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)

DRAFT GUIDANCE

This guidance is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that published in the *Federal Register*.

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For questions on the scientific content of this guidance regarding blood donors, contact Maria Rios, Ph.D., in the Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review at 301-827-3008. For questions regarding labeling or licensing issues, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3524. For questions regarding HCT/P donors, contact Melissa Greenwald, M.D., in the Division of Human Tissues, Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

U.S. Department of Health and Human Services
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I. INTRODUCTION

We, FDA, are issuing this guidance to provide you[1] with recommendations for testing of donations of Whole Blood and blood components and HCT/P donor specimens for West Nile Virus (WNV) using an FDA licensed donor screening assay. We believe that the use of a licensed nucleic acid test (NAT) will reduce the risk of transmission of WNV, and therefore recommend that you use a licensed NAT to screen donors of Whole Blood and blood components intended for transfusion and for testing donors of HCT/Ps for infection with WNV. We recommend that you implement NAT testing for WNV within 6 months after a final guidance is issued.

The recommendations in Section III of this guidance apply to all donations of Whole Blood (as defined in Title 21 Code of Federal Regulations (CFR) 640.1) and blood components for transfusion[2]. The recommendations in Section IV of this guidance apply to HCT/Ps and supplement the recommendations in the "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 8, 2007 (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] This guidance is intended for establishments that collect Whole Blood and blood components intended for transfusion and establishments that make donor eligibility determinations for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

[2] This guidance does not apply to Source Plasma or plasma derivatives.

II. BACKGROUND

WNV first appeared in the United States in 1999 and has become endemic with high viral activity during the warm months of the year. WNV is a mosquito-borne agent that is maintained in nature primarily between birds and mosquitoes but can also infect other animals, including humans. The potential for WNV transmission by blood transfusion during the acute phase of infection, when infected individuals are viremic and asymptomatic, was first recognized in 2002 (Ref. 2). At that time, test kit manufacturers and blood organizations, with input from the Public Health Service (National Institutes of Health, FDA, and Centers for Disease Control and Prevention (CDC)), actively pursued development of NAT systems for WNV. Retrospective studies have subsequently confirmed human-to-human transmission of WNV by blood transfusion and by organ transplantation (Refs. 3, 4).

Nationwide clinical studies to evaluate a NAT for the detection of WNV were initiated in 2003, under FDA's Investigational New Drug Application (IND) regulations (21 CFR Part 312). Such large-scale studies were necessary to help assure blood safety and to determine the efficacy of investigational 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.

Since 2005, FDA has approved biologics license applications for two NAT assays for detecting WNV ribonucleic acid (RNA) using plasma specimens from human donors of blood, organs and tissues, and from other living donors. The assays are intended for use in testing individual donor samples and for use in testing pools of human plasma comprised of equal aliquots of not more than either 6 or 16 individual donations (minipools) from volunteer donors of whole blood and blood components depending, on the manufacturer. Both assays also are intended for use in testing individual plasma specimens from organ donors when specimens are obtained while the donor's heart is still beating. One of the assays also has been licensed for testing individual blood specimens from cadaveric (non-heart-beating) donors.

As explained below in Section III, if the result of a licensed minipool NAT (MP-NAT) is reactive, and subsequent testing of the individual donation(s) (ID-NAT) comprising the tested minipool is reactive, then FDA would recommend treating the reactive unit(s) as though they are infectious.

Evaluation of additional testing performed on specimens that were reactive on screening by ID-NAT has shown that the sensitivity of repeat ID-NAT on index donation specimens (i.e., the same or an independent specimen from the index donation), using either the same screening assay or an equally sensitive alternate NAT, together with a test result for antibody to WNV, has a positive predictive value of 98% (Ref. 5).

Current data indicate that up to 10% of donors who have a reactive ID-NAT that fails to be reactive on repeat testing by ID-NAT actually are infected, based on the presence of antibodies to WNV either in the index donation (ca. 8%) or on a follow-up test (ca. 2%) (Ref. 5). Therefore, as described below, we consider it appropriate in such cases to perform repeat ID-

NAT and WNV antibody testing prior to counseling the donor regarding his or her WNV status, and, in some cases, encourage additional follow-up testing.

