Guidance for Industry

Revised 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.

This guidance supersedes the October 2002 guidance, issued in final for immediate implementation with an opportunity for public comment on the guidance after issuance. The agency received no comments on the October 2002 guidance.

FDA invites comments on this document. Please submit comments at anytime 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 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)
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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance document provides our revisions to our previously published recommendations for assessing donor suitability and product safety for donors with proven West Nile Virus (WNV) infections or with illnesses potentially due to WNV (October 2002). To better identify donors potentially at risk for WNV, this revised guidance adds a new recommendation to ask donors a specific question about history of fever with headache within the week prior to donation. This guidance applies to Whole Blood and blood components intended for transfusion and blood components intended for use in further manufacturing into injectable products or non-injectable products, including recovered plasma, Source Leukocytes and Source Plasma. Within this document, "donors" refers to donors of all such 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. This guidance does not apply to tissue establishments or human cells and tissues other than blood. However, tissue establishments may consider implementing similar donor screening practices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

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 mammals including horses, cats, and domestic mammals. 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. WNV was first identified in the United States 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 United States. In 2001, 66 human cases of WNV encephalitis or meningitis occurred in 10 states. In 2002, a major epizootic outbreak of WNV was detected in many parts of the United States combined with the largest human WNV meningoencephalitis outbreak ever documented, and the largest outbreak of meningoencephalitis from any cause in North America. In 2002, the number of human cases far surpassed those reported in 2001 with 4161 cases of WNV illness and 277 deaths reported as of March 12, 2003. Ninety-nine percent of the human cases occurred between July 1 and October 31, 2002. Human cases were reported in 736 counties in 39 states and the District of Columbia. The 2002 WNV epidemic involved the first documented cases of WNV transmission through organ transplantation, blood transfusion and possibly breastfeeding. (Ref. 1) In addition, intrauterine infection was reported. It appears that the peak of the 2002 WNV epidemic occurred in August – late September 2002 and abated as female mosquitoes entered diapause (dormant state) and stopped biting. Nevertheless, it is possible that year round transmission may occur in southern states with warmer winter climates. It is not possible to predict whether there will be an epidemic of WNV infection in 2003 or in the future.

The pre-clinical incubation period is thought to range from 2–14 days following infection by mosquito bite. Although most people infected with WNV (~80%) remain asymptomatic, approximately 20% of those infected will develop mild symptoms, which are often indistinguishable from other viral infections. These symptoms may include fever, headache, body aches, gastrointestinal complaints, eye pain, or occasionally a generalized rash, or swollen lymph nodes.

It is estimated that 1 in 150 – 200 persons infected with WNV develops a more severe form of the disease. Severe disease may culminate in fatal encephalitis in about 1 in 1000 infections. The risk of severe disease increases by age, with persons older than 50 years at particular risk. Persons who are immunocompromised appear to be at very high risk. Severe illness may include encephalitis, meningitis, meningoencephalitis, or acute flaccid paralysis, which may occur singly or in combination. Symptoms may include: headache, high fever, neck stiffness, stupor,

disorientation, coma, tremors, convulsions, and muscle weakness or paralysis. Severe symptoms may last weeks to months, and some permanent neurologic impairment may occur. Case fatalities among patients who were hospitalized in the United States 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 may occur within 1-3 days following infection by mosquito bite, and last 1–11 days (with a mean of 6 days), although longer periods of viremia were noted in some patients with advanced malignancies or who were taking immunosuppressive drugs. (Ref. 2) Currently there are no FDA approved tests for WNV medical diagnosis or donor screening; however, we have actively encouraged development of such tests. In particular, we are facilitating the development of donor screening tests that may be practically implemented on a large scale. At the meeting of the Blood Products Advisory Committee on March 13, 2003, several manufacturers presented preliminary data on screening and diagnostic tests currently under development. (Ref. 3) WNV diagnostic testing based on detection of immunoglobulin M (IgM) antibodies to WNV can be obtained through local or state health departments. In at least 90% of patients, IgM antibodies against WNV can be detected in sera or cerebral spinal fluid collected on or after 8 days of illness 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. Once developed, IgM antibodies persist for greater than 6 months after illness in over 50% of patients and may be detected for up to 500 days. Due to the persistence of IgM antibodies to WNV, a positive test for IgM is not suggestive of an acute infection by WNV unless it is associated with a recent compatible illness. WNV antibodies are known to cross-react 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 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 United States. 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.

