

Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2016
Corrected May 2017**

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NOTE: A correction has been made to this guidance as follows:

- Under section III.A.1, the “Note” has been reformatted.

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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 HCT/Ps, with recommendations for testing living donors for West Nile Virus (WNV) using an FDA-licensed donor screening test. We (FDA) believe that the use of an FDA-licensed nucleic acid test (NAT) will reduce the risk of transmission of WNV from living donors of HCT/Ps and therefore recommend that you use an FDA-licensed NAT to test living donors of HCT/Ps for evidence of infection with WNV as set forth in this guidance. This guidance does not provide information regarding testing of cadaveric HCT/P donors for WNV. This guidance finalizes the draft guidance entitled “Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry” dated December 2015 (80 FR 77645). This guidance supplements WNV donor screening recommendations in sections IV.E. (recommendations 15 and 16) and IV.F. (recommendation 5), and supersedes the “West Nile Virus (WNV)” section in Appendix 6, of the guidance entitled “Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (2007 Donor Eligibility Guidance) dated August 2007¹ (Ref. 1).

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.

¹ The 2007 Donor Eligibility Guidance updated the guidance of the same title dated February 2007 (February 28, 2007, 72 FR 9007).

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II. BACKGROUND

A. Regulatory Background

In 2002, test manufacturers and blood organizations, with input from Public Health Service representatives (National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and FDA), actively pursued development of NAT systems for WNV. A workshop entitled “Development of Donor Screening Assays for West Nile Virus” was held on November 4-5, 2002 (Ref. 2). The workshop discussed the possibility that WNV would be recognized as a relevant communicable disease agent or disease for HCT/Ps when appropriate screening measures were developed.

Since 2002, studies have documented human-to-human transmission of WNV by blood transfusion and transplantation of vascularized human organs (Refs. 3, 4, 5).

As discussed in the 2007 Donor Eligibility Guidance, FDA determined WNV to be a relevant communicable disease agent or disease in accordance with 21 CFR 1271.3(r)(2). This determination was based on the severity of the effects of WNV, its incidence and prevalence in the donor population, the potential for transmission of WNV by HCT/Ps, and the availability of appropriate screening measures. The 2007 Donor Eligibility Guidance contained specific recommendations for donor screening for WNV but not for donor testing.

Under 21 CFR 1271.80(a) and 1271.85(a), establishments must perform donor testing to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents and diseases, unless an exception identified in 21 CFR 1271.90(a) applies. An establishment may determine a donor to be eligible only if the results of donor testing are negative or nonreactive (21 CFR 1271.50(b)(2)). However, in 2007, we did not recommend testing of HCT/P donors for WNV in recognition of the limited availability of such tests. We stated in the 2007 Donor Eligibility Guidance that we may recommend routine use of an appropriate, licensed donor screening test(s) to detect acute infections with WNV using NAT technology once such tests were available (Ref. 1).

In April 2008, we published a draft guidance entitled “Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (Ref. 6). The following year, we finalized the recommendations in that guidance for donations of whole blood and blood components in the guidance entitled “Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion” dated

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November 2009 (Ref. 7)². In the notice of availability that announced the finalized guidance, we stated that we were continuing to review public comments submitted on our recommendations for testing HCT/P donor specimens for WNV. In the notice, we also expressed our intention to seek additional public input and to issue guidance for testing HCT/P donor specimens for WNV in the future.

In July 2010, the American Association of Tissue Banks (AATB) hosted a public workshop entitled, “West Nile Virus Workshop: Scientific Considerations for Tissue Donors” (Ref. 8). Workshop participants included subject-matter experts from AATB-accredited tissue banks (including reproductive tissue banks), Eye Bank Association of America (EBAA) representing accredited eye banks, FDA, CDC, the United States Department of Health and Human Services (HHS), Health Canada, the Public Health Agency of Canada, and other stakeholders. The goal of the workshop was to develop public interest in relevant scientific studies to fill the gaps in the knowledge of WNV in human tissues. The data generated by such studies could further inform regulatory decisions regarding HCT/P donor screening and testing for WNV.

