




June 8, 2018

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Submitted via** http://www.regulations.gov

**Re: Docket No. FDA–2016–D–0545**, "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components Guidance for Industry," 31 August 2016.

Dear Dockets Manager:

AABB, America's Blood Centers (ABC) and the American Red Cross (ARC) appreciate the opportunity to provide new information to the Food and Drug Administration (FDA) related to the August 2016 FDA Guidance, "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components; Guidance for Industry" (the August 2016 Guidance). Members of the AABB's Transfusion Transmitted Diseases Committee (TTD Committee), its Arbovirus Subgroup, and representatives from ARC and ABC prepared these comments. We have included specific recommendations for consideration as FDA prepares updated recommendations. Based on the information provided here, it is our urgent request that FDA move to finalize the recommendations in the next guidance without issuing a draft guidance for comments.

**Background**

FDA's August 2016 decision to require Zika virus (ZIKV) individual donation nucleic acid testing (ID-NAT) for all donors, unrelated to geographical risk, was "*based upon: 1) the potential severity of outcomes related to ZIKV, 2) the widespread nature of the global spread of ZIKV, 3) the risk of transmission of ZIKV by blood and blood components, and 4) the availability of investigational testing under IND to help reduce the risk of transmission of ZIKV through the blood supply"* (footnote 4, page 6 of the August 2016 Guidance). While under certain circumstances FDA could determine that potential transmission risks and the potential severity of outcomes would justify these unprecedented actions, it should be noted that there is no provision to "walk back" from the unprecedented testing requirements if and when data demonstrate that the potential severity of outcomes and

transmission did not occur as feared. Without a mechanism to resume pre-2016 Guidance operations in the absence of the anticipated threat to public health, this excessive level of testing places an adverse impact on blood collectors each day it continues.

At the December 2017 BPAC Meeting, AABB presented a Joint Statement with ABC and ARC. The Joint Statement provided a comprehensive review of events and data from the blood community's experience with ZIKV ID-NAT during the first year, and the evidence supporting an option for use of ZIKV minipool (MP) NAT. The Joint Statement strongly encouraged the FDA "to consider options other than ID-NAT, especially a MP-NAT option that is consistent with on-going testing for other viruses capable of causing significant disease in transfusion recipients, including HIV, HBV, HCV and WNV. Finally, the Joint Statement asked FDA to articulate its approach to a decision to modify the testing recommendations of this guidance if the epidemic has waned and does not appear to be recrudescing in the near future.

By vote, BPAC showed strong support for conversion, nationwide, to MP-NAT with a temporary transition to ID-NAT based on trigger/detrigger criteria to be agreed upon.

**Development of Trigger and Detrigger Criteria for ZIKV MP-NAT**

Consistent with the stated position of AABB, ARC and ABC, a review of the data and the blood community's experience with ZIKV testing supports an evidence-based decision to transition to MP-NAT for ZIKV at this time. As discussed at the March 2018 FDA Liaison Committee Meeting, the Arbovirus Subgroup of the AABB's TTD Committee, along with representatives from the CDC and FDA have reviewed the options for use of criteria to trigger from MP-NAT to ID-NAT for ZIKV, as well as the criteria to detrigger and resume MP-NAT.

Ultimately, the ZIKV risks were minimal and did not impact public health in the U.S. as originally feared by public health authorities and others in early 2016. Clearly, the continuation of excessive precautionary measures, resulting in on-going ZIKV ID-NAT, are not necessary to protect the safety of the blood supply while they continue to have a detrimental impact on operations within the blood community.

We respectfully repeat our urgent request that FDA re-evaluate the current policy using a risk-based approach, commit resources to expedite the process, and issue a final guidance permitting use of MP-NAT based on our recommended trigger/detrigger criteria.

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**RECOMMENDATIONS**
Our recommendations are provided, with flowcharts in Appendix 1, for your consideration:

**Zika virus (ZIKV) MP-NAT Triggering and Detriggering Criteria**

**Definitions**

Individual donation NAT: ID-NAT

Minipool NAT: MP-NAT

MPs of 6 (MP-6) for Roche

MPs of 16 (MP-16) for Grifols

Failed Repeat ID-NAT (FR-ID-NAT) initially reactive result:

An initially reactive ID-NAT result for which all replicates from further testing of the index donation failed to repeat (are non-reactive).

