Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products

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Guidance for Industry

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Contains Nonbinding Recommendations

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Guidance for Industry

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I. INTRODUCTION

This guidance provides you, establishments that make donor eligibility (DE) determinations for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps), with recommendations for screening donors for evidence of, and risk factors for, infection with Zika virus (ZIKV). This guidance updates and supersedes the guidance of the same title dated March 2016 which identified ZIKV as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR Part 1271. This guidance also supplements the recommendations contained in the guidance titled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated August 2007.

This guidance updates information in the March 2016 guidance by: 1) providing findings from more recent epidemiological studies including impact on public health; 2) reporting new data that informs the potential for transmission of ZIKV; 3) discussing the current status of availability of ZIKV tests; 4) updating sexual contact risk factors; 5) updating when an area is considered to have an increased risk for ZIKV transmission; and, 6) providing additional scientific references. This update supports the continuation of recommendations to screen living donors of HCT/Ps for risks of infection with ZIKV based on geographic areas with risk.

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II. BACKGROUND

A. ZIKV Epidemiology and Public Health Impact

ZIKV is an RNA arbovirus from the *Flaviviridae* family, genus *Flavivirus*. It is transmitted to humans primarily by the *Aedes aegypti* mosquito, but it may also be transmitted by other mosquitoes such as *Aedes albopictus* (Ref. 1). Past studies indicate that the vast majority of infected individuals are asymptomatic (Ref. 2). Even for those who experience symptoms, the symptoms are usually mild. In individuals with clinical manifestations, current estimates suggest symptoms may occur between 3-14 days after mosquito bite and most commonly include low-grade fever, arthralgia, myalgia, headache, retro-ocular headaches, non-purulent conjunctivitis, and cutaneous maculopapular rash (Refs. 3, 4).

Infection with ZIKV is also associated with neurologic manifestations, including Guillain-Barré syndrome, for which an increased incidence has been reported in areas experiencing a ZIKV outbreak (Refs. 5-9). Although rare, deaths have been reported in ZIKV-infected persons; however, the contribution of other comorbidities remains uncertain (Refs. 10-12).

ZIKV infection can also be vertically transmitted to a fetus during pregnancy, including from asymptomatic mothers (Refs. 13, 14). Symptoms of congenital infections include microcephaly, ophthalmologic abnormalities, and other neurologic abnormalities (Ref. 15). Nascent ZIKV infection during the first few weeks of pregnancy also can result in a miscarriage (Refs. 16, 17).

The virus was first isolated in 1947 from a rhesus monkey in the Zika Forest of Uganda, and isolated from a human in 1968 in Nigeria (Ref. 18). Epidemiological studies showed that the virus has circulated in humans between 1951 and 1981 in African and Asian countries (Ref. 8). In 2007, ZIKV illness was first detected outside of Africa and Asia causing an outbreak on Yap Island, Micronesia (Ref. 19). The next large outbreak of ZIKV was reported in French Polynesia from October 2013 to February 2014, possibly sickening up to 11% of the population (Ref. 20). Autochthonous (local) transmission was reported in Brazil in early 2015 (Ref. 21). In February 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern in response to the clusters of microcephaly and other neurological disorders and their possible association with ZIKV. The disease became a nationally notifiable condition in the United States (U.S.) in January 2016, and the first case of local, mosquito-borne transmission of ZIKV was reported in July 2016 (Refs. 22, 23).

In general, an area is considered to have an increased risk for ZIKV transmission when locally transmitted, mosquito-borne ZIKV has been reported or the potential is suspected based on epidemiological evidence. For the purposes of this guidance, areas with increased risk for ZIKV infection are provided on the Centers for Disease Control and Prevention (CDC) website for Blood and Tissue Safety: https://www.cdc.gov/zika/areasatrisk.html.

B. Potential for Transmission of ZIKV by Blood Products and Solid Organs

ZIKV can be transmitted through transfusion of blood and blood products. During the 2013-2014 outbreak in French Polynesia, 2.8% of specimens collected from asymptomatic blood donors were found to contain detectable ZIKV RNA (Refs. 20, 24). In 2016, screening of asymptomatic blood donors in Puerto Rico identified that approximately 1% of donor specimens were ZIKV RNA positive (Ref. 25). Likely ZIKV transmission by transfused blood products has also been reported in Brazil (Refs. 26, 27).

