Blood Products Advisory Committee Meeting
FDA White Oak Campus, Silver Spring, MD
December 1, 2017

Topic III: Strategies to Reduce the Risk of Zika Virus (ZIKV) Transmission by Blood and Blood Components

Issue: FDA seeks advice from the Committee on whether individual donation nucleic acid testing (ID NAT) of all blood donations for ZIKV remains appropriate or whether other candidate selective screening strategies would provide acceptable alternatives to safeguard against the current and future risk of ZIKV transmission through blood transfusion.

The BPAC will hear presentations on ZIKV epidemiology and the current status of ZIKV in the U.S. and territories, including Puerto Rico, U.S. Virgin Islands, American Samoa; on the US experience with ZIKV ID NAT testing in blood donors and performance characteristics of NAT tests; and on possible donor screening options for ZIKV or their discontinuation.

Background:

A. Experience with ZIKV outbreaks since 2007

Zika virus (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 also chikungunya virus (CHIKV), ZIKV is primarily transmitted by *Aedes* mosquitoes, most commonly *Aedes aegypti* (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 77 countries by 2017 (1,2). Local transmission of ZIKV in the U.S. and its territories was reported in Puerto Rico in December 2015, in Florida in July 2016 and in Texas in November 2016 (3-5). In addition to vector-borne disease, ZIKV infection was documented during the epidemic to occur through other routes of exposure, including perinatal, intrauterine, sexual, laboratory-acquired and blood-borne transmission (1, 6-11).

Most people infected with ZIKV are asymptomatic or have only mild symptoms such as fever, rash, headache, joint pain or conjunctivitis that lasts up to a week. However, ZIKV infection can cause Guillain-Barre syndrome and severe neurological complications (1, 12). ZIKV infection during pregnancy can cause microcephaly, severe congenital defects, and infant death (1, 13). ZIKV may be detected in serum or plasma for 1-2 weeks and has been detected for longer periods of time after infection in whole blood, semen, and urine (13). 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 (14). In 95% of infected men, ZIKV

RNA was cleared from semen in about 3 months [81 days (95% CI, 64 to 98 days)] with the longest reported duration of detection up to 188 days after onset (14).

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 NAT (15). Media outlets reported the first cases of transfusion-transmitted ZIKV in Brazil in December 2015; soon thereafter, three cases in peer-reviewed articles described 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 (9-11). 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 twelve of the patients (16). None of the transfusion recipients in this report or other published cases to date developed ZIKV-related symptoms after transfusion. However, risk of transfusion-transmitted ZIKV is considered substantial, especially to fetuses *in utero* and to neonates, and there is additional concern about potential secondary exposure of sexual partners in addition to transfusion recipients.

B. FDA policies to address transfusion risk from ZIKV

Because of concern about severe ZIKV disease, rapid virus spread in the Americas, recovery of RNA from blood of asymptomatic donors, and reports of transfusion transmission, FDA issued guidance in February 2016, with recommendations specific to areas with or without active (local, vector-borne) transmission of ZIKV (17). For areas without active transmission, FDA recommended deferral of donors who reported a diagnosis of ZIKV infection, traveled to areas with local ZIKV transmission, or had sexual contact with men diagnosed with ZIKV or 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 ID NAT or FDA-approved pathogen reduction technology for indicated components (i.e., plasma, platelets). Beginning in March 2016, Puerto Rico obtained blood and blood components from unaffected areas of the continental U.S., and in April 2016 initiated testing under IND using the cobas ID -NAT Zika test.