A. Whole Blood and Blood Components

In 2002, there were 23 confirmed cases of WNV transmission by blood and blood components (Ref. 3). In 2003, only six transmissions of WNV by transfusion were documented (Ref. 6) following nationwide implementation of screening for WNV by MP-NAT under an IND in July 2003. Retrospective studies using ID-NAT to test specimens collected during that season, which had been MP-NAT non-reactive, identified additional reactive donations and indicated that up to 25% of viremic units were not detected by MP-NAT, presumably due to low viral load (Ref. 7). Results of these studies show that for detecting WNV, ID-NAT has greater sensitivity than MP-NAT.

As a result, ID-NAT may identify additional reactive donations not detected by MP-NAT. However, limitations in reagent availability, and personnel and logistical issues related to blood donor screening may not allow full implementation of ID-NAT. During test development and implementation under IND, MP-NAT of plasma samples (pools of 6 or 16 samples), rather than ID-NAT, was the only feasible format for performing the test. In addition, testing using the MP-NAT format was similar to the assay platforms being used for human immunodeficiency virus type 1 (HIV-1) NAT and hepatitis C virus (HCV) NAT at that time. As reagent availability increases, technology advances, and personnel and logistical issues related to blood donor screening diminish, ID-NAT for all blood and blood components, using a licensed NAT year-round may become feasible and practical.

Although year-round ID-NAT testing of all blood and blood components may not be currently feasible, we believe that ID-NAT on a limited basis during periods of high WNV activity to maximize the benefit to the public health is more practicable. Statistical analyses were performed on the data from the retrospective studies described above to establish criteria for defining high WNV activity in a particular geographic region (Ref. 8). These criteria were used as a "trigger" for ID-NAT implementation and for reversion to MP-NAT testing when the high WNV activity in that region subsided. Since 2004, ID-NAT has been implemented in those geographic regions of high WNV activity during epidemic periods (Refs. 8, 9) when a threshold was reached, triggering a switch from MP-NAT to ID-NAT. The threshold was usually based on the number of MP-NAT-reactive screening test results obtained during a one-week interval or on a cumulative rate for ID-NAT reactive screening test results attained in a particular region (Ref. 5).

After selective implementation of ID-NAT during epidemic seasons, there were three additional transmissions of WNV by transfusion between 2004 and 2006: one in 2004 and two in 2006. The WNV transmission in 2004 resulted from a non-reactive MP-NAT donation, subsequently found to be ID-NAT reactive, from which red blood cells were transfused. Plasma from the donation retrospectively tested reactive by ID-NAT. However, ID-NAT had not yet been implemented (Ref. 10). The two WNV transmissions in 2006 resulted from a non-reactive MP-NAT donation from which red blood cells and fresh frozen plasma were transfused to two

immunosuppressed recipients (Ref. 11). Investigation of the 2006 cases showed that: 1) there were no established methods of communication linking WNV MP-NAT data from multiple collecting and testing facilities serving overlapping or adjacent geographic areas; and 2) if efficient communication mechanisms had been in place, the corresponding collection area would have reached the trigger for ID-NAT, and the WNV-contaminated components would likely have been detected and removed from the blood supply (Ref. 5).

B. HCT/Ps

In August 2007, we published a guidance entitled, "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 1). In that guidance we determined WNV to be a "relevant communicable disease agent or disease" for HCT/Ps even though WNV is not specifically listed in the regulations under 21 CFR 1271.3(r)(1). This determination was based on the fact that WNV meets the definition of a relevant communicable disease in 21 CFR 1271.3(r)(2) regarding risk of transmission (21 CFR 1271.3(r)(2)(i)), severity of effect (see 21 CFR 1271.3(r)(2)(ii)), and availability of appropriate screening measures or tests (see 21 CFR 1271.3(r)(2)(iii)). The August 2007 guidance contained specific recommendations for donor screening for WNV but not for donor testing. However, we noted that a donor screening test for WNV using NAT technology had been licensed for use in living and cadaveric HCT/P donors and that IND studies were also ongoing for the development of other NAT screening tests for WNV. We also indicated in the August 2007 guidance that we might recommend routine use of appropriate licensed donor screening test(s) to detect acute infections with WNV using a NAT once such tests were available.

III. RECOMMENDATIONS FOR DONATIONS OF WHOLE BLOOD AND BLOOD COMPONENTS

NAT testing of donations of Whole Blood and blood components for WNV involves the use of defined pooling and testing systems. We recognize that licensed testing technology in semi-automated or fully automated format is not universally available, and that if you are currently performing NAT for WNV under an IND you would need time to fully implement a licensed system with all approved components, including the supporting software cleared as a device. If you are therefore using some, but not all, of the licensed or cleared components, you should continue your existing IND and report the use of the licensed assay or the related cleared components as an amendment to your existing IND. When you implement all licensed or cleared components of the test system, you may withdraw the IND in accordance with the procedures provided in 21 CFR 312.38.

