

報告企業の意見	今後の対応
<p>ウエストナイルウイルスの伝播リスクを低減するための核酸検査 (NAT) の使用に関する業界ガイダンスである。FDA は、2005 年 6 月の業界向けガイダンス改訂版において、「FDA は全ての血漿分画製剤について現在行われているウイルス低減工程を再調査した。現在行われている方法は、WNV と分類上関連しているフラビウイルスを不活化することがバリデートされている。」と評価し、CPMP もまたポジションステートメントにおいて、血漿分画製剤の製造工程で WNV は不活化・除去されると評価している。万一、原料血漿に WNV が混入しても、BVD をモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。</p>	<p>本報告は本剤の安全性に影響を与えないものと考えるので、特段の措置はとらない。</p>

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ハプトグロビン

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

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2009

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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

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to provide you¹ with recommendations for testing donations of Whole Blood and blood components for West Nile Virus (WNV) using an FDA-licensed donor screening assay². 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 for infection with WNV.

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 transfusion³.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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

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

¹ This guidance is intended for establishments that collect Whole Blood and blood components intended for transfusion.

² This guidance finalizes the recommendations for donations of Whole Blood and blood components in the draft guidance titled, *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/TPs)*, dated April 2008 (April 28, 2008, 73 FR 22958).

³ This guidance does not apply to Source Plasma or plasma derivatives.

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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. 1). 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. 2, 3).

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 ensure 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. The assays are intended for use in testing individual donor samples and in testing pools of human plasma comprised of equal aliquots of not more than either 6 or 16 individual donations (minipools) of whole blood and blood components, depending on the manufacturer.

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 a repeat ID-NAT on index donation specimens (i.e., the same or an independent specimen from the index donation, which is the donation for which the test result was reactive), 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. 4).

Data show 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. 4). Therefore, additional testing that would include repeat testing by ID-NAT along with testing for antibody to WNV may be of value in donor counseling.

A. Whole Blood and Blood Components

In 2002, there were 23 confirmed cases of WNV transmission by blood or blood components (Ref. 3). Only six transmissions of WNV by transfusion were documented in 2003 (Ref. 5) following nationwide implementation of screening for WNV by MP-NAT under an IND in July 2003. Retrospective studies using ID-NAT to test MP-NAT non-reactive specimens collected during that season 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. 6). Results

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of these studies show that for detecting WNV, ID-NAT has greater sensitivity than MP-NAT.

As a result, ID-NAT may identify 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 the development and implementation of the ID-NAT test 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, year-round ID-NAT testing of all donations of blood and blood components, using a licensed NAT, 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 using ID-NAT instead of MP-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. 7). 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 screening replaced MP-NAT screening in those geographic regions of high WNV activity during epidemic periods (Refs. 7, 8) when a threshold was reached. 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 in a particular region (Ref. 4).

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 donation of red blood cells which tested non-reactive in a MP-NAT assay, but which was subsequently found to be reactive in an ID-NAT test. Plasma from the donation retrospectively tested reactive by ID-NAT. However, ID-NAT had not yet been implemented (Ref. 9). 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. 10). 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 threshold for switching to ID-NAT screening, and the WNV-contaminated components would likely have been detected and removed from the blood supply (Ref. 4).

At this time, there is insufficient data to support recommendation of uniform threshold criteria for switching from MP-NAT screening to ID-NAT screening. Pending development of suitable uniform threshold criteria, we consider it appropriate for each blood establishment to define its own threshold criteria for switching from MP-NAT to ID-NAT screening and for reverting to MP-NAT screening. Each blood establishment should follow an established standard operating procedure (SOP) for this decision process. Voluntary industry practice of switching from MP-

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NAT to ID-NAT screening during seasonal activity has been useful in increasing the effectiveness of the WNV screening process.

III. RECOMMENDATIONS FOR DONATIONS OF WHOLE BLOOD AND BLOOD COMPONENTS

Testing donations of Whole Blood and blood components for WNV using NAT involves the use of defined pooling and testing systems. We recognize that licensed testing technology in a 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 use ID-NAT screening during high WNV activity in your region (using a previously defined geographic area). See section B.
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 test each specimen in the minipool in order 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. We recommend that you notify the donor of his or her deferral and counsel the donor. Further testing on the index donation using the same ID-NAT or an alternate NAT with sensitivity equal to or greater than that of the screening assay, in addition to testing the

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specimen using a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

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. Switching from MP-NAT to ID-NAT

We recommend that you:

1. Establish and validate criteria that define high WNV activity in your geographic area of collection.
2. Define a threshold for switching from MP-NAT to ID-NAT screening during high WNV activity in your geographic area of collection, and for reverting to MP-NAT screening when the high WNV activity in your geographic area has subsided.
3. Switch from MP-NAT to ID-NAT screening as soon as feasible, but within 48 hours of reaching that threshold.
4. Establish and follow an SOP for this decision process.

NOTE: To define the geographic area for which the threshold criteria would apply, 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 in 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 switching to ID-NAT screening that utilize defined geographic areas based on residential zip codes, counties, or other comparable well-specified regions provide a standardized method for collecting data on the number of NAT-reactive donations and the number of donations tested.