With the first locally-acquired vector-borne cases of ZIKV reported in Florida in July 2016, FDA recognized the potential for rapid expansion of the ZIKV epidemic in the U.S., the significant delays in reporting cases of travel-associated or locally-acquired mosquito-borne transmission that likely rendered travel deferrals increasingly ineffective and impractical, and the risk of sexual transmission for up to 6 months after infection. This also raised concern about the potential for the epidemic to be sustained independent of mosquito-borne transmission. Based

on these concerns, and in the face of the uncertain course of the epidemic, in August 2016, FDA issued revised guidance on reducing the risk of ZIKV transmission through blood and blood components by recommending universal ID NAT or pathogen reduction for approved blood components (i.e., platelets, plasma) using a risk-based phased approach for implementation (18). In states with one or more locally-acquired (vector-borne) ZIKV cases, blood establishments were to immediately implement the recommendations. States proximate to areas with locally acquired mosquito-borne cases of Zika virus or with other epidemiological linkage to Zika virus (such as the number of travel-associated cases reported in a state) were to implement the recommendations within four weeks; whereas blood establishments that collected in the remaining states and territories were to implement the recommendations within 12 weeks of the guidance issue date (18). At that time, there were over 8,000 cases of locally-acquired ZIKV infection in Puerto Rico and U.S. territories; 2,245 travel associated cases in U.S. states; and 14 locally-acquired, mosquito-borne cases in Florida. Nationwide and territorial implementation of ID NAT testing of all blood donations ("universal" ID-NAT) has effectively intercepted potentially infectious units from asymptomatic blood donors (See Section C.2).

FDA's revised guidance in August 2016 was issued to address an exceptionally urgent, uncertain, and evolving situation, taking into account the potentially severe consequences of ZIKV infection. At that time, FDA considered measures to assess a donor for risk factors closely associated with ZIKV but recognized the limitations of donor screening for symptoms of illness, geographic risk and sexual exposure. The majority of infected individuals and their sexual partners are asymptomatic and could be unaware of their risk at the time of blood donation.

Considerable difficulty in the timely identification of cases in areas in the continental U.S. with mosquito-borne exposure led to heightened concern about the extent of spread that could occur before a risk area was identified. There was also concern that as the areas with risk of locally acquired mosquito-borne transmission expanded, screening donors for risk factors would become increasingly logistically complex and decreasingly effective while resulting in significant travel-related donor deferrals that could potentially compromise the adequacy of the blood supply. Additionally, the possibility existed that sexual transmission might evolve as a significant mode of transmission independent of vector-borne disease to sustain the epidemic, rendering risk factor-based screening an inadequate safeguard for the blood supply. FDA acknowledged the need to continue to evaluate the situation in real time, and committed to re-examining its recommendations for donor testing as additional information on the Zika epidemic and the safety impact of donor testing would become available.

C. Current Status of ZIKV in the United States and its Territories

1. Clinical cases of ZIKV

CDC designated ZIKV disease a nationally notifiable condition in the U.S. in 2016. In 2016, states reported 5,102 symptomatic ZIKV disease cases of which 4,830 cases were in travelers returning from affected areas, 224 cases were acquired through presumed local mosquito-borne transmission in Florida (n=218) and Texas (n=6); 48 cases were acquired through other routes, including sexual transmission (n=46), laboratory transmission (n=1), and person-to-person through an unknown route (n=1) (5). During the same period, U.S. territories (principally Puerto Rico) reported 36,079 symptomatic ZIKV cases of which 142 cases were in travelers returning from affected areas, and 35,937 cases were acquired through presumed local mosquito-borne transmission (5).

By comparison, the number of ZIKV cases has decreased considerably in the U.S. and its territories in 2017 (5). Between January 1 and October 11, 2017, states reported 291symptomatic ZIKV disease cases of which 287 cases were in travelers returning from affected areas, one case was acquired through presumed local mosquito-borne transmission, and three cases were acquired through sexual transmission; U.S. territories reported 582 symptomatic ZIKV disease cases, all acquired through presumed local mosquito-borne transmission (5). As of this writing (October 12, 2017), there are no active areas of ZIKV transmission in U.S. states. Previously listed areas of activity were Brownsville Cameron County, Texas (October 29, 2016 – August 29, 2017), Miami Dade County, Florida (July 29, 2016 – June 2, 2017), and Palm Beach County Florida (August 24, 2016 – November 2, 2016). Again this year, New York, Florida, and California have the highest number of ZIKV cases related to travel, accounting for 47% of all symptomatic clinical cases in U.S. states in 2017, compared to 50% in 2016 (5). Despite the dramatic decrease in reported cases, the course of ZIKV prevalence and transmission in the U.S., its territories and abroad cannot be predicted with certainty.

