.cd76717676629d47704170ecbdb5f820.
38. Dichtelmuller, H., et al., “Robustness of solvent/detergent treatment of plasma derivatives: a data collection from Plasma Protein Therapeutics Association member companies.” *Transfusion*, 2009; 49:1931-1943.

Contains Nonbinding Recommendations

39. Kühnel, D., et al., “Inactivation of Zika virus by solvent/detergent treatment of human plasma and other plasma-derived products and pasteurization of human serum albumin.” *Transfusion* 2017; 57:802-810.
40. Aubry, M., et al., “Inactivation of Zika virus in plasma with Amotosalen and ultraviolet A illumination.” *Transfusion*. 2016 Jan; 56(1):33-40. doi: 10.1111/trf.13271.
41. Santa Maria, F., et al., “Inactivation of Zika virus in platelets with amotosalen and ultraviolet A illumination.” *Transfusion* 2017; 57:2016-2025.
42. Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products, (May 2018). Available at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/default.htm>.