In October 2013, we published a revised draft guidance for HCT/Ps entitled “Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” to provide establishments that make donor eligibility determinations for donors of HCT/Ps, with recommendations for donor testing for WNV using an FDA-licensed donor screening test (Ref. 9). The guidance provided information and recommendations regarding NAT testing of HCT/P donors for WNV.

B. WNV Epidemiology in the United States and Public Health Impact

WNV is an arthropod-borne virus (arbovirus) in the family *Flaviviridae* which has a single-stranded ribonucleic acid (RNA). WNV was first detected in the United States (U.S.) in 1999 during an outbreak in the New York City area (Ref. 10). WNV has become endemic with high viral activity during warmer months of the year. WNV is maintained in nature primarily in a mosquito-bird-mosquito transmission cycle predominantly involving *Culex* (*Cx.*) species mosquitoes (*Cx. pipiens*, *Cx. tarsalis*, and *Cx. quinquefasciatus*), but can also infect other animals, such as horses and humans (Refs. 10, 11, 12).

Birds are the natural reservoir hosts for WNV. Many WNV-infected avian species develop transient viremia sufficient to infect feeding mosquitoes (Ref. 13). Birds commonly survive their infections and develop permanent immunity, although certain

² The final guidance, “Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion” provides recommendations for testing blood and blood components which include allowing minipool testing in times of low incidence of WNV. The policy determination regarding the appropriate type of testing recommended to protect the public health is dependent on both the epidemiology of the communicable disease, and the characteristics of the product type for which the testing applies.

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species become ill and die (Ref. 14). Humans are considered dead-end hosts for the virus since they do not develop viremia sufficient to allow virus transmission to feeding mosquitoes (Ref. 15).

Approximately 80% of WNV infections in humans result in an asymptomatic infection. The clinical features of WNV infections in the 20% of humans who are symptomatic are broad-ranging and vary from febrile illness that includes headache, myalgia, arthralgia, rash, or gastrointestinal symptoms (Refs. 16, 17) to the development of neuroinvasive disease, which occurs in less than 1% of infected humans. West Nile virus neuroinvasive disease, which typically presents as a panencephalitis, meningitis, or acute flaccid paralysis may lead to irreversible neurological damage, coma, and death (Refs. 17, 18, 19). From 2002 to 2013, the annual incidence of WNV neuroinvasive disease in the U.S. has ranged from 0.12 to 1.02 per 100,000 population, with peaks in 2002, 2003, and 2012 (Refs. 20, 21, 22, 23, 24). People over the age of 50 and some immunocompromised persons may have a higher risk of developing WNV neuroinvasive disease (Refs. 25, 26).

C. Seasonality of WNV in the United States

WNV became a nationally notifiable disease in 2002. Therefore, state and local health authorities use standard case definitions to report cases of WNV to CDC via ArboNET (Ref. 27). As noted above, WNV has become endemic in the United States with high viral activity during warmer months of the year, which means the HCT/P donor population has a higher risk of becoming infected with WNV during these months. In an effort to identify the months during which the risk of infection is greatest, FDA-CBER's Office of Biostatistics and Epidemiology performed an analysis of the data collected via ArboNET from 1999 through 2013 (provided by CDC) to assess the seasonal and geographical patterns of WNV infections in the United States. Analysis of these data indicates that > 98.5% of WNV infections in each region of the United States (50 states and the District of Columbia) occur between June 1st and October 31st. The data also indicate that the pattern of seasonal activity has been consistent since the appearance of WNV in the United States. Publically available data that support this observation are maintained by CDC (Ref. 28).

Since adequate data for locations outside of the United States (50 states and District of Columbia) are not necessarily available for analysis and routine monitoring, establishments located outside of the United States (50 states and District of Columbia) should not rely upon these analyses to support seasonal testing.

D. Transfusion-Transmitted WNV Infection

The potential for WNV transmission by blood transfusion was first recognized in 2002 (Ref. 3). WNV transmission usually occurs during the acute phase of infection when infected individuals are viremic and asymptomatic (Ref. 29). Few infected donors develop clinically significant disease. Studies have shown that questioning blood donors for recent illness suggestive of WNV infection is ineffective at identifying infected/seropositive donors (Refs. 30, 31, 32). During 2002, CDC conducted

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investigations of five blood transfusion recipients who subsequently developed neurologic disease. In four of these five cases, there was WNV-associated disease in the blood recipients, including one fatality. In the fifth of the five transfusion cases, there was an unspecified encephalopathy in a recipient of a WNV TaqMan-positive blood product, but there was no documentation of seroconversion in this recipient (Ref. 33).