2. Rate of detection of ZIKV in blood donors

i. Puerto Rico:

In April 2016, blood establishments in Puerto Rico implemented ID NAT under IND using the investigational cobas Zika test (Roche Molecular Systems Inc., Pleasanton CA) (19-21).

As of September 23, 2017, there have been 369 initially reactive donations of 111,842 screened (1 in 303 donations). Of these, 356 were confirmed positive. The prevalence of donations reactive for ZIKV RNA peaked at 1.8% in July 2016 and has since declined (19, 20). As of September 23, 2017, the last ZIKV-reactive donation in Puerto Rico was collected in May, 2017.

ii. U.S. States:

Between May and November 2016, U.S. blood centers implemented ID NAT under IND in phases, using the investigational cobas Zika (Roche) or the investigational Procleix Zika Virus assay (Hologic/Grifols) (22,23).

As of September 23, 2017, there have been 398 initially reactive blood donations from more than 11 million donations screened under the two ongoing INDs, for a rate of 0.0034% (1 in 28,996 donations). Of these, 50 donors were confirmed positive (1 in 230,806 donations) by additional tests for ZIKV. As of September 23, 2017, the last confirmed-positive ZIKV donation in the U.S. was collected in August, 2017.

3. Performance characteristics of investigational ZIKV NAT

The BPAC Committee will hear presentations by the IND sponsors on the performance characteristics of the investigational tests that have been used to screen the U.S. blood supply.

Based on published abstracts at the time of this writing, the following data are available:

- In Puerto Rico between April 3, 2016 to October 9, 2016, a total of 35,543 blood donations were tested with cobas Zika (Roche) (21). Of 316 initially reactive donations, 303 met the criteria for true positives on the index donation and 5 were IgM-positive on follow-up (0.87% or 1 in 115 donations). All initially reactive donations were also tested after diluting the index sample 1:6 with Zika-negative plasma. Retesting these simulated minipools by the investigational NAT detected 231 of the 316 (73%) initially reactive donations.

- In the U.S. between April 3, 2016 to February 28, 2017, a total of 1,776,190 blood donations were tested by investigational ID NAT with cobas Zika (Roche) (24). Of 56 initially reactive donations, 12 were repeatedly reactive and a total of 22 met criteria for true positives on the index donation (0.001%). Retesting simulated minipools (1:6) by the investigational NAT detected nine of the 22 (41%) true-positive donations.

- In the U.S. between June 20, 2016 and April 8, 2017, a total of 1,895,142 blood donations were tested by investigational ID NAT and 393,713 donations were tested in 24,611 minipools of 16 donations with Procleix Zika Virus Assay (Grifols) (25). Of 72 initially reactive ID NAT donations, 8 confirmed positive by subsequent testing (1 in 286,107 donations). No reactive donations were identified by MP NAT.

Discussion:

Consideration of Alternatives to Universal Donation Testing by ID-NAT for ZIKV in the U.S. and U.S. Territories

Given the available information about the recent course of the ZIKV epidemic, FDA is evaluating its August 2016 recommendations that required testing of blood donations by ID NAT for ZIKV unless blood components (presently limited to plasma and certain platelet collections) are treated with an approved device to reduce pathogens.