At this time, we believe WNV is unlikely to be transmitted through derivatives manufactured from plasma, since lipid-enveloped RNA virus(es) such as WNV should be removed and/or inactivated during manufacture of plasma derivatives. (Ref. 4, 5) Although direct studies on the clearance of WNV during manufacturing of plasma derivatives are limited, licensed plasma derivatives undergo intentional viral clearance procedures that are validated to be effective against lipid-enveloped RNA viruses. These procedures include: filtration, heating,

acidification, and detergent treatment. Based on any new scientific information about the safety of plasma derivatives, we intend to revise these recommendations as appropriate.

Transmission by Blood Transfusion

Between August 28, 2002 and March 1, 2003, the Centers for Disease Control and Prevention (CDC) received reports of 61 possible cases of transfusion transmitted WNV infection. Since a large number of WNV infections resulting from mosquito bites have occurred in the United States, including the areas where these cases occurred, recent receipt of a blood transfusion by a person with WNV infection did not necessarily indicate that the transfusion was the source of infection. Nevertheless, based on epidemiological and laboratory data, the CDC concluded that WNV can be transmitted through blood transfusion. Testing of retained donor blood samples, where available, and epidemiological investigations demonstrated that transfusion transmission was the likely source of WNV infection in 21 of these cases. WNV meningoencephalitis was diagnosed in 12 patients and WNV fever in one patient. Onset of illness was between 2 and 21 days (median 11 days) after the implicated transfusion. The 21 cases involved 14 implicated donors. Seven instances of transmission to two or more patients occurred when the patients received different blood products derived from a single blood donation subsequently found to have evidence of WNV. Nine of the 14 donors reported symptoms compatible with WNV infection before or after donation. In one instance, WNV was isolated from a withdrawn unit of frozen plasma from the suspect donation, indicating that the virus can survive in frozen 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. (Ref. 6)

To assist in identification of other possible cases of WNV infection potentially associated with transfusion, patients with diagnosed WNV infection who have received blood transfusions or organs within the 4 weeks preceding the onset of symptoms should be reported to CDC through state and 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, medical directors of blood establishments are recommended to carefully evaluate the potential need for product quarantine and retrieval and consult FDA if necessary.

On October 25, 2002, we issued guidance to industry on Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection. At that time we did not recommend changes to standard donor screening and blood collection procedures to identify or otherwise query donors who may have been exposed to WNV. This policy was based on the assessment that there was 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. We recommend that donors who are symptomatic at the time of donation be excluded from donation. Additionally, we are advising blood collection centers to actively encourage donors to report post-donation illnesses that could be associated with infection by WNV.

The most common flu-like symptom reported from donors implicated in the 2002 cases of transfusion-transmitted WNV infection were fever and headache. (Ref. 3) Based on extrapolations from a survey of current donors, the implementation of a donor question regarding fever with headache in the week prior to donation will result in less than a 1.0 % donor loss. 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 pre-donation or post-donation illnesses in the donor, or WNV infection in recipients of blood.

Our recommendation is that you initiate implementation of a donor deferral question regarding history of fever with headache in the last week no later than June 1, 2003. You may discontinue asking this donor deferral question after November 30, 2003. Additionally, at this time, we are recommending that the relevant donor deferral question be asked each year between June 1 and November 30. Note that the applicable period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV, and end later in states where human infections with WNV are reported in November. We are continuing to consult with experts on WNV at the CDC and elsewhere to ensure the greatest possible safety of the blood supply. Epidemiological and laboratory investigations are rapidly evolving; therefore, we promptly will evaluate 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 results to detect donor infections with WNV will be needed if the epidemic persists. Our current thinking is that we would recommend routine and appropriate use of licensed donor screening tests to detect acute donor infections with WNV once such tests are available. We also anticipate that appropriate tests could be used in widespread investigational studies conducted under FDA regulations.

III. RECOMMENDATIONS ON DONOR DEFERRAL

Consistent with existing regulations and applicable guidance, donors must be in good health at the time of donation and free of diseases transmissible by blood (21 CFR 640.3 and 21 CFR 640.63). Standard procedures that are already in place should result in deferral of potentially

infected individuals who have symptoms consistent with WNV illness at the time of donation. Such individuals are likely to manifest fever, headache, eye pain, body aches, a generalized skin rash, or swollen lymph nodes. WNV transmission has occurred from donors with an unexplained febrile illness within one week prior to donation. In the interest of reducing the risk of transfusion transmitted WNV we are recommending a donor deferral procedure that is based upon the characteristics of infection reported in humans in 2002. We recommend that this procedure be initiated by June 1, 2003. Medical directors may decide to implement this question earlier than June 1, 2003. Note that the applicable period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV. 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, plus an additional safety margin.