A. Testing, Unit Management, and Donor Management

1. We recommend that you screen year-round for WNV using a licensed NAT on donor samples of Whole Blood and blood components intended for transfusion. In general, you may use either MP-NAT or ID-NAT for screening (see Figure 1

and Table 1), except that we recommend that you implement ID-NAT during high WNV activity in your region (using a previously defined geographic area). See section B below for specific recommendations on when to convert to ID-NAT if you use MP-NAT.

2. If you perform screening using MP-NAT, you may release all units whose test samples comprise a non-reactive minipool, if those units are otherwise suitable for release.

   We recommend that you resolve a NAT-reactive minipool using ID-NAT to identify the unit(s) that led to the reactivity of the minipool. Based on the ID-NAT results, we recommend the following:

   a. You may release all ID-NAT non-reactive units if they are otherwise suitable for release.

   b. If one or more individual donation(s) is (are) reactive, we recommend that you discard the unit(s), defer the donor(s) for a period of 120 days and retrieve and quarantine in-date products from prior collections dating back 120 days prior to the donation that is ID-NAT-reactive. Prior to notifying the donor of his or her deferral and counseling the donor, we recommend that you perform additional testing on the specimen from the index donation using the same ID-NAT or using an alternate NAT with sensitivity equal to or greater than that of the screening assay. We also encourage you to test the specimen using a cleared test for antibodies to WNV (see Figure 1 and Table 2).

      i. If the repeat ID-NAT is reactive, we recommend that you notify the donor of his or her deferral and that you counsel the donor that he or she tests positive for WNV infection.

      ii. If the repeat ID-NAT is non-reactive but the test for antibodies to WNV is reactive, we recommend that you notify the donor of his or her deferral and that you counsel the donor that he or she tested positive for WNV infection.

      Note: Members of the Japanese Encephalitis (JE) serogroup (Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus) may present antibodies that are cross-reactive on the test for antibodies to WNV (Refs. 12, 13). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

      iii. If the repeat ID-NAT is non-reactive and the test for antibodies to WNV is also non-reactive, the test results are inconclusive. We recommend that you notify the donor of his or her deferral and inform the donor about a

possible infection with WNV. We encourage you to offer the donor additional counseling and follow-up testing using both ID-NAT and a cleared test for WNV antibodies on a new specimen obtained at least 30 days after the initially reactive index donation.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the JE serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), we encourage you to use a WNV-specific discriminatory NAT assay to assist donor counseling.

3. If you perform screening using ID-NAT, we recommend that you follow the steps in 2.a. and 2.b. for testing, unit management, and donor management.

B. Converting from MP-NAT to ID-NAT

1. We recommend that you convert from MP-NAT to ID-NAT if there is one (1) WNV NAT-reactive individual donation(s) from your region.

   NOTE: To define the geographic area in which to implement ID-NAT you may consider using the donor's residential zip code or county, or other well specified region of comparable size that includes the donor's residence. Although exposure to WNV may occur at any location, it is reasonable to assume that exposure most likely occurred while the donor was near his or her residence because mosquito activity is highest at dawn and dusk, times when many donors are at home. Mechanisms for initiating ID-NAT that utilize defined geographic areas based on residential zip codes, county, or other comparable well specified regions provide a standardized method for collecting data on number of NAT-reactive donations and number of donations tested.

   In addition to the use of this criterion, consideration of other epidemiological data may be useful to "trigger" the conversion from MP-NAT to ID-NAT, if such data are available. Examples include the number of clinical cases or the number of positive birds or mosquito pools reported in a particular geographic area, as well as prior ID-NAT implementation history.

   You should apply uniform criteria for converting from WNV MP-NAT to ID-NAT when the threshold has been met or exceeded in a defined geographic area. Collecting facilities that share geographic collection areas should consider a communication plan so that data from overlapping and adjacent collection areas may be shared and used to determine whether the trigger for implementing ID-NAT has been met.

2. We recommend that you convert from MP-NAT to ID-NAT within 24 hours of obtaining the test result(s) that caused the threshold for implementing ID-NAT to be met or exceeded.

3. If you obtain WNV NAT-reactive test result(s) for individual donation(s) more than 24 hours after collection of the individual donation(s), we recommend that you consider retrospective ID-NAT testing of retained samples from donations collected between the date of collection of those donations whose test results caused the threshold for implementing ID-NAT to be met or exceeded and the date of actual ID-NAT implementation.