Pealer et al., reported a total of 23 confirmed cases of WNV transmission by blood and blood components in 2002, including the five above mentioned investigations reported by CDC (Ref. 3). Of the 23 confirmed cases, 10 (43%) of the patients were immunocompromised due to immune suppression related to transplantation or cancer, and 8 (35%) were older than 70 years of age. All 23 infected recipients were linked to 16 donors with evidence of viremia at the time of donation. In follow-up studies with the donors, 9 of the 16 donors reported viral symptoms before or after donation, five were asymptomatic, and two were lost to follow-up. All 16 donors were immunoglobulin M (IgM) seronegative at the time of donation (Ref. 3).

The cases in 2002 involving transfusion-transmitted WNV infection prompted the initiation of donor testing in 2003. In June 2003, blood establishments began to screen blood donations for WNV by NAT using two different tests under FDA's Investigational New Drug Application (IND) regulations (21 CFR Part 312). The protocols implemented to screen donations included minipool NAT (MP-NAT) testing of samples using minipools of either 6 or 16 donations, depending on the manufacturer, followed by individual testing (ID-NAT) of each donation that was part of any reactive minipool (Ref. 19). Between July 1 and October 31, 2003, blood donor testing by American Red Cross (ARC) and participating members of America's Blood Centers (ABC) yielded 944 confirmed viremic donors out of 4,585,573 units screened (1 in 4,858 donations), thereby preventing the use of approximately 1,500 potentially infectious blood components (Ref. 32).

Additionally, in 2003, a total of 36 suspected cases of WNV transfusion-transmitted infections were reported to CDC. Upon investigation, five of the 36 cases were classified as probable cases and one was classified as a confirmed case. In each of these six cases, the recipients received blood components from multiple donations; however, only one infectious blood component was found in each case. All six infectious donations had been collected between July 29, 2003 and September 18, 2003 and had not been detected by MP-NAT (Ref. 34).

Until 2004, all WNV testing in blood donors was performed using MP-NAT. Late in 2004, there was a transition from MP-NAT testing to ID-NAT in geographic regions with high WNV activity during epidemic periods. While there were 15 suspected cases of transfusion-transmitted WNV infections investigated in 2004, only one probable transfusion-transmitted case was documented. The WNV transmission resulted from a blood donation which tested nonreactive in a MP-NAT assay. In 2005, there were eight suspected cases investigated, and there was no documented transfusion-transmitted WNV infection (Ref. 34).

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Since the implementation of routine screening of blood products for WNV, transfusion-associated WNV infections have been rare (Refs. 7, 35). Since implementation of screening in 2003, 12 transfusion-associated transmissions of WNV have been documented, according to the CDC (Ref. 35). Most recently, CDC reported a case of fatal WNV encephalitis in a severely immunosuppressed patient after probable transfusion-associated transmission. The subsequent investigation suggested that the implicated donation contained a level of viral load that was near the limit of detection of the NAT assays used for the screening and therefore produced inconsistent results on repeat testing (Ref. 35).

In 2006, transfusion-transmitted WNV infection occurred in two immunocompromised individuals who experienced onset of WNV neuroinvasive disease after receiving blood products from a single infected donor, despite a negative MP-NAT result at the time of donation (Ref. 36). In October 2008, the Louisiana Department of Health (LDH) reported two cases of probable transfusion-transmitted WNV infections from a common blood donor. One infection resulted in WNV neuroinvasive disease via organ donation from an organ donor who had received blood from a WNV-infected blood donor. The other case resulted in asymptomatic WNV infection directly to the blood transfusion recipient (Ref. 37).