Presumptive viremic donor(s) (PVD):

1. A donor (or donors) from a reactive MP whose sample(s) are reactive by ID-NAT following reactive MP resolution testing, or
2. A donor (or donors) whose sample(s) are repeat reactive (RR) on ID-NAT.
3. More than one FR-ID-NAT initially reactive result in a rolling 7-day interval from the same geographic area.

**ZIKV ID-NAT trigger criteria based on ZIKV-reactive donations**
**Refer to Appendix 1, ZIKV MP-NAT Trigger to ID-NAT Flowchart**

1. One (1) PVD from a reactive MP that resolves to one or more reactive donation samples, or
2. One (1) PVD from a blood collection facility performing ID-NAT will trigger ID-NAT at other blood centers in the same geographic area that are still testing in MP-NAT, or
3. Multiple (2 or more) FR-ID-NAT initially reactive results reported within a 7-day period by a blood center performing ID-NAT will trigger ID-NAT at other blood centers in the same geographic area that are still testing in MP-NAT. All recommended actions apply to multiple FR-ID-NAT initially reactive results since these may represent early, seronegative true positives with very low viral loads during the first days of a local transmission event.

In the event of a PVD (and for each subsequent PVD), the facility that collected the PVD, and other facilities collecting in that geographic area, should trigger ID-NAT within 24-hours of receipt of the result for collections from that area if not already in ID-NAT unless the donor has been contacted and reports travel or sexual-related risk factors (see below; Actions to be taken upon triggering). Triggering facilities should consider having their untested in-process samples tested by ID-NAT including those where results have not yet been released (i.e., if already tested by MP-NAT). This will decrease the time from collection of the PVD to the initiation of ID-NAT.

**Actions to be taken upon triggering**

Immediately upon triggering ID-NAT, the blood collection facility should perform the communication functions listed below to facilitate triggering by other centers in the affected area.

1. Send a blast email to AABB group listing.
2. Enter data into the AABB ZIKV Biovigilance website site, supplying all the available information that is requested.
3. Notify the appropriate public health jurisdiction of the PVD.

Blood collection facilities should contact all ID-NAT-reactive donors (whether meeting the definition of a PVD or not) within 24-hours of receipt of the reactive result to determine if the donor has risk factors that suggest infection acquired by a route other than local vector-borne transmission (i.e., local vector-borne transmission refers to mosquito exposure occurring within the same county as the ID-NAT-reactive donation).

If the donor has traveled to areas with ongoing vector-borne transmission, or if sexual exposure is identified, then it is reasonable to conclude that the PVD was not infected from local vector-borne transmission; consequently, ID-NAT does not have to occur, or can be discontinued and MP-NAT may be resumed, with the following exception:

> When a PVD is found in a geographic area with both competent vectors and a high density of travelers returning from areas currently experiencing ZIKV outbreaks, then ID-NAT should be continued. An area with competent vectors and a high density of travelers returning from ZIKV-active areas should be determined in consultation with relevant public health authorities. Unless public health authorities provide specific guidance, recognizing the difficulty in accruing data on what is considered a high density of travelers, then ID-NAT does not have to occur, or can be discontinued and MP-NAT may be resumed.

If the donor cannot be reached, ID-NAT should be implemented according to the triggering criteria defined above.

For the blast email sent to the AABB group listing, indicate if the donor was contacted (yes/no), and if the donor was contacted, were travel or sexual-related risk factors identified as defined above (yes/no).

Furthermore, once additional testing results on the PVD or ID-NAT-reactive donor are obtained, the blood center should update the Biovigilance website with these final testing results as soon as possible.

When concerns about the presence or absence of local vector-borne transmission risk arise, appropriate public health authorities should be contacted to provide an assessment of this risk. If local transmission risk is present in the given geographic area, ID-NAT should be maintained for a minimum of 14 days and until local transmission risk has been resolved according to public health authorities (see Detriggering below).

**Triggering based solely on outbreaks from local vector-borne transmission risk in the absence of donor test reactivity**

State or local health departments, the Centers for Disease Control and Prevention (CDC) or Food and Drug Administration (FDA) may have information that a vector-borne ZIKV outbreak is occurring within the United States (US) or its territories, or in an area outside the US or its territories with extensive travel to and from an area in the US having competent vectors. When this information is communicated to blood collection facilities in such an at-risk geographic area they should immediately trigger ID-NAT (irrespective of donor test results and within 24-hours of notification) for a minimum of 14 days and until the risk from the vector-borne outbreak has ended according to public health. This should occur whether or not a PVD has been detected.