A. Diagnosed Acute West Nile Virus Illness or Infection

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

B. Suspected Acute West Nile Virus Illness or Infection

1. Predonation question:

Prior to blood donation, we recommend that donors be asked about fever with headache in the past week. For example:

"In the past week, have you had a fever with headache?"

If no, do not defer.

If yes, defer for 28 days from the date of interview.

Pending implementation in the donor questionnaire of a donor question about fever with headache in the past week, some blood establishments may wish to utilize a printed information sheet as a mechanism to provide donors with appropriate background information on WNV, and an appropriate question. In such cases, we recommend that you specify how the donor will be instructed to respond, and how the response will be documented, consistent with the requirements in 21 CFR 606.160(b)(1)(i). We believe that this practice may be used on a short term basis. In the long term, we believe that incorporation of all donor screening questions into the donor questionnaire will better assure that an adequate record of the donor interview is maintained.

Our recommendation is that you question donors beginning on June 1 of each year and discontinue asking donors this question after November 30. Note that the applicable

period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV, and end later in states where human infections with WNV are reported in November. If human infections with WNV are reported in your state in November, we recommend the continued use of the donor deferral question until there have been at least two consecutive weeks without any report of human infection in your state.

2. Post Donation information

We recommend that donors who report between June 1 and November 30 an otherwise unexplained post-donation febrile illness with headache or other symptoms suggestive of WNV infection (i.e. flu-like symptoms that include fever with headache, eye pain, body aches, generalized weakness, new skin rash or swollen lymph nodes or other evidence of WNV infection), 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. Note that the applicable period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV, and end later in states where human infections with WNV are reported in November.

We recommend that blood donors whose blood or blood components were potentially associated with a transfusion-related WNV transmission be deferred for 28 days from the date of the implicated donation. 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_states.htm

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

We recommend that between June 1 and November 30 you actively encourage donors to report unexplained post-donation febrile illness with headache or other symptoms suggestive of WNV infection (i.e. flu-like symptoms that include fever with headache, eye pain, body aches, generalized weakness, new skin rash or swollen lymph nodes), occurring within one week after blood donation. Note that the applicable period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV, and end later in states where human infections with WNV are reported in November.

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

We recommend that in-date components from relevant collections be quarantined and retrieved promptly if a donor later reports a medical diagnosis of WNV. Relevant collections include those occurring between 14 days prior to the onset of illness and either 28 days subsequent to the onset of illness, or 14 days after the condition is considered to be resolved, whichever is the later date.

(The 28-day periods allow for the possibility of prolonged viremia in an individual with diagnosed WNV infection, consistent with earlier studies in some patient groups). Absent a recent compatible illness, an IgM positive WNV 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 a recipient of blood or transfusible blood components is diagnosed with WNV and received 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, we recommend that you conduct prompt product quarantine and retrieval for in-date components collected in the period between 28 days before the suspect donation and 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 medical directors exercise judgment in assessing whether a donor's illness may represent infection by WNV, in particular, during the dates of WNV transmission potential recommended in this guidance (June 1 to November 30). We recommend that medical directors consider whether an otherwise unexplained post-donation febrile illness suggestive of WNV infection is occurring. Note that the applicable period may start earlier in local areas where the medical director is aware of reports of epizootic activity or human transmission of WNV, and end later in states where human infections with WNV are reported in November.

Current information on WNV activity in different geographical areas can be found at www.cdc.gov/ncidod/dvbid/westnile/city_states.htm, or by contacting the local or state public health department. WNV data from state health departments (by county) can also be accessed at www.npic.orst.edu/wnv/statelinks.htm.

When you decide to quarantine and retrieve in-date prior collections, we recommend that you do so promptly, and 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

A blood establishment may receive information that a donor has a medical diagnosis of WNV that is relevant to prior donations. We recommend that establishments that receive such information consider tracing records and notifying transfusion services so that they, in turn, may consider notifying 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. If a post-donation illness is not diagnosed as WNV infection, we are not recommending record tracing and notification of the transfusion services to identify prior recipients of blood and blood components collected from that donor.

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 consider notifying treating physicians of prior recipients of relevant units 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, we are not recommending notification of the transfusion services.

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. Under 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

We recommend that quarantined products described in Section IV above, that are distributed for further manufacturing into non-injectable products or for research use, 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 as soon as feasible, but not later than 30 days after the guidance issue date. 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

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6. MMWR (2002) vol. 51 (35) 790-791.