FDA seeks advice from the Committee on five candidate options as alternatives to universal donation testing by ID NAT:

1. No policy change at this time
2. Regional use of ID NAT and MP NAT testing
3. Test all donors by ID NAT in areas with active vector-borne infection and selectively test at-risk donors by ID NAT in all other areas based on donor screening for ZIKV risk factors
4. Maintain a ZIKV-tested-negative blood inventory for at-risk recipients
5. Eliminate all blood safeguards for ZIKV pending another significant outbreak in the United States or its territories.

Option 1: No policy change at this time

Continue universal ID NAT testing of blood collections, but reassess the policy periodically.

Pro:

- Provides nationwide monitoring for blood donors with asymptomatic infection resulting from all modes of transmission (e.g., vector-borne, sexually-transmitted and travel-related cases)

Con:

- Maintains a resource-intensive approach, placing burdens on the blood system in the face of significantly diminished risk

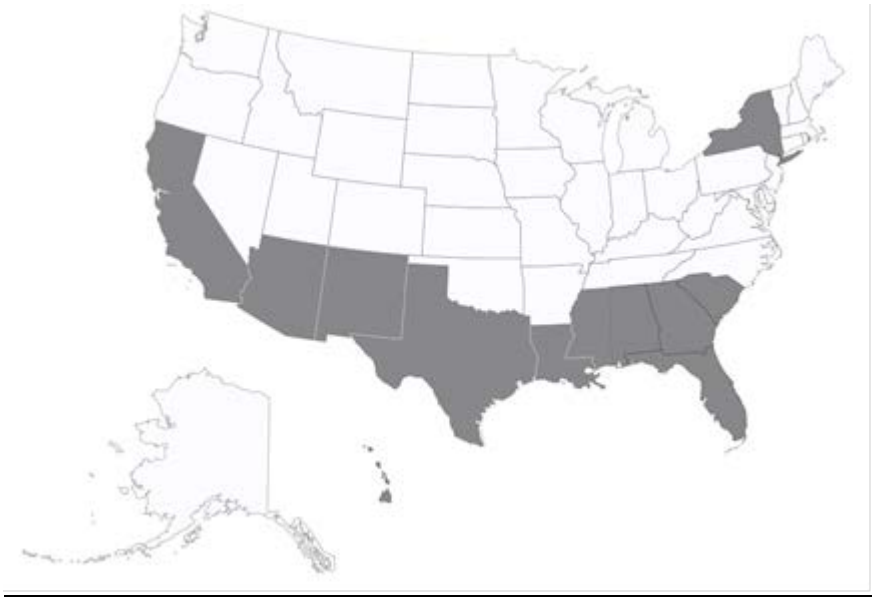
Option 2: Regional use of ID NAT and MP NAT testing

a) Continue ID NAT year-round in the following <u>inclusive</u> and overlapping locations (shown as shaded in the figure):

1. States and territories previously reported to have locally acquired ZIKV or other *Aedes aegypti* borne viruses (CHIKV, DENV): FL, TX HI, Puerto Rico, U.S. Virgin Islands, American Samoa, and

2. States with a documented presence or favorable climate for *Aedes aegypti* (26,27)*:* GA, FL, TX, NM, AZ, CA, SC, AL, MS, LA, and

3. States with a high number of returning travelers (100,000/month) from Zika-endemic areas (27) and the highest historical number of travel-related symptomatic ZIKV cases (5): NY, CA, FL, AZ, NM, TX, GA



b) Additionally, substitute minipool NAT (MP NAT) for ID NAT year-round in all other, lower risk states, and trigger ID NAT in areas when a threshold number of ZIKV cases of either community-identified infections or presumptive viremic donations occur in a defined time period.