ZIKV RNA has been detected in brain, liver, kidney, lung, and other organs of persons with ZIKV-associated deaths (Refs. 10, 28, 29). Studies in rhesus macaques also indicate presence of ZIKV in these and other organs and tissues, although the impact of inoculation methods on tissue tropism is unclear (Refs. 30, 31).

C. Potential for Transmission of ZIKV by HCT/Ps

There is a theoretical risk for transmission of ZIKV by HCT/Ps. In particular, HCT/Ps typically recovered from living donors, such as amnion/chorion, hematopoietic stem/progenitor cells (HPCs) from cord blood and peripheral blood, and reproductive tissues such as semen and oocytes, appear to have the highest potential for harboring ZIKV. For example, infectious virus has been isolated from semen up to 69 days after onset of symptoms, and sexual transmission of ZIKV from male partners has been confirmed for both symptomatic and asymptomatic persons (Refs. 32-34). Although the upper limit of duration of infectious ZIKV in semen is unclear, ZIKV RNA has been detected in semen months after initial infection, including a few reports of ZIKV RNA detected at approximately 6 and 12 months after onset of symptoms; however, the studies did not indicate the virus was infectious (Refs. 34-43). Furthermore, ZIKV may directly infect spermatozoa thereby rendering preventive measures commonly used in assisted reproductive technology (ART) procedures, such as sperm washing, ineffective for preventing transmission of ZIKV (Refs. 44-46). A single case of female-to-male sexual transmission of ZIKV has also been reported, and ZIKV has been detected in genital and endocervical swabs from infected females (Refs. 47-50).

In addition to detection of ZIKV in reproductive cells and tissues, ZIKV has been identified in HPCs derived from peripheral blood and umbilical cord blood indicating potential risk for transmission of ZIKV through HPCs (Refs. 45, 51, 52). Transmission through HPCs is presumably similar to that of blood transfusion given the similarities in product composition and donor characteristics (e.g., recovered from similar populations composed of healthy, living donors). Moreover, typical recipients of HPCs are severely immunocompromised which may affect outcomes of infection. ZIKV infection and some deaths have been reported in persons with suppressed immune systems and autoimmune disorders. However, the contribution of a compromised immune system on ZIKV disease presentation remains unclear (Refs. 10, 53-55).

There is also the potential for transmission of ZIKV by HCT/Ps derived from gestational tissues such as HCT/Ps derived from amniotic membrane and umbilical cord. ZIKV is readily identified in gestational tissues from both symptomatic and asymptomatic mothers when infection occurred early or late in pregnancy (Refs. 16, 51, 56, 57). In some cases, ZIKV RNA and antigens have been detected in third trimester placentas when maternal infection occurred during the first trimester and in placentas from apparently healthy infants (Refs. 56, 57). In laboratory settings, ZIKV has been shown to infect and replicate in primary human placental macrophages (also known as Hofbauer cells), cytotrophoblasts, and umbilical cord mesenchymal stromal cells (Refs. 58-62).

Based on current information, as summarized above, the types of HCT/Ps with the highest potential for transmission of ZIKV appear to be those recovered from living donors. Less evidence exists regarding the potential for transmission of ZIKV by HCT/Ps typically recovered from non-heart-beating (cadaveric) donors. As more information regarding the pathogenesis of ZIKV becomes available, the understanding of risks to recipients of HCT/Ps, including HCT/Ps recovered from non-heart-beating donors, may evolve.

III. DISCUSSION

FDA has identified ZIKV as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2). This determination was based on the risk of transmission, severity of effect, and availability of appropriate screening measures. Since ZIKV is an RCDAD and appropriate screening measures exist, you must screen donors of HCT/Ps for risk factors for, and clinical evidence of, infection with ZIKV (21 CFR 1271.75(a)). Appropriate testing measures to prevent the transmission of ZIKV through HCT/Ps are not available at this time.

Risk of Transmission: There is a potential risk of transmission of ZIKV by HCT/Ps. This is supported by evidence that ZIKV has been detected in tissues such as semen, placenta and others described above. Although it is not possible to predict the incidence or severity of future ZIKV epidemics, the rapid geographic spread of the disease, together with the widespread presence of mosquito vectors in parts of the U.S., suggests that ZIKV will be a persistent threat to the potential HCT/P donor population. Local mosquito-borne transmissions of ZIKV are actively occurring or have recently been reported in three U.S. territories (Puerto Rico, U.S. Virgin Islands, and American Samoa) and specific counties in the continental U.S. Furthermore, travel-associated cases, as well as cases in their sexual partners, have occurred throughout the continental U.S. (Refs. 4, 63).

