

Guidance for Industry

Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection

FINAL GUIDANCE

This guidance is being distributed for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)3 without initially seeking prior comment because the agency has determined that prior public participation is not appropriate because of the immediate public health hazard from West Nile Virus. FDA invites comments on this document. Please submit comments to Dockets Management Branch (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 document when appropriate.

Additional copies of this guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville, MD 20852-1448, or by calling 1-800-835-4709 or (301) 827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance contact the Division of Blood Applications, Office of Blood Research and Review at (301) 827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
October 2002

Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
III.	RECOMMENDATIONS ON DONOR DEFERRAL	5
	A. Diagnosed Acute West Nile Virus Illness or Infection.....	5
	B. Suspected Acute West Nile Virus Illness or Infection	5
IV.	RECOMMENDATIONS FOR RETRIEVAL AND QUARANTINE OF BLOOD AND BLOOD COMPONENTS INCLUDING RECOVERED PLASMA, SOURCE PLASMA, AND SOURCE LEUKOCYTES.....	6
	A. Diagnosed West Nile Virus Infection or Illness in the Donor	6
	B. Blood Donors Associated with a Potential Case of Transmission to a Transfusion Recipient.....	6
	C. Undiagnosed Post-donation Illness in Potentially Exposed Individuals.....	6
V.	RECOMMENDATIONS ON NOTIFICATION OF PRIOR TRANSFUSION RECIPIENTS	7
VI.	BIOLOGIC PRODUCT DEVIATION AND FATALITY REPORTING	7
VII.	LABELING OF PRODUCTS DISTRIBUTED FOR RESEARCH OR INTENDED FOR FURTHER MANUFACTURING INTO NON-INJECTABLE PRODUCTS ...	8
VIII.	IMPLEMENTATION	8
IX.	REFERENCES	9

Guidance for Industry

Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection

This guidance document represents the agency'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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes or regulations.

I. INTRODUCTION

This guidance document provides our recommendations for assessing donor suitability and product safety for donors with proven West Nile Virus (WNV) infections or with illnesses potentially due to WNV. This guidance applies to Whole Blood and blood components intended for transfusion and blood components including recovered plasma, Source Leukocytes and Source Plasma intended for use in further manufacturing into injectable products or non-injectable products. The Food and Drug Administration (FDA) developed the recommendations in this guidance in consultation with other Public Health Service Agencies of the Department of Health and Human Services. Within this guidance, “you” refers to blood establishments and “we” refers to FDA.

II. BACKGROUND

WNV is an arthropod-borne virus that belongs to the Japanese encephalitis complex of flaviviridae. WNV is a small (50nm) spherical, lipid enveloped virus enclosing a single-stranded positive sense ribonucleic acid (RNA) genome of approximately 11,000 nucleotides that lacks a 3 prime poly A tract. The viral genome encodes a polyprotein that is further processed to form three viral structural proteins (capsid, membrane, and envelope) and seven nonstructural proteins. Other members of the flaviviridae family are known to be inactivated by heat or solvent detergent treatments used to prepare plasma derivatives.

WNV is primarily transmitted in birds through mosquito bites while humans are incidental hosts. Incidental mosquito borne infection may also occur in other animals including horses, cats, squirrels, and domestic animals. WNV outbreaks have been reported in Europe, the Middle East, and Russia during the past decade and have been associated with human encephalitis and meningitis. A poliomyelitis-like illness of acute asymmetrical flaccid paralysis in the absence of pain or sensory loss has also been reported recently. WNV was first identified in the United States (U.S.) in 1999, in an epizootic outbreak among birds and horses and an epidemic of meningitis and encephalitis in humans in the New York City area. Throughout 2000 - 2001,

avian mortality surveillance documented geographic spread to about half of the U.S. In 2001, 66 human cases of WNV encephalitis or meningitis occurred in 10 states. In 2002, a major outbreak of WNV has been detected in many parts of the U.S. in animals as well as humans. In 2002, the number of human cases has far surpassed those reported in 2001 with 2530 cases of WNV illness and 116 deaths reported as of October 2nd. It is believed that the peak of the current WNV epidemic occurred in August - September 2002 and that the current outbreak will abate as the weather becomes colder and mosquito activity declines. Nevertheless, it is possible that year round transmission may occur in southern states with warmer climates.

