

Information for Blood Establishments Regarding FDA's Determination that Zika Virus is no Longer a Relevant Transfusion-Transmitted Infection, and Withdrawal of Guidance titled "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components"

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FDA requires blood establishments to test blood donations for new or emerging infectious agents that may affect blood product safety if certain conditions outlined in FDA regulations are met. Specifically, if a transfusion-transmitted infection "may have sufficient incidence and/or prevalence to affect the potential donor population" and meets certain other criteria described in FDA's regulations, then FDA may determine the transfusion-transmitted infection is a "relevant transfusion-transmitted infection" (RTTI). Testing for an RTTI is required under FDA's regulations if FDA-licensed, approved, or cleared screening tests are available and testing is necessary to reduce adequately and appropriately the risk of transmission.

FDA has determined Zika virus (ZIKV) is no longer an RTTI under FDA's regulations because, as discussed further below, the available evidence demonstrates that ZIKV no longer has sufficient incidence and/or prevalence to affect the potential donor population. Accordingly, FDA withdrew the guidance titled, "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components," dated July 2018. Because ZIKV is no longer an RTTI, blood establishments may discontinue testing for ZIKV. Licensed blood establishments that discontinue testing blood donations for ZIKV must report this change to FDA in the annual report under 21 CFR 601.12(d), noting the date testing was discontinued. Corresponding changes to the circular of information must also be reported in the annual report under 21 CFR 601.12(d).

FDA will continue to monitor ZIKV epidemiology in the United States (U.S.) and worldwide. If there is a change in epidemiology that leads FDA to conclude that ZIKV again "may have sufficient incidence and/or prevalence to affect the potential donor population," then FDA may again determine that ZIKV is an RTTI and issue guidance with recommendations for blood donor screening and testing, if necessary to reduce adequately and appropriately the risk of transmission.

#### Additional Background

In 2016, FDA determined that ZIKV was a "transfusion-transmitted infection" and a "relevant transfusion-transmitted infection" under its regulations in 21 CFR 630.3(l) and 21 CFR 630.3(h)(2), respectively. These determinations were based on the severity of the disease, the risk of transmission by blood and blood components, the availability of appropriate screening measures, and the available evidence that demonstrated, at the time, that ZIKV had significant incidence and prevalence to affect the potential donor population in the U.S. Additionally, FDA determined that testing for ZIKV was necessary to reduce adequately and appropriately the risk of transmission of ZIKV by blood and blood components. Accordingly, FDA issued guidance recommending nationwide and territorial implementation of individual-donor nucleic acid testing on all blood donations, or pathogen reduction.

Most recently, in 2018, FDA issued a revised guidance and explained that blood establishments must comply with 21 CFR 610.40(a)(3) by testing all donations using either an FDA-licensed mini-pool nucleic acid test, or an FDA-licensed individual donor nucleic acid test when certain threshold conditions were met that indicated an increased risk of suspected mosquito-borne transmission in a defined geographic blood collection area. As an alternative to testing blood donations for ZIKV, consistent with 21 CFR 610.40(a)(3)(ii)(B), this guidance explained that blood establishments could comply with 21 CFR 610.40(a)(3) by using an FDA-approved pathogen reduction device.

In March 2019, FDA's Blood Products Advisory Committee (BPAC or Committee) reviewed the available data on testing blood donations for ZIKV, given the continued decrease in ZIKV cases that has been observed in the U.S. and worldwide since 2017. While the majority of the Committee voted that the available data supported continuation of testing for ZIKV, the Committee recommended re-evaluating the topic once more data were obtained regarding the ongoing levels of ZIKV transmission in the U.S. and worldwide.

Consistent with this BPAC recommendation, FDA has re-evaluated the issue now that more data have been obtained. FDA has determined that although ZIKV is still a "transfusion-transmitted infection" under 21 CFR 630.3(l), it is no longer an RTTI under 630.3(h)(2), because a transfusion-transmitted infection is not an RTTI unless it "may have sufficient incidence and/or prevalence to affect the potential donor population." This determination is based on the following data:

- *ZIKV Epidemiology Since the 2016 Outbreaks in the U.S. and Worldwide*

The number of ZIKV cases decreased substantially from 2017 to 2020, not only in the U.S. but also worldwide. As of this writing (May 12, 2021), there are no areas of local, mosquito-borne ZIKV transmission in U.S. states and no local, mosquito-borne transmission has occurred since 2017. The number of travel-associated ZIKV cases in the U.S. has declined annually from 437 reported in 2017 to 73 in 2018, 27 in 2019 and 4 in 2020 as of April 1, 2021. In U.S. territories, there have been no confirmed ZIKV disease cases reported in 2019 or 2020.

Worldwide, the Centers for Disease Control and Prevention does not identify any countries or territories with current ZIKV outbreaks on their world map travel advisory, at the time of this writing.

- *Experience with ZIKV Testing of Blood Donations in the U.S.*

At the peak of the 2016 outbreak in Puerto Rico, about 1.8% of blood donations were reactive for ZIKV by individual donor nucleic acid testing. Over 400 potentially infectious units from asymptomatic blood donors in Puerto Rico and U.S. states were intercepted by individual donor nucleic acid testing between April 2016 and December 2017. Based on final data for U.S. states reported by the AABB Zika Biovigilance Network from participating blood collection organizations, 17 donations in 2017 and 2 donations in 2018 were confirmed positive for ZIKV.

The last confirmed ZIKV-positive blood donation in the U.S. occurred in March 2018—more than three years ago. There have been no reported cases of transfusion-transmitted ZIKV in the U.S.

For these reasons, FDA has determined that ZIKV no longer meets the definition of a “relevant transfusion-transmitted infection” under 21 CFR 630.30(h)(2), and that testing of each blood donation in the U.S. and its territories for ZIKV is no longer necessary to adequately and appropriately reduce the risk of transmission of such infection by blood and blood components. Similarly, we have determined that the use of FDA-approved pathogen reduction technology as an alternative to testing for ZIKV is no longer necessary to comply with 21 CFR 610.40(a)(3). Thus, testing for ZIKV, or pathogen reduction as an alternative to testing for ZIKV, is not necessary to comply with the requirements of 21 CFR 610.40(a)(3). As noted above, however, FDA will continue to monitor ZIKV epidemiology in the U.S. and worldwide.