Consideration of other epidemiological data may be useful in defining a threshold for switching from MP-NAT to ID-NAT screening, if such data are available.

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Examples include the number of clinical cases, the number of positive birds or mosquito pools reported in a particular geographic area, and prior ID-NAT implementation history.

You should switch from MP-NAT to ID-NAT screening when the WNV case threshold has been met or exceeded in your defined geographic area. Blood establishments 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 assess WNV activity in a defined geographic area. You may use this data to determine whether your defined threshold for switching to ID-NAT screening has been met.

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, 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, in accordance with 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 Effectuated" in accordance with 21 CFR 601.12(c)(1) and (5), also known as changes being effectuated 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:

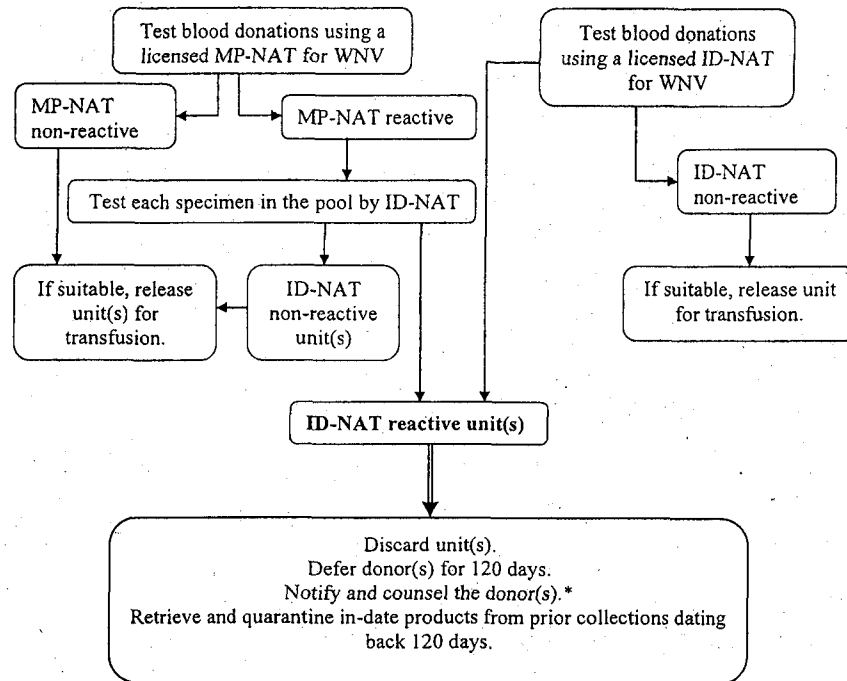
"A Licensed Nucleic Acid Test (NAT) for West Nile Virus (WNV) RNA has

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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



* Additional testing on the index donation using the same ID-NAT assay or an alternate NAT of comparable sensitivity in addition to a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

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

MP- NAT	ID-NAT	Actions
Reactive	Reactive unit(s)	Discard the unit(s).
		Defer the donor(s) for 120 days.
		Notify and counsel the donor(s).*
	Retrieve and quarantine in-date products from prior collections dating back 120 days.	
	Non-Reactive unit(s)	If suitable, release units for transfusion.
Non-Reactive	Not needed	If suitable, release units for transfusion.

* Additional testing on the index donation using the same ID-NAT assay or an alternate NAT of comparable sensitivity in addition to a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

IV. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than six months after the guidance issue date.

V. REFERENCES

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番号: 2

別紙様式第2-1

医薬品 研究報告 調査報告書

識別番号・報告回数	報告日	第一報入手日	新医薬品等の区分	機構処理欄
		平成 22 年 1 月 5 日	該当なし	
一般的名称	研究報告の公表状況	Google News Dec 18, 2009 (追加情報: The New York Times December 19, 2009)	公表国 米国	
販売名(企業名)	放射性ヨウ化人血清アルブミン注射液(富士フイルムRIファーマ株式会社)			
研究報告の概要	<p>要約: 米国においてアメーバ性髄膜炎の初めてのヒトからヒトへの伝播が報告された: 米国にて、臓器ドナーから腎移植を受けたレシピエント2例がアメーバ性髄膜炎に感染し、患者は重篤な状態にあることが保健当局により報告された。これは、おそらく初めてのヒトからヒトへのアメーバ性髄膜炎の伝播であると思われる。レシピエント2例は重症であるが、同患者からの別の臓器の移植を受けたその他の患者は症状を呈していない。後に検査により、ドナーと腎移植を受けたレシピエント2例から髄膜炎の原因とされる「<i>Balamuthia mandrillaris</i>」というアメーバが検出され、感染が確認された。</p>			<p>使用上の注意記載状況・その他参考事項等</p> <p>特になし</p>
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	初めての人から人への感染報告であり、新たな感染経路かつ重大な感染症に関するものであるため、感染症定期報告の対象と判断する。	本研究報告は、ヒト血液を原料とする血漿分画製剤とは直接関連しないことから、現時点で当該生物由来製品に関し、措置等を行う必要はないと判断する。		

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