The pre-clinical incubation period is thought to range from 2 – 14 days following infection by mosquito bite. Most people infected with WNV do not develop any illness.

However, approximately 20% of people who become infected with WNV will develop mild symptoms. Mild symptoms which are often indistinguishable from other viral infections, may include: fever, headache, body aches, nausea, vomiting, eye pain, occasionally with a skin rash on the trunk of the body, and swollen lymph glands.

It is estimated that 1 in 150 persons infected with WNV develops a more severe form of the disease. In general, individuals who are older than 50 years and probably those who are immunocompromised are at greatest risk of severe disease. Severe illness may include encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis. Symptoms may include: headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, and muscle weakness or paralysis. More severe symptoms may last several weeks and some permanent neurologic impairment may occur. Case fatalities among patients who were hospitalized in the U.S. with severe WNV illness have ranged from 10 to 14%. WNV encephalitis is on the list of designated nationally notifiable arboviral encephalitides.

There are limited data suggesting that transient viremia commonly occurs within 1-3 days following infection by mosquito bite. The overall period of viremia is commonly thought to last a few days, although in one study in the 1950s, longer periods of viremia were noted in some cancer patients. Although there currently are no FDA approved tests for WNV medical diagnosis or donor screening, we are actively encouraging the development of such tests. In particular, we are facilitating the development of donor screening tests that may be practically implemented on a large scale. Until such tests are available, WNV diagnostic testing based on detection of immunoglobulin M (IgM) antibodies to WNV (a test not suitable for donor blood screening) can be obtained through local or state health departments. In approximately 90% of patients, IgM antibodies against WNV can be detected in sera or cerebral spinal fluid collected on or after 8 days of illness onset using an IgM capture Enzyme-Linked Immunosorbent Assay (ELISA). The majority of antibodies are directed against the envelope protein and the non-structural NS1 and NS3 proteins. IgM antibodies that develop persist for greater than 6 months after illness in over 50% of patients and may be detected for up to 500 days in some cases. Sera or cerebrospinal fluid can be screened for both IgM and immunoglobulin G (IgG) antibodies by ELISA. However, there is cross-reactivity of antibodies with other flaviviruses. Plaque reduction neutralization assays can be performed to help distinguish among the flaviviruses. Experimental tests that use reverse transcription followed by nucleic acid amplification have been used to document the presence of virus in blood or tissues, but are commonly negative in the blood once clinical illness has occurred.

Currently, treatment for WNV illness is supportive. In severe cases, this often involves hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. Although ribavirin and interferon alpha-2b have some activity against WNV in vitro, there is not, at this time, clinical evidence to support their efficacy in patients.

Although this guidance is intended to address WNV, the recommendations suggested below may also be helpful in reducing the potential risk of Saint Louis encephalitis virus (SLE). SLE is also an arbovirus that can be transmitted by mosquito bite to humans and like WNV is a member of the flaviviridae family. There have been intermittent epidemics of SLE in the U.S. Like WNV, most infections by SLE are subclinical or result in a mild illness. Encephalitis or meningitis may occur in a small number of infected individuals with the elderly being the most at risk for serious illness. At present, there is no known transmission of SLE by blood transfusion; however, such a possibility cannot be excluded.

Transmission by Blood Transfusion

From August 28 to October 2, 2002, the Centers for Disease Control and Prevention (CDC) received reports from 10 states of 15 patients with confirmed WNV meningoencephalitis (WNME) or meningitis diagnosed after receiving blood components within 1 month of illness onset. All 15 of these patients resided in areas of high WNV activity. Since a large number of WNV infections resulting from mosquito bites have occurred in the U.S., including the areas where these cases occurred, recent receipt of a blood transfusion by a person with WNV infection does not necessarily indicate that the transfusion was the source of infection. Investigations, including testing of retained donor blood samples, where available, are ongoing to determine whether transfusion was the likely source of WNV transmission in these cases.