**Defining a geographic area**

Until better information is obtained, the minimum geographic region for triggering determinations should be defined as the county of residence of the PVD.

**Additional testing for final classification of a PVD (e.g., Confirmation)**

Additional testing under investigational new drug (IND) protocols has included performance of an alternate NAT (which has lesser sensitivity than the screening NAT assay) and IgM serology. While under an IND, the manufacturer's testing protocol, including the additional testing algorithm, must be followed. Following licensure, there are no requirements from the manufacturer or FDA to continue with additional testing. For epidemiologic purposes, including tracking outbreaks in both magnitude and geography, as well as for detriggering decisions (see below), the additional testing algorithm recommended below should be followed for all ID-NAT-reactive donations, regardless of the screening protocol and whether the test is investigational or licensed.

Once two licensed screening NATs are available, a repeat NAT algorithm using the second manufacturer's NAT assay to confirm reactivity in the test-of-record or repeating the test-of-record is recommended. In either case, the use of an independent sample, if available, is recommended to avoid contamination issues that may have occurred with the originally tested sample. Both repeat NAT (same or alternate manufacturer's assay) and IgM are required for additional testing to confirm pre- and post-seroconversion infection. Follow-up samples may be needed to characterize a donation as confirmed positive if IgM or RNA reactivity cannot be confirmed when testing the index donation. A donor with IgM reactivity at index or follow-up is considered confirmed positive. In the absence of IgM, repeat NAT reactivity by an alternate or the test-of-record NAT assay using an independent sample (plasma or whole blood/red cells), confirms initial NAT reactivity.

Following triggering to ID-NAT, donors may be identified with results that are FR-ID-NAT initially reactive but are IgM positive and who have returned from travel to a ZIKV-active area beyond 30 days. Gathering such travel information for travel extending beyond 30 days is useful for the purposes of donor counseling; i.e., antibody positivity is retained for long periods of time following the resolution of ZIKV infection.

**Detriggering (i.e., reverting to MP-NAT) based on donor ID-NAT screening results and assessment of local vector-borne transmission**
**Refer to Appendix 1 – ZIKV ID-NAT Detrigger to resume MP-NAT Flowchart**

1. If the trigger was a PVD (using the ID-NAT trigger criteria described in 1-3 above):
   - If no local outbreak has been identified following the initiation of ID-NAT and no additional initial reactive donations have been identified after 14 days of the last ID-NAT reactive donation in the geographic area, MP-NAT may resume.
   - If any further initial reactive donations have been identified, additional testing is required to determine if the initial reactive donation is a confirmed positive (i.e., repeat NAT reactive using the primary or alternate test, or IgM reactive; see above).
   - If the initial reactive donation does not meet the criteria for a confirmed positive, then MP-NAT may resume.
2. If the trigger was local vector-borne transmission:
   - In an area with a local vector-borne outbreak, ID-NAT should continue until public health declares the area free of transmission, and 14 days have elapsed without an initial reactive donation. When this occurs, then MP-NAT may resume.
   - If any further initial reactive donations have been identified, additional testing is required to determine if the initial reactive donation is a confirmed positive (i.e., repeat NAT reactive using the primary or alternate test, or IgM reactive; see above). If the initial reactive donation does not meet the criteria for a confirmed positive, then MP-NAT may resume.

   *Note: local transmission is defined by public health as 2 or more local cases that are not travel or sexually related (i.e., partner with known travel) within a county within 45 days.*
3. If the trigger was due to an area having competent vectors combined with the area being at risk for travel-related cases originating from on-going ZIKV-outbreak areas, as defined by the CDC/FDA:
   - If no local outbreak is identified and the threat from ZIKV-active areas has resolved, and no initial reactive donations have been identified within 14 days, then MP-NAT may resume.
   - If any further initial reactive donations have been identified, additional testing is required to determine if the initial reactive donation is a confirmed positive (i.e., repeat NAT reactive using the primary or alternate test, or IgM reactive; see above).
   - If the initial reactive donation does not meet the criteria for a confirmed positive, then MP-NAT may resume.

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donor care and safety. AABB membership includes physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers. AABB members are located in more than 80 countries and AABB accredits institutions in over 50 countries.

Founded in 1962, ABC is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The ARC shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer these comments. We look forward to continuing to work with the FDA on patient and donor safety initiatives. Questions concerning these comments may be directed to scarayiannis@aabb.org.