Severity of Effect: ZIKV disease is associated with a risk for development of neurologic complications including Guillain-Barré syndrome. Deaths have also been reported in association with the infection. The disease also causes microcephaly and other abnormalities in infants born to mothers with ZIKV infection during pregnancy. Therefore, infection with ZIKV could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure.

Availability of Appropriate Screening and/or Testing Measures: Appropriate screening measures have been developed for ZIKV, such as review of medical and travel history (discussed in section IV. of this document). Appropriate testing measures to prevent the transmission of ZIKV through HCT/Ps are not currently available.

Although nucleic acid tests (NATs) for donor screening are available, they are not considered appropriate for preventing transmission of ZIKV through HCT/Ps. The currently available NATs are designed to detect ZIKV RNA in plasma isolated from a donor blood specimen. ZIKV is readily detected in HCT/Ps, such as semen and umbilical cord blood or other gestational tissues, after viral RNA is no longer detectable in plasma; therefore, blood plasma NAT alone is not sufficient to determine whether a donor's HCT/Ps may be infected with ZIKV (Refs. 35, 43, 49, 50, 62-65). NAT screening tests using donor specimens other than blood plasma and ZIKV antibody screening tests are not currently available, therefore the potential utility of current tests for preventing transmission of ZIKV through HCT/Ps remains unclear at this time. If appropriate tests become available, we will consider recommending their use for donor testing within the context of the current knowledge of ZIKV, the performance characteristics of the test, and any additional screening methods in place at the time appropriate tests become available.

IV. RECOMMENDATIONS

As noted in section I. of this document, FDA identified in March 2016 that ZIKV is an RCDAD as defined in 21 CFR 1271.3(r)(2). Therefore, review of relevant medical records, as defined in 21 CFR 1271.3(s) and required under 21 CFR 1271.75, must indicate that a donor of an HCT/P is free from risk factors for, or clinical evidence of, ZIKV infection for purposes of determining donor eligibility. The following recommendations are intended to reduce the risk of transmission of ZIKV by HCT/Ps.

A. Recommendations for Living Donors of HCT/Ps[1]

Living donors of HCT/Ps should be considered ineligible if they have any of the following risk factors:

1. Medical diagnosis of ZIKV in the past 6 months.
2. Residence in, or travel to, an area with an increased risk for ZIKV transmission within the past 6 months.
3. Sex within the past 6 months with a person who has either of the risk factors listed in items 1 or 2, above.

[1] In some instances, donor screening for certain living donors of HCT/Ps may be performed within the few weeks prior to recovery of the HCT/Ps. Establishments performing a DE determination for such donors may wish to screen the donor again at the time of recovery. This additional screening on the day of recovery is not required for determining donor eligibility, but may be useful for making informed decisions about the use of an HCT/P. Similarly, establishments performing a DE determination for donors of cord blood may wish to request post-donation donor health information.

Additionally, donors of umbilical cord blood, placenta, or other gestational tissues should be considered ineligible if the birth mother who seeks to donate gestational tissues has any of the following risk factors:

4. Medical diagnosis of ZIKV infection at any point during that pregnancy.
5. Residence in, or travel to, an area with an increased risk for ZIKV transmission at any point during that pregnancy.
6. Sex at any point during that pregnancy with a person who has either of the risk factors listed in items 1 or 2, above.

Note: Limited instances for which use of HCT/Ps recovered from an ineligible donor is not prohibited, or in which a DE determination is not required, are described in 21 CFR 1271.65(b) and 21 CFR 1271.90, respectively.

B. Recommendations for Non-Heart-Beating (Cadaveric) Donors of HCT/Ps

The following non-heart-beating (cadaveric) donors should be considered ineligible:

Persons with a medical diagnosis of ZIKV infection in the past 6 months.

V. IMPLEMENTATION

FDA recommends that you implement the recommendations in this guidance as soon as feasible, but not later than 4 weeks after the guidance issue date.

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