Of the 15 cases, eight were reported since September 25. One patient, an organ donor from Georgia, was positive for WNV at the time of organ recovery following receipt of multiple blood transfusions. The onset of symptoms for the remaining 14 patients began in July (two patients), August (five patients), and September (seven patients). Among these patients, the reasons for hospitalization or the underlying conditions included a surgical or obstetrical procedure, solid organ or bone marrow transplantation, and hematological disorders including myelodysplasia, acute myelogenous leukemia, and thrombotic thrombocytopenic purpura. These 15 patients received blood components from a median of 18 donors (range: 2-185 donors). West Nile virus meningoencephalitis was the probable cause of death for at least three of the four patients who died.

While studies are ongoing, some of these investigations provide strong evidence that WNV can be transmitted through blood transfusion. Two patients tested positive for WNV infection after receiving different blood products derived from a single blood donation subsequently found to have evidence of WNV. In another case, WNV was isolated from a withdrawn unit of frozen plasma from the suspect donation, indicating that the virus can survive in some blood components. Follow-up investigation of the same donor revealed that the donor developed an acute febrile illness associated with seroconversion to WNV following the suspect collection. In addition to these patients, investigations in Georgia and Florida have demonstrated transmission of WNV in four recipients of solid organs from a single organ donor.

To assist in identification of other possible cases of WNV infection potentially associated with transfusion, patients with diagnosed WNV infection who have received blood transfusion or organs within the 4 weeks preceding the onset of symptoms should be reported to CDC through local public health authorities. Serum or tissue samples should be retained for later studies. In addition, the Public Health Service has requested that cases of WNV infection in individuals who had onset of symptoms within 2 weeks of blood or organ donation be reported to CDC through state and local public health departments.

On August 17, 2002, we issued an alert to blood establishments entitled “Information about WNV and Blood Safety” which was updated on October 3, 2002. We urged blood establishments to pay careful attention to their existing donor screening procedures that should identify persons with symptomatic infection. We also advised establishments that when cases of probable or proven WNV infection are discovered post-donation, that medical directors of blood establishments should carefully evaluate the potential need for product quarantine and retrieval and consult FDA if necessary.

We are not recommending any changes to standard donor screening and blood collection procedures to identify or otherwise query donors who may have been exposed to WNV. This policy is based on the assessment that there currently is no practical method to distinguish the vast majority of donors who may have received mosquito bites from uninfected mosquitoes, and the fact that existing standard blood collection procedures include deferral of any donor who is not in good health and feeling well at the time of donation.

If an asymptomatic donor mentions a previous diagnosis of WNV infection or illness, medical directors should consider the time since the diagnosis of WNV and whether symptoms have resolved when determining whether to defer such donors. Donors who are symptomatic would be excluded based on current regulations. Additionally, we are advising blood collection centers to actively encourage donors to report post-donation illnesses that could be associated with infection by WNV.

As a prudent measure to address the possible risk of transmission of WNV by blood transfusion, we are providing recommendations for donor deferral, and for product quarantine and retrieval related to reports of post-donation illnesses in the donor, or WNV infection in recipients of blood. We are continuing to consult with experts on WNV at the CDC and elsewhere to ensure the greatest possible safety of the blood supply. In addition, epidemiologic and laboratory investigations are rapidly evolving. We will evaluate promptly any new data or experiences related to this issue and provide further updates as appropriate.

Because symptoms occur in only approximately 20 percent of persons infected with WNV, donor exclusions based on health screening, and product retrievals based on reports of post-donation donor illness will have limited effectiveness. Laboratory screening tests to detect donor infections with WNV will be needed if the epidemic persists. Our current thinking is that we would recommend routine use of licensed donor screening tests to detect acute donor infections with WNV once such tests are available. If necessary, we also would allow widespread use of appropriate tests under an Investigational New Drug Application (IND).

III. RECOMMENDATIONS ON DONOR DEFERRAL

Consistent with existing regulations and applicable guidance, donors must be in good health at the time of donation (21 CFR 640.3 and 21 CFR 640.63). Standard procedures that are already in place should result in deferral of the estimated 20% of potentially infected donors who have symptoms consistent with WNV illness at the time of donation. Such persons are likely to develop a fever, headache, body aches, occasionally a skin rash on the trunk of the body, or swollen lymph glands and should be identified as not being in good health. We emphasize the potential importance of these measures in reducing the risk of transfusion transmitted WNV, particularly in areas where human cases are occurring. We are not proposing revisions to standard donor questions.