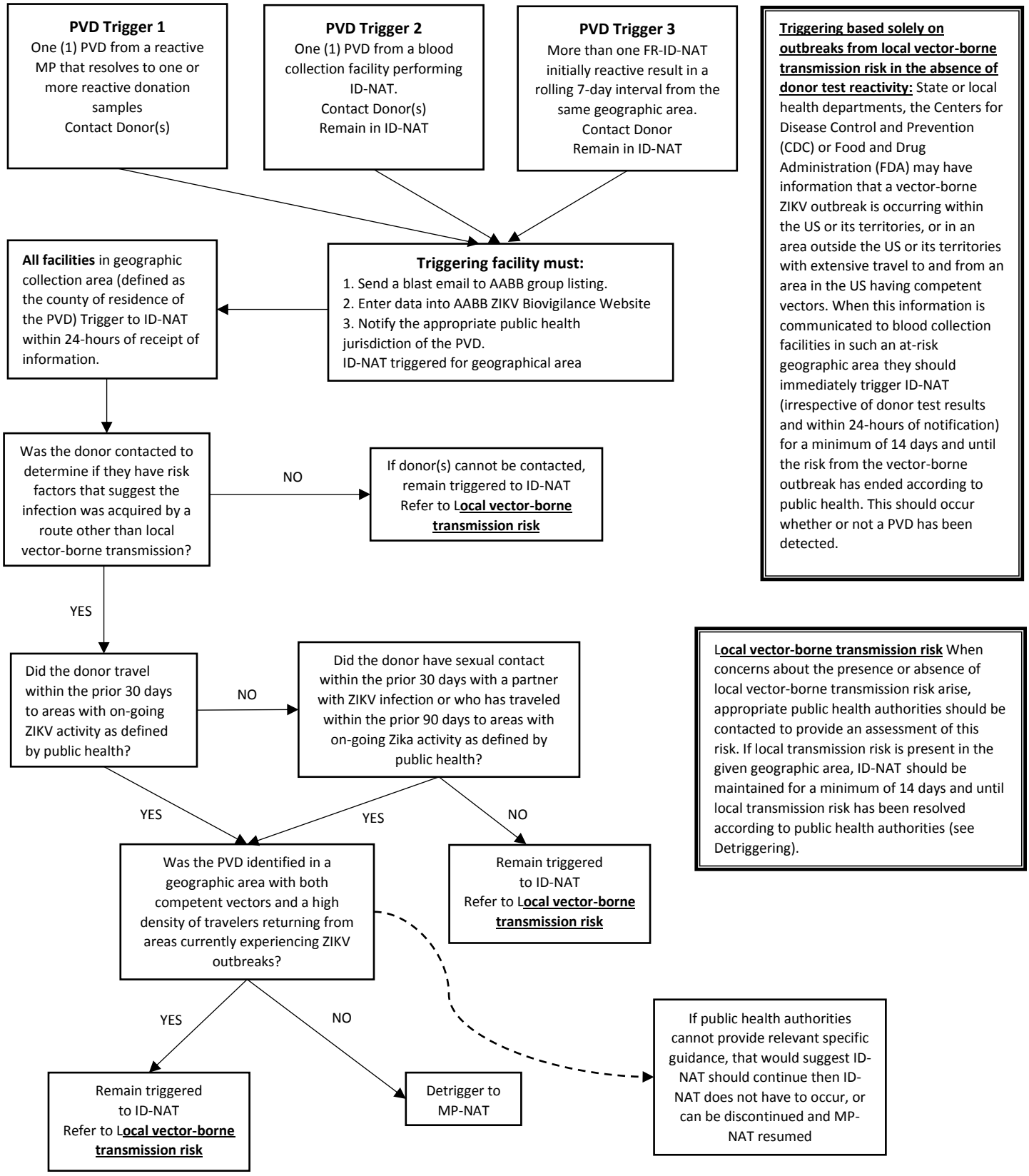
Sincerely,

Sharon Carayiannis, MT(ASCP)HP
Director, Regulatory Affairs
AABB

Celia P. Clifford
Vice President, Quality Regulatory Affairs
American Red Cross

Louis M. Katz, MD
Chief Medical Officer
America's Blood Centers

**Appendix 1:** **ZIKA MP-NAT Trigger to ID-NAT Flowchart**



# ZIKV ID-NAT Detrigger to resume MP-NAT Flowchart