E. Transplant-Transmitted WNV Infection

1. WNV Transmission via Transplantation of Vascularized Human Organs

WNV is also transmissible via transplantation of vascularized human organs. Although organ donors are not always tested for WNV (Refs. 37, 38), multiple WNV transmissions via transplantation of vascularized human organs have been reported in the published medical literature. For example, in 2002, a published report from CDC identified four recipients of vascularized human organs that developed WNV infection (Refs. 4, 39). Three of the four recipients developed WNV neuroinvasive disease, and one recipient died. The attributed mortality rate is therefore 25%. Additionally, since 2002, there have been at least 14 reported cases of WNV infections transmitted to recipients by transplantation of vascularized human organs. In three recipients from a single donor who had a febrile illness prior to fatal head injury, retrospective testing of stored donor blood samples were reactive for WNV IgM, but not for WNV RNA by NAT testing (Ref. 40). In the remaining 11 cases, there was a probable or confirmed transmission via transplantation of vascularized human organs. Of these 14 cases, three (21%) were asymptomatic, one (7%) developed a febrile illness, one (7%) was found to be viremic, and nine (64%) developed WNV neuroinvasive disease. Of those nine individuals who developed WNV neuroinvasive disease, one (11%) resulted in death, three (33%) resulted in coma, two (22%) had severe motor or cognitive permanent damage, two (22%) recovered, and one has an unknown outcome (Refs. 4, 37, 40, 41, 42, 43).

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2. WNV Transmission via HCT/P Transplantation

The documented transmission of WNV by blood transfusion and transplantation of vascularized human organs combined with WNV epidemiology, increasing understanding of WNV biology, and experience with transmission of other relevant communicable disease agents and diseases by HCT/P's indicate the potential for transmission of WNV by HCT/P transplantation. HCT/P's constitute a heterogeneous group of products that differ in many ways, such as: donor source (living vs. cadaveric); type of tissue or cell product (hematopoietic progenitor cells (HPCs), reproductive, structural tissue); extent of processing and storage conditions; recipient clinical condition (otherwise healthy to severely compromised). It is impractical to have different DE testing recommendations for every type of HCT/P. However, for certain emerging infectious diseases such as WNV, testing living donors only may be both practical and adequate to reduce the transmission by HCT/Ps.

In a reported case of intrauterine transmission for WNV, placenta and umbilical cord tissue were PCR-positive for the virus, and umbilical cord blood was positive for WNV IgM antibodies (Ref. 44). The potential for WNV transmission through HPCs and certain other HCT/Ps containing live cells 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 WNV infection. Therefore, the risk of WNV transmission is a particularly important consideration for this patient population. In 2003, there was a published report of two cases of WNV neuroinvasive disease in patients receiving HPCs for the treatment of acute myeloid leukemia. In one of these patients, the source of the WNV was not determined; in the other patient, the WNV was traced to a blood transfusion (Ref. 45). More recently, there is a published report of WNV transmission as a result of a granulocyte transfusion to a patient with persistent neutropenia related to cancer chemotherapy (Ref. 46). In this case, although the donor was tested for WNV, the limited shelf life of the granulocyte necessitated transfusion of the patient with the granulocyte apheresis product prior to obtaining results of the WNV testing. Because of the increased susceptibility to infection in these immunosuppressed patients, and the potential for donors to contract WNV infection between DE determination and HPC recovery during certain months, medical practitioners may wish to order supplemental testing of the donor at the time of HPC recovery. This additional "day of" test is not required for determining donor eligibility, but may be a useful medical practice in post-HPC transplant care.

Scientific data on the risk of transmission of WNV through transplantation of HCT/Ps recovered from cadaveric donors are limited. The paucity of reports of WNV transmission via transplantation of such tissue products may reflect factors such as differences in viral load, viral inactivation, or other processing steps

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which differ between tissues. For example, we note that tissues recovered from cadaveric donors for processing to decellularized HCT/Ps typically undergo more extensive processing than HCT/Ps donated by living donors, and therefore there may be potential for decreased transmissibility of WNV from these HCT/Ps. We continue to recognize the value of future studies to better understand the risk of transmission through HCT/Ps of various types, and therefore, the recommendations in this guidance are limited to living donors of HCT/Ps.