The following recommendations apply to cases of known or suspected WNV illness, or active infection. Although there are limited data on the natural course of WNV infection, the deferral periods we are recommending are based on the largest known viremic periods and an additional safety margin.

A. Diagnosed Acute West Nile Virus Illness or Infection

We recommend that a potential donor with a medical diagnosis of WNV infection (including diagnosis based on symptoms and laboratory results, or confirmed WNV viremia) be deferred until 14 days after the condition is considered to be resolved and at least 28 days from onset of symptoms or diagnosis whichever is the later date. In the absence of current or recent symptoms, an IgM positive antibody test result alone should not be grounds for deferral.

B. Suspected Acute West Nile Virus Illness or Infection

We recommend that donors who report an otherwise unexplained post-donation febrile illness suggestive of WNV infection in the setting of active WNV transmission in the community be deferred for 28 days from the onset of illness or 14 days after the condition is considered to be resolved whichever is the later date.

We recommend that blood donors whose blood or blood components were received by a patient with a possible case of transfusion related WNV should be deferred for 28 days from the date of potential transmission.

The following sites provide information that may be helpful to blood establishments in counseling of blood donors:

www.cdc.gov/ncidod/dvbid/westnile/clinical_guidance.htm

www.cdc.gov/ncidod/dvbid/westnile/city_state.htm

IV. RECOMMENDATIONS FOR RETRIEVAL AND QUARANTINE OF BLOOD AND BLOOD COMPONENTS INCLUDING RECOVERED PLASMA, SOURCE PLASMA, AND SOURCE LEUKOCYTES

We recommend that you actively encourage donors to report post donation illness potentially associated with WNV (i.e., flu-like symptoms that include a fever), occurring within 2 weeks of blood donation in the setting of active WNV transmission in the community.

We recommend that you quarantine and retrieve previously collected in-date units of blood and blood components intended for transfusion, as well as unpooled units of Source Plasma, recovered plasma and Source Leukocytes intended for further manufacturing into injectable products under the circumstances listed below.

A. Diagnosed West Nile Virus Infection or Illness in the Donor

We recommend that the in-date components from current, prior, and subsequent collections be quarantined and retrieved promptly if a donor later reports a medical diagnosis of WNV. Product quarantine and retrieval should cover a time period dating back to 14 days prior to the onset of illness and 28 days subsequent to the onset of illness. In the absence of symptoms, an IgM positive antibody test result alone should not be grounds for product quarantine and retrieval.

B. Blood Donors Associated with a Potential Case of Transmission to a Transfusion Recipient

Based on the observation that time to development of illness may be prolonged in some blood recipients, donors are considered to be potentially associated with transmission of WNV if the index recipient received their blood components within the 28 days before the onset of symptoms in the recipient. The collection from which the infected recipient received a blood component is regarded as a “suspect” donation from each such donor.

For each associated donor, prompt product quarantine and retrieval should be applied to in-date components that were collected in the period from 28 days prior to the suspect donation to 28 days after the suspect donation. (The 28-day period allows for the possibility of prolonged viremia in the potentially implicated donor, consistent with earlier studies in some patient groups.)

C. Undiagnosed Post-donation Illness in Potentially Exposed Individuals.

We recommend that blood establishment medical directors exercise judgment in assessing whether a donor’s illness may represent infection by WNV. In particular, we recommend that medical directors consider whether an otherwise unexplained post-donation febrile illness suggestive of WNV infection is occurring in the setting of active WNV transmission in the community. Current information on WNV activity in different

geographical areas can be found at www.cdc.gov/ncidod/dvbid/westnile/#case or by contacting the local or state public health department. If a decision is made to quarantine and retrieve prior collections, then product quarantine and retrieval should be performed promptly and should include the current donation and any others that date back to 14 days prior to the onset of symptoms in the donor. We recommend that quarantine or retrieval of blood or blood components not be performed for otherwise suitable donors who report mild symptoms of upper respiratory infection unassociated with fever or for donors who only report mosquito bites.

In the event that Source Plasma, recovered plasma or Source Leukocytes have been pooled for fractionation, quarantine and retrieval are not recommended. FDA has reviewed the viral reduction processes in place for all plasma derivatives. The methods in place have been validated to inactivate flaviviruses related to WNV.