4. If you wish to revert to MP-NAT testing, we recommend that you do so when the high WNV activity in the defined geographic area has subsided (for example, when a minimum of 7 days has passed without a single WNV ID-NAT-reactive donation).

C. Reporting Test Implementation

1. If you are a licensed blood establishment and are already FDA approved to perform infectious disease testing of blood products, you may use at your facility a licensed WNV NAT according to the manufacturer's product insert at your facility, and you must notify us in your annual report of the testing change in accordance with 21 CFR 601.12(d). Also, if you have already filed a supplement to your Biologics License Application to use a contract laboratory to perform infectious disease testing of blood products, and the contract laboratory will now perform a NAT for WNV, you must report this change in your annual report (21 CFR 601.12(d)).

2. If you are a licensed blood establishment and you use a new contract laboratory to perform a NAT for WNV and the laboratory already performs infectious disease testing for blood products, then you must report this change to FDA, and may do so through submission of a "Supplement – Changes Being Effected" in accordance with 21 CFR 601.12(c)(1) and (5), also known as changes being effected immediately (CBE). If your contract laboratory previously has not performed infectious disease testing for blood products, then you must submit this change in a prior approval supplement (PAS) in accordance with 21 CFR 601.12(b).

D. Labeling of Whole Blood and Blood Components Intended for Transfusion

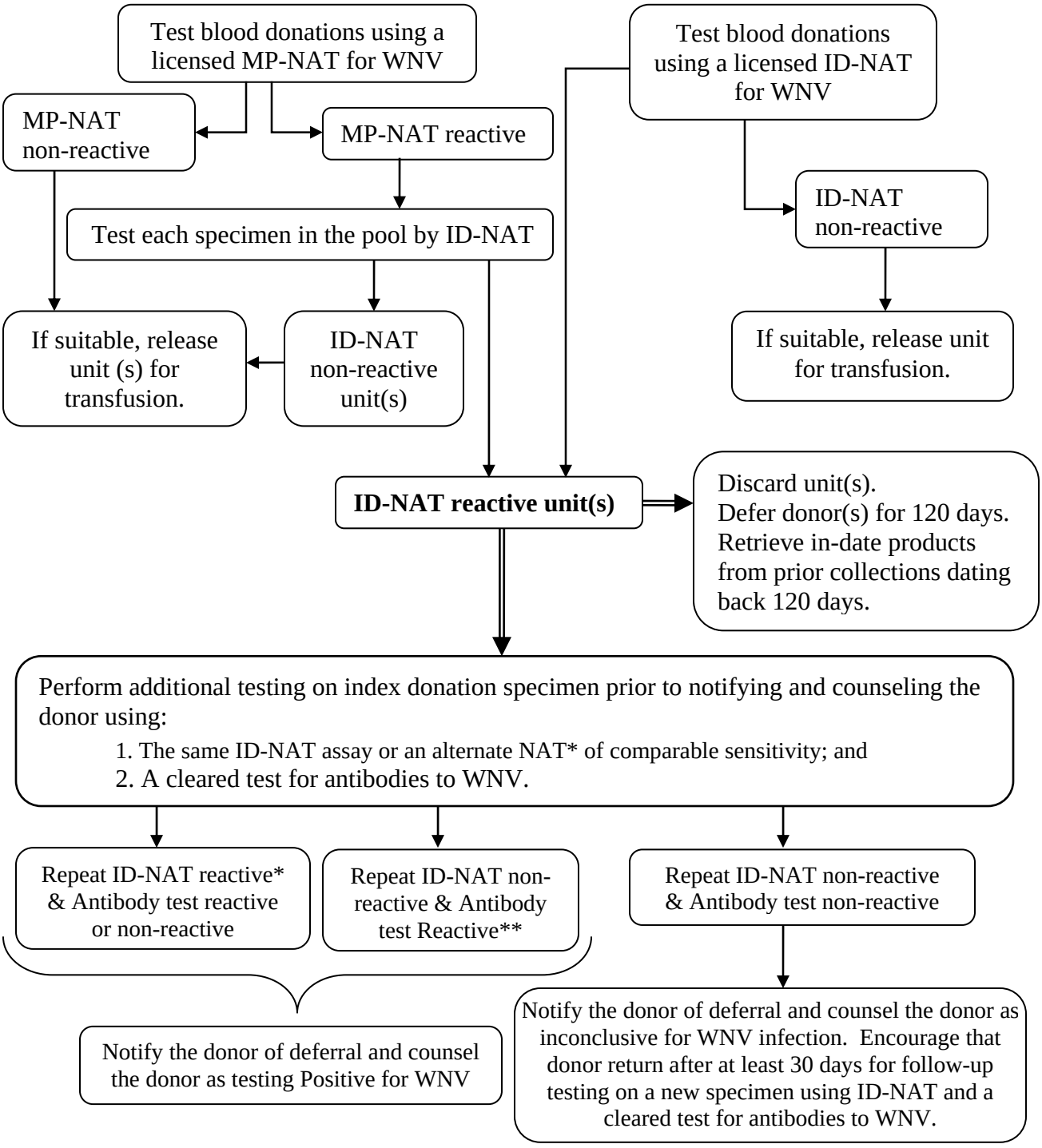
Title 21 CFR 606.122(h) requires that an instruction circular, also known as the "Circular of Information," for blood products intended for transfusion include the names and results of all tests performed when necessary for safe and effective use. To comply with 21 CFR 606.122(h), upon implementation of a licensed NAT for WNV, both licensed and unlicensed blood establishments must revise such instruction circular to include the non-