   Consideration for switching from MP NAT to ID NAT in states with lower risk will be based on the following criteria:

   a. A defined number of presumptive viremic donors in a 7-day rolling period based on results of MP NAT in a defined geographic collection area

   b. A defined threshold of symptomatic clinical cases reported by national surveillance in a defined geographic collection area

Pro:

- Reduces the volume of testing
- Continues testing in areas of highest risk with the most sensitive test while decreasing the resources needed in areas of lower risk
- Offers the likelihood of detecting most of the travel-associated symptomatic cases in the U.S.
- Maintains capability to rapidly respond to local outbreaks
- Similar to the WNV approach which has been used for many years with only rare breakthrough cases of transfusion transmission (28, 29)

Con:

- Maintains testing of blood in the areas of the U.S. where there are no reported cases of ZIKV
- MP NAT is less sensitive than ID NAT and criteria for switching introduces operational complexity and potential for error
- Criteria to revert from ID NAT to MP NAT remain to be defined
- Though less resource intensive that universal ID NAT, still places some increased burdens on the blood system in the face of significantly diminished risk

Option 3: Test all donors by ID NAT in areas with active vector-borne infection and selectively test at-risk donors by ID NAT in all other areas based on donor screening for ZIKV risk factors

a) Perform ID NAT on all collections in areas with active mosquito-borne ZIKV transmission (e.g., TX, FL, U.S. territories)

b) Perform ID NAT in all other states based on the donors' responses to pre-donation questions about

   - travel to ZIKV endemic or epidemic countries, and
   - sexual contact with partners diagnosed with ZIKV or with history of recent travel to countries with active transmission of ZIKV

c) Trigger ID NAT selectively in areas with a large number of reported travel-related or sexually-transmitted ZIKV infections

Pro:

- Reduces the volume of testing
- Maintains testing in areas of highest potential risk with the most sensitive test, while decreasing the resources needed in areas of lower risk

Con:

- Donor screening to identify which donors need to be tested based on a questionnaire is nonspecific, insensitive and error-prone compared to ID NAT or MP NAT.
- 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.
- Information is not available to define risk areas within endemic or epidemic countries, unlike malaria surveillance. Country-based travel risk (e.g., Mexico) could still require high volume of testing and would be error-prone.
- Identifying domestic travel risk within the U.S. in the event of resurgence of local transmission may not be practical or feasible.
- Criteria to trigger to and revert from ID NAT in a given area are not well defined.

Option 4: Maintain a ZIKV-tested-negative blood inventory for at-risk recipients

Provide ZIKV ID NAT-negative blood components only for patients with certain clinical indications (e.g., pregnant women, intrauterine transfusion, neonates) and ZIKV-untested blood components to all other recipients, similar to current practices for CMV serologic testing.

Pro:

- Reduces testing burden and directs ZIKV-tested blood components to at-risk recipients

Con:

- Poses operational complexity in managing a dual inventory of ZIKV-tested and -untested blood components
- Introduces the potential for ordering and release errors given the inability to reliably identify all patients at risk
- Might compromise the ability to scale up testing rapidly if there is a major resurgence of the global or local epidemic of ZIKV

- Undefined risk of ZIKV infection in several populations, including immunocompromised patients
- Potential for sexual transmission to a pregnant woman if her partner receives an untested ZIKV infected unit

Option 5: Eliminate all blood safeguards for ZIKV

Eliminate donation testing for ZIKV without re-introduction of donor screening for risk factors pending another significant outbreak in the United States or its territories

Pro:

- Provides relief from ZIKV testing when ZIKV risk is substantially reduced
- Increases the availability of resources for other blood safety initiatives

Con:

- Will not prevent transfusion transmission of ZIKV and poses risk of ZIKV complications among at risk patients
- Reduces preparedness against possible resurgence of the ZIKV epidemic

Questions for the Committee:

1. At this time, do the available scientific data on the course of the ZIKV epidemic justify the elimination of all blood safeguards for ZIKV pending another significant outbreak in the United States or its territories (Option 5)?

2. If the answer to Q1 is "No," do the available scientific data on the course of the ZIKV epidemic identify a risk to the blood supply that justifies continuing universal ID NAT testing (Option 1)? Alternatively, if the answer to Q1 is "Yes," please comment on the pros and cons of this approach.