V. RECOMMENDATIONS ON NOTIFICATION OF PRIOR TRANSFUSION RECIPIENTS

When a blood establishment receives information that a donor has a medical diagnosis of WNV, we recommend that establishments consider tracing records and notifying transfusion services so that they, in turn, may notify treating physicians of prior recipients of blood and blood components collected from that donor. We consider relevant units to be those dating from 14 days prior through 28 days after the onset of illness in the donor. Conversely, if a post-donation illness is not diagnosed as WNV infection, record tracing and notification of the transfusion services to identify prior recipients of blood and blood components collected from that donor would not be appropriate.

In cases where an epidemiological investigation suggests that a specific donor is the likely source of transmission of WNV to a transfusion recipient, we recommend that blood establishments consider tracing records and notifying transfusion services so that they, in turn, may notify treating physicians of prior recipients of blood and blood components collected from that donor. We consider relevant units to be those dating from 28 days prior to 28 days subsequent to the date of the donation that was implicated in transmission of WNV. However, in cases where a donor is potentially associated with a case of transmission of WNV, but the epidemiological investigation has not established the specific donor as a likely source of transmission of WNV, notification of the transfusion services would not be appropriate.

VI. BIOLOGIC PRODUCT DEVIATION AND FATALITY REPORTING

Regulations on Reporting of Product Deviations by Licensed Manufacturers, Unlicensed Registered Blood Establishments, and Transfusion Services are at 21 CFR 606.171. Pursuant to these regulations, blood and plasma collection establishments must submit biological product deviation reports in instances of post-donation information related to WNV in cases where product retrieval and quarantine and/or notification of recipients of prior or subsequent collections from the donor occurs. Additionally, if a suspect donation results in fatality in a

transfusion recipient, blood establishments must report the fatality to the FDA [21 CFR 606.170(b)], and the cases of WNV should be reported to the CDC.

VII. LABELING OF PRODUCTS DISTRIBUTED FOR RESEARCH OR INTENDED FOR FURTHER MANUFACTURING INTO NON-INJECTABLE PRODUCTS

Quarantined products described in Section IV above, that are distributed for further manufacturing into non-injectable products or for research use should be labeled consistent with recommended labeling described below:

"Biohazard;"

"Collected from a donor determined to be at risk for West Nile Virus," or "Collected from a donor positive for evidence of infection with West Nile Virus;" and

"For laboratory research use only" or "Intended only for further manufacturing into non-injectable products," whichever is applicable.

VIII. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance immediately. Consistent with 21 CFR 601.12, licensed establishments implementing these recommendations should submit by official correspondence a statement in their annual reports indicating the date that the revised standard operating procedures, consistent with these recommendations, have been established and implemented. These changes do not require our prior approval.

IX. REFERENCES

1. Petersen, Lyle R. and Marfin, Anthony A.(2002); *Annals of Internal Medicine*, vol. 137(3) pages 173-179.
2. Biggerstaff, Brad I. and Petersen, Lyle R. (2002); *Transfusion*, vol. 42 pages 1019–1026.
3. *MMWR* (2002) vol. 51 (35) 790-791.
4. *MMWR* (2002) vol. 51 (36) 823.
5. *MMWR* (2002) vol. 51 (37), 825-828.
6. *MMWR* (2002) vol. 51 (37), 833-836.
7. *MMWR* (2002) vol. 51 (37) 1-2.
8. *MMWR* (2002) vol. 51 (37) 825-828.
9. *MMWR* (2002) vol. 51 (39), 879.
10. *MMWR* (2002) vol. 51 (39), 884-895.
11. Brinton, Margo A. (2002) *Annual Review of Microbiology*, vol. 56 pages 371-402.
12. Kramer, L.D., and Bernard, K.A. (2001) *Current Opinion in Infectious Diseases* vol. 14, pages 1-7.
13. Martin, D., et al. (2002) *Clinical Diag. Lab. Immun.* 9, 544-549.
14. Tardei, G., et al. (2002) *J. Clin. Micro* 38, 2232-2239.
15. Southam, C.M. and Moore, A.E. (1954) *Am. J. Trop. Med. Hyg.* 3, 19-50.