A Joint Statement to the Food and Drug Administration's Blood Product Advisory Committee

December 1, 2017

"Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus," August 2016 Guidance Document

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AABB, America's Blood Centers and the American Red Cross appreciate the opportunity to present this statement on the blood community's experience with Zika virus testing. AABB's Transfusion Transmitted Diseases Committee and its Arbovirus subgroup prepared the statement with assistance from America's Blood Centers and American Red Cross representatives to the TTD committee. While we recognize that the August 26, 2016 guidance document entitled, *"Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components,"* also allows the use of FDA-licensed pathogen inactivation for plasma and platelets or licensed pathogen inactivation for red cells or whole blood, when available, this statement will only focus on the first year's testing experience.

The AABB TTD presented a statement at the November 18, 2016 Blood Products Advisory Committee meeting recognizing the nature and extent of the worldwide Zika-related health emergency focused in the Americas during 2015 to the first quarter of 2017. We were supportive of efforts to reduce transfusion transmission and provide the safest blood possible, but raised some concerns. These involved the process used to develop and implement the Guidance, the balance of resource commitment to potential benefits, and the precedent being set about further expectations for blood donation testing. Nevertheless, the industry complied with the Guidance and individual donation, nucleic acid testing (ID-NAT) was fully implemented by December 2016. As part of our prior statement, we asked the FDA to have a formal public review of the policies recommended in the Guidance with the specific objective of modifying the Guidance, if appropriate, to achieve a balance of benefits and resource use, and we thank the agency for doing so.

Starting in May 2016, in response to the growing Zika virus epidemic, increasing reports of linkage to a congenital Zika syndrome of unknown scope, neurologic complications in adults, 4

ZIKV-infected transfusion recipients in Brazil and the threat of local transmission, blood centers in the continental US began implementing investigational NAT. The August 26 Guidance required a phased approach to nationwide implementation beginning immediately in areas with on-going local transmission, followed in 4 weeks in the southern tier of states where competent vectors are concentrated as well as NY, and lastly with national implementation by November 18. These efforts were supported by the two NAT manufacturers, Roche and Grifols. We commend their efforts that provided high quality reagents, new testing platforms, software, training and support. Without this effort, implementation could not have occurred, especially given the requirement to test each donation individually while other viral agents are tested by NAT in small minipools. The addition of Zika virus ID-NAT consumed all available resources and surplus capacity at most blood centers, at the expense of the implementation of other projects, and at a cost (using cost-recovery pricing) of $137 million per year (Ellingson et al., *Transfusion* 2017;57:1625-33). As previously noted, we doubt, under current circumstances, that the blood community can be expected or able to repeat a similar regulatory mandate in the near future. Simply stated, we have limited personnel and laboratory capacity to urgently increase testing volume should the need arise.

The combined data collected under the two investigational NAT protocols in the continental US through November 4, 2017 show that testing of 13.58 million donations yielded 469 initial reactives of which 54 were confirmed positive using FDA-allowed IND definitions, for a confirmed-positive rate of 1:250,000. The specificity of these tests is excellent at 99.997% for each; however, due to the low frequency in a non-epidemic area, the positive predictive value of testing is 11.5%. As is characteristic of many mosquito-borne arboviral infections, the epidemic has been explosive followed by a decline over months, with a limited number of infections detected on the US mainland and in Puerto Rico for the past several months. Blood donation testing in Puerto Rico, using one of the investigational assays yielded a total of 338 reactives but only 2 since the middle of February 2017. In contrast to the data collected in the continental US, the positive predictive value of testing in Puerto Rico was 97.5% due to a far higher background rate of transmission. Closer examination of the data from the continental US shows that only 10 (18.5%) confirmed-positive donations were antibody negative (i.e., window-period units confirmed by less sensitive alternate NAT); all others were antibody positive of which 7 had sufficient viral loads to be reactive by the alternate NAT assay, and 37 (68.5%) had very low viral loads (not repeatable) in the presence of antibody. The vast majority of those donors who confirmed positive, when risk was identified, were attributable to travel-related remote infection. All available data to date indicate that units from donors with remote infections are not infectious versus those units with higher viral titers prior to seroconversion. It is the antibody-negative units that have been linked to transmissions of other arboviral agents (such as West Nile virus, and dengue viruses). Of note, the last confirmed-positive donations in the continental US, all related to travel, occurred during the weeks of August 30 (1), Sept 20 (1), Oct 4 (1) and Oct 16 (1). No blood donors were identified during this period due to local transmission events in the 50 US states.

Our proposal for on-going NAT in the continental US is to follow a comparable model as used for WNV, which is MP-NAT in small pools with conversion to ID-NAT following reports of

local vector-borne transmission. Such transmissions have been reported promptly in South Florida and Texas and would serve to trigger ID-NAT, which would continue until all evidence of local transmission has passed. From review of the Puerto Rican experience, there were 206 Zika IgM-negative donations (i.e., window period) of which only 14 (6.8%) failed to be detected by MP-NAT (by the one manufacturer that was used for testing). The 206 window-period donations in Puerto Rico are approximately 21-times more than the 10 window-period units observed in blood donations over the entire Zika-epidemic period in the continental US. Since each dataset represents just over 1 year of testing, we can assume a potential false-negative rate for MP-NAT in a comparable outbreak of 10 x 6.8% or 0.7 donations per year, or 1 every 1.4 years. With ID-NAT in place, the sensitivity of testing is increased during the time in which it is needed without wasting resources. This appears to be a viable compromise especially as the Zika epidemic has declined. Resources would be available to trigger ID-NAT as needed.

As shown by the low PPV of the screening assay in the continental US, accurate tracking of test results in blood donors requires confirmatory (supplemental) testing. This issue is of vital importance as it effects donor counseling, consignee notification, the triggering of lookback procedures, and also impacts public health surveillance due to the sharing of blood donor screening results with state public health departments. With FDA licensure of a screening assay, the availability of confirmatory testing is an issue as it is no longer required for users of this assay. We have asked the manufacturer of the approved test and the central laboratory used for additional testing during the corresponding IND to make that testing available going forward and will report the progress of those discussions to the agency when they are complete. Another important post-licensure issue is how to effectively monitor the number and rate of confirmed-positive donations since such information will no longer be collected by the test kit manufacturer. Of note, a switch to MP-NAT dramatically lessens the impact of the lack of supplemental testing since many fewer false positives are detected. Finally, these issues will be amplified if and when the second manufacturer's screening test becomes licensed.

In conclusion, we strongly encourage the FDA to consider options other than ID-NAT, especially a MP testing option that is consistent with on-going testing for other viruses, capable of causing significant disease in a transfusion recipient, including HIV, HBV, HCV and WNV. Finally, the agency needs 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.

Thank you for the opportunity to offer these comments.

AABB is an international, not-for-profit association representing individuals and institutions involved in the fields of transfusion medicine and cellular therapies. The association is committed to improving health through the development and delivery of standards, accreditation and educational programs that focus on optimizing patient and 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, America's Blood Centers 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 American Red Cross 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.