3. If the answer to Q2 is "No," do the available scientific data on the risk of transfusion-transmitted ZIKV support the regional use of ID NAT in at-risk states and territories combined with the use of MP NAT in all other states (Option 2)? Alternatively, if the answer to Q1 or Q2 is "Yes," please comment on the pros and cons of this approach.

4. If the answer to Q3 is "Yes," please comment on the following criteria to switch from MP NAT to ID NAT within a defined geographic area or a state:

    a. A defined number of presumptive viremic donors in a 7-day rolling period based on results of MP NAT in a defined geographic collection area

    b. A defined number of cases based on 1) presumptive viremic donors in a 7-day rolling period and 2) a defined threshold of symptomatic clinical cases reported by national surveillance in a defined geographic collection area

<u>If the answers to questions 2 and 3 are both "No":</u>

5. Would selective ID NAT performed based on the donors' responses to questions about 1) travel to ZIKV endemic or epidemic countries; 2) sexual contact with partners diagnosed with ZIKV; and/or 3) sexual contact with partners having travel risk for ZIKV provide an adequate and appropriate safeguard against transfusion transmission of ZIKV (Option 3)?

6. Would the option to provide ID NAT-negative blood components to selected patients based on clinical indications (e.g., pregnant women, intrauterine transfusion, neonates) and ZIKV-untested blood components for all other transfusion recipients provide an adequate and appropriate safeguard against transfusion transmission of ZIKV (Option 4)?

7. Please provide any additional comments on considerations for selective testing of blood donations using ID NAT or MP NAT for ZIKV.

Summary Table of ZIKV Screening and/or Testing Options

Option	Recommendation	Arguments Pro	Arguments Con
1	No policy change (universal ID NAT)	Nationwide coverage against all modes of ZIKV transmission (e.g., vector-borne, sexually transmitted- and travel-related cases)	Maintains resource-intensive approach placing burden on the blood system in the face of significantly diminished risk
2	Regional ID NAT and MP NAT	• Reduces testing volume • Covers the areas of highest risk with the most sensitive test • Offers the likelihood of detecting most travel-related ZIKV cases • Maintains capability to rapidly respond to local outbreaks • Similar to the WNV approach to blood safety	• Maintains testing of blood in the areas of the U.S. where there are no reported cases of ZIKV • MP NAT is less sensitive than ID NAT and criteria for switching introduce operational complexity and potential for error • Criteria to revert from ID NAT to MP NAT remain to be defined
3	ID NAT in areas of active transmission; Selective use of ID-NAT in states without active transmission based on donor screening for ZIKV risk factors	• Reduces testing volume • Maintains testing in areas of highest potential risk with the most sensitive test • Decreases resources needed in areas with lower risk	• Donor screening based on a questionnaire is nonspecific, insensitive and error-prone compared to ID NAT or MP NAT • 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 • Identifying domestic travel risk within U.S. in the event of resurgence of local transmission may not be practical or feasible • Criteria to trigger to and revert from ID NAT in a given area are not well defined

4	Maintain ZIKV-tested-negative blood inventory for at-risk recipients	• Reduces testing burden and directs ZIKV-tested blood components to at-risk patients	• Poses operational complexity in managing a dual inventory of ZIKV-tested and -untested blood components • Introduces the potential for ordering and release errors given the inability to reliably identify all patients at risk • Might compromise the ability to scale up testing rapidly if there is a major resurgence of the global or local epidemic of ZIKV • Undefined risk of ZIKV infection in several populations, including immunocompromised patients
5	Eliminate all blood safeguards for ZIKV pending another significant outbreak in the United States or its territories	• Provides relief from ZIKV testing when risk is substantially reduced • Increases the availability of resources for other blood safety initiatives	• Provides no safeguard against ZIKV transfusion transmission • Reduces preparedness against possible resurgence of the ZIKV epidemic

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