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

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance when appropriate.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

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Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 identifies ZIKV as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR Part 1271. This guidance 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.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

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* mosquitoes *A. aegypti* and *A. albopictus*, but it may also be transmitted by other *Aedes* species (Refs. 1, 2). Past studies indicate that the vast majority (up to 80 percent of infected individuals) are asymptomatic (Ref. 3). Even for those who experience symptoms, the symptoms are usually mild. In individuals with clinical manifestations, current estimates suggest symptoms may occur between 2-12 days after mosquito bite and may include low-grade fever, arthralgia, myalgia, headache, retro-ocular headaches, non-purulent conjunctivitis, and cutaneous

maculopapular rash (Refs. 4, 5). An association of microcephaly in infants born to mothers with ZIKV infection has been observed, although a direct causal connection has yet to be confirmed. In some cases, autopsies have shown ZIKV to be present in the brains of neonates born to mothers infected with ZIKV during pregnancy (Refs. 6, 7). One such report identified full-length ZIKV in the brain of a fetus at 32 weeks of gestation; based on symptoms, ZIKV infection is suspected to have occurred 19 weeks prior to termination of pregnancy (Ref. 7). Infection with ZIKV may also be associated with neurologic manifestations, including Guillain-Barré syndrome, although a direct connection has yet to be confirmed (Ref. 3). Associations with death have also been reported, although the contribution of other comorbidities remains uncertain (Ref. 19).

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. 8). 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 (Refs. 9, 10). 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. 9). Autochthonous (local) transmission was reported in Brazil in early 2015 (Ref. 3). According to the Centers for Disease Control and Prevention (CDC) as of February 23, 2016, 34 countries and territories had reported active transmission of ZIKV (Ref. 11). In general, an area is considered to have active transmission of ZIKV when locally transmitted, mosquito-borne ZIKV has been reported. For the purpose of the guidance, an area with "active ZIKV transmission" is an area included on the CDC website listing of countries and U.S. states and territories with local vector-borne (i.e., mosquito-acquired) transmission of ZIKV: http://www.cdc.gov/zika/geo/index.html.

In February 2016, the World Health Organization (WHO) Director Dr. Margaret Chan declared a Public Health Emergency of International Concern in response to the clusters of microcephaly and other neurological disorders and their possible association with Zika virus and its apparent association with microcephaly. The disease became a nationally notifiable condition in the United States in January 2016 (Ref. 12). As of February 26, 2016, local mosquito-borne transmission of ZIKV has not been reported in the continental United States, but at least 107 travel-associated cases have been reported (Ref. 13). Mosquito-borne transmissions have been documented in the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa.

Viremia can be detected 10 days or more after onset of symptoms (Ref. 10). ZIKV has also been detected in urine and saliva, even after viremia has resolved (Refs. 14, 15). While ZIKV has also been detected in breast milk there are no known cases of transmission to infants by breast milk to date (Ref. 16).

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

Although ZIKV transmission by blood transfusion has not been conclusively documented, there have been two instances of possible transfusion-transmission

described in media announcements in Campinas, Brazil (Ref. 17). During an outbreak in French Polynesia, specimens from 3% of asymptomatic blood donors were found to be positive for ZIKV RNA by NAT (Ref. 18).

ZIKV RNA was detected in brain, liver, spleen, kidney, lung, and heart from one fatal case in adult with lupus erythematosus, rheumatoid arthritis, chronic use of corticosteroids, and alcoholism; however, there is no information as to whether the virus could be infectious in those organs if transplanted (Ref. 19).

C. Potential for Transmission of ZIKV by HCT/Ps

There is a theoretical risk for transmission of ZIKV by HCT/Ps, which include, among others, corneas, bone, skin, heart valves, hematopoietic stem/progenitor cells (HPCs) from cord blood and peripheral blood, and reproductive tissues such as semen and oocytes. For example, the virus was detected in semen 62 days after onset of symptoms in one individual, and possibly up to 10 weeks after onset of symptoms in a different individual (Refs. 20, 21). The upper duration of persistence of the virus in semen is not known, but it can be detected even after viremia has cleared. As of February 25, 2016 there have been numerous reports of ZIKV sexual transmission in the United States from men to their sexual partners, including at least two laboratory-confirmed cases, four probable cases, and still others that remain under investigation (Refs. 22, 23, 24). Sexual transmission of ZIKV from infected women to their sexual partners has not been reported; however, more research is needed to understand this issue.

In addition to reproductive tissues, there is a potential risk for transmission of ZIKV through other HCT/Ps. Transmission through HPCs is presumably similar to that of blood transfusion given the similarities in the product composition and donor characteristics (e.g., recovered from similar populations composed of healthy, living donors). Moreover, typical recipients of HPCs are severely immunocompromised and are more likely to experience serious outcomes as a result of ZIKV infection.

Based on limited available information, there is potential for transmission of ZIKV by HCT/Ps derived from gestational tissues, such as HCT/Ps derived from amniotic membrane and amniotic fluid. Maternal-fetal transmission of ZIKV, most likely by transplacental transmission (as early as the first trimester) or during delivery, has been reported (Refs. 6, 7, 17, 19, 25). ZIKV has also been detected in placenta and amniotic fluid (Refs. 26, 27).

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.

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 and placenta. 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 in three U.S. territories (Puerto Rico, U.S. Virgin Islands, and American Samoa), and travel-associated cases, as well as cases in their sexual partners, have occurred throughout the continental U.S (Ref. 11).

Severity of Effect: ZIKV disease may be 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 may also be potentially associated with microcephaly 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). Although a donor antibody screening test for ZIKV is not currently available, if such a test becomes available we will consider recommending its 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 the test becomes available.

IV. RECOMMENDATIONS

As noted in section I of this document, FDA has identified 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), must indicate that a potential donor of HCT/Ps is free from risk factors for, or clinical evidence of, ZIKV infection for the purpose 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 infection in the past 6 months.
2. Residence in, or travel to, an area with active ZIKV transmission within the past 6 months.
3. Sex within the past 6 months with a male who is known to have either of the risk factors listed in items 1 or 2, above.

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 active ZIKV transmission at any point during that pregnancy.
6. Sex at any point during that pregnancy with a male who is known to have 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.

[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.

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