reactive results of a NAT for WNV. If you are a licensed blood establishment, you may submit this labeling as a CBE (21 CFR 601.12(c)(1) and (5)), provided the revision is identical to the following statement:

> "A Licensed Nucleic Acid Test (NAT) for West Nile Virus (WNV) RNA has been performed and found to be non-reactive."

If you are a licensed blood establishment and you wish to use a different statement, then you must submit the labeling change as a PAS (21 CFR 601.12(b)). If you are an unlicensed blood establishment, you must revise the instruction circular under 21 CFR 606.122(h), but you are not required to submit the revision as a supplement.

Figure 1. Recommendations on Testing, Unit Management, and Donor Management for Whole Blood and Blood Components



* In the event that the screening assay does not discriminate between WNV and other JE serogroup viruses, we encourage you to use a WNV-specific discriminatory assay to assist with donor counseling.

** Please note that there is high degree of cross-reactivity among different Flaviviruses.

Table 1. Recommendations on Testing, Unit Management, and Donor Management for Blood and Blood Components

MP- NAT	ID-NAT	Actions
Reactive	Reactive unit(s)	Discard the unit(s).
		Defer the donor(s) for 120 days.
		Retrieve in-date products from prior collections dating back 120 days.
		Perform additional testing using an ID-NAT and a cleared test for antibodies to WNV (see Table 2).
	Non-Reactive unit(s)	If suitable, release units for transfusion.
Non-Reactive	Not needed	If suitable, release units for transfusion.

Table 2. Recommendations on Additional Testing of Blood and Blood Components

Repeat ID-NAT*	Test for Antibodies to WNV	Donor Status
Reactive	Reactive	WNV Positive
	Non-Reactive	WNV Positive
Non-Reactive	Reactive	WNV Positive**
	Non-Reactive	Inconclusive***

* Using either the ID-NAT screening assay or an alternate NAT of equal or greater sensitivity. In the event that the screening assay does not discriminate between WNV and other Flaviviruses that belongs to the JE serogroup, we encourage you to use a WNV-specific discriminatory assay to assist with donor counseling.

** Please note that there is high degree of cross-reactivity among different Flaviviruses.

*** Due to the potential for false negative test results, encourage that donor return after at least 30 days for follow-up testing on a new specimen using ID-NAT and a cleared test for antibodies to WNV. Counsel the donor about their WNV status.

IV. RECOMMENDATIONS FOR TESTING OF HCT/P DONORS[3]

1. We recommend that blood specimens from all HCT/P donors be tested year-round for WNV by ID-NAT using a licensed screening NAT test.

2. Any HCT/P donor whose specimen tests non-reactive by ID-NAT may be considered to be negative for WNV for purposes of determining donor eligibility.

3. We recommend that any HCT/P donor whose specimen tests reactive by ID-NAT be ineligible for donation.

V. IMPLEMENTATION

We recommend that you implement this guidance within 6 months after a final guidance is issued.

[3] Recommendations regarding donor screening for WNV can be found in "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)", Sections IV. E, F and G (Ref. 1).

VI. REFERENCES

1. Food and Drug Administration, Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (August 2007). http://www.fda.gov/cber/tissue/docs.htm.
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