Scientific data on the risk of transmission of WNV through transplantation of HCT/Ps recovered from living donors outside the United States are limited. We continue to recognize the value of future studies to better understand the risk of transmission through HCT/Ps of various types recovered outside the United States.

F. Assay Development and Performance

Nationwide clinical studies to evaluate NAT for the detection of WNV were initiated in 2003 under FDA's IND regulations. Such large-scale studies were undertaken to help ensure blood safety and to determine the efficacy of investigational blood assays to prevent the transmission of WNV through blood transfusion because, at that time, there was no FDA-licensed screening assay available to detect WNV infection. Donors of HPCs were also tested in this initiative as part of the IND studies.

Since 2005, FDA has approved biologics license applications (BLAs) for NAT assays for detecting WNV RNA in plasma specimens from donors of Whole Blood and blood components, and blood specimens from donors of organs and tissues. Two assays that are licensed for testing specimens from donors of whole blood and blood components are also licensed for testing both living and cadaveric (non-heart-beating) HCT/P donors. These assays are intended for use in testing individual donor (ID) specimen from such donors. In addition, these assays may also be used for testing pools of human plasma in minipools comprised of equal aliquots of individual donations from volunteer donors of Whole Blood and blood components.

III. RECOMMENDATIONS

As noted above and as described at greater length in the 2007 Donor Eligibility Guidance, WNV is a relevant communicable disease agent or disease as defined in 21 CFR 1271.3(r)(2). We now determine that testing for WNV is necessary to adequately and appropriately reduce the risk of transmission of WNV in living donors of HCT/Ps. Therefore, FDA recommends that:

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- A. Living HCT/P donors should be tested for WNV using an FDA-licensed NAT donor screening test.^{3,4}
1. For establishments located within the United States (includes the 50 states and District of Columbia), we recommend performing WNV testing on HCT/Ps recovered from June 1st through October 31st every year.
- Note: In the case of a repeat semen donor from whom a specimen has already been collected and tested, and for whom retesting is required under § 1271.85(d), you are not required to collect a donor specimen at the time of each donation (§ 1271.80(b)(2)). However, you should collect a specimen for WNV NAT testing at the time of (or within 7 days before or after) the first donation that is recovered within the June 1st through October 31st testing period, even if an earlier specimen was already collected and tested.
- Due to the increased potential for donors, to contract WNV infection from June 1st through October 31st, establishments may want to consider collecting a specimen for WNV NAT testing at the time of (or within 7 days before or after) each donation made during this time period. Although this additional testing for subsequent donations is not required, any reactive results must be considered when making a donor eligibility determination.
2. For all other establishments not specified above, and intending to import HCT/Ps into the United States, testing of HCT/P donors for WNV should be performed year-round.
- B. Any HCT/P donor whose specimen tests negative (or nonreactive) for WNV NAT should be considered to be negative (or nonreactive) for WNV for purposes of determining donor eligibility.⁵
- C. Any HCT/P donor whose specimen tests positive (or reactive) for WNV must be considered ineligible to donate (21 CFR 1271.50(b)(2), 1271.80(d)(1)).

³ This recommendation for testing does not apply to donations that fall within the scope of any of the exceptions described in 21 CFR 1271.90(a), including cells and tissues for autologous use; reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; and, in certain circumstances, cryopreserved cells or tissue for reproductive use that were originally exempt from the donor eligibility requirements. In these instances, we do not believe that testing for WNV is necessary to adequately and appropriately reduce the risk of transmission of WNV in living donors of HCT/Ps.

⁴ If a repeat anonymous semen donor, for whom retesting at least 6 months after donation is required under 21 CFR 1271.85(d), discontinues donations, then you may use the results for WNV obtained at the final donation, or any time later than that, as the test of record to qualify that final donation.

⁵ FDA's recommendations regarding donor screening for WNV can be found in sections IV.E. and IV.F. of the 2007 Donor Eligibility Guidance (Ref. 1). Consistent with this guidance, persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days should be considered ineligible.

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IV. IMPLEMENTATION

FDA recommends that you implement the recommendations in this guidance as soon as feasible, but not later than 6 months after the final guidance issuance date. These recommendations apply to all HCT/Ps recovered on or after the implementation date.

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V. REFERENCES

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