Guidance for Industry

Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (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/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
June 2005

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry

Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection

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

This guidance document finalizes the draft "Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection," dated April 2005, and provides revisions to our previously published final guidance entitled "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," dated May 2003. We, FDA, recommend that these revised recommendations be applied prospectively, i.e., that actions taken under previous guidance do not need to be reconsidered subject to the additional provisions of this guidance. This guidance revises the final May 2003 West Nile Virus (WNV) guidance to add a recommendation to defer donors suspected of having WNV infection or diagnosed with WNV infection for 120 days after diagnosis or onset of illness, whichever is later.

This guidance further recommends that donors be deferred on the basis of a reactive investigational screening test for WNV. At their discretion, blood establishments may reenter such donors after 120 days from the date of their reactive donation. Although we are not at this time recommending additional testing of the donor during the recommended 120 day deferral period, individual donation testing using a nucleic acid test (IDT NAT) for WNV on a follow-up sample obtained during the 120 day deferral period will provide useful additional scientific information on the duration of WNV viremia in donors. If such a follow-up sample is reactive for WNV, we recommend that the donor be deferred for an additional 120 days from the date the sample was collected.

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, and "you" refers to blood establishments. We use the term "typical WNV season" to mean May 1 to November 30; however, isolated WNV infections may occur at any time during the year. We recommend that

your Medical Director monitor reports of epizootic activity or human transmission of WNV in your local area throughout the year. We developed the recommendations in this guidance in consultation with other Public Health Service agencies of the Department of Health and Human Services (HHS). This guidance does not apply to human cells, tissues, and cellular and tissue-based products that are subject to 21 Code of Federal Regulations (CFR) Part 1271.

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.

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. While only limited data specific to the inactivation of WNV are available, other members of the flaviviridae family are 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 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.

A. U.S. Experience with WNV

WNV was first identified in the United States in 1999 as 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. The 2002 epidemic of WNV neuroinvasive disease was the largest ever reported. In 2002, 4,156 cases of human illness were reported, including 2,946 neuroinvasive disease cases and 284 fatalities. In 2003, a total of 9,862 cases of human illness, including 2,775 neuroinvasive disease cases and 264 fatalities, were reported. While more human illnesses were reported in 2003 than in 2002, the number of neuroinvasive disease cases and fatalities were comparable. In 2002, 28% of the cases reported were West Nile fever; in 2003, 69% were West Nile fever. The Centers for Disease Control and Prevention (CDC) stated in 2002 that West Nile fever is underreported, but as described above, reporting increased in 2003 due in

part to increased awareness by public health providers and officials, the availability of two FDA-cleared WNV diagnostic tests, and the widespread use of the investigational WNV NAT in the blood donation setting. The 2002 WNV epidemic involved the first documented cases of WNV transmission through organ transplantation, blood transfusion and possibly breastfeeding (Refs. 1-3). In addition, intrauterine infection was reported. Based upon two years of epidemiologic observation, it appears that the peak WNV epidemic period occurs in August to late September and abates as female mosquitoes enter diapause (dormant state) and stop biting.

In the 2004 WNV epidemic, CDC reported WNV activity in 47 continental states, with 2,470 reported human cases and 88 fatalities (Ref. 2). A total of 199 presumptive WNV NAT reactive donors were observed in 28 states. Although the reported levels of human infection were lower than the same period in 2003, projections for the distribution and extent of WNV infection in 2005 are unknown. CDC advised that it is likely that WNV activity may still occur in areas that experienced high levels of epidemic and epizootic infection in previous years. The earliest onset of human infection in the United States was in July 2000 and 2001; May 2002; and April 2003 and 2004. However, WNV activity in birds and mosquitoes has been documented year-round in states with warm winter climates. Human infection in these areas is a theoretical risk at all times of the year.

The pre-clinical incubation period is thought to range from 2 to 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 generalized rash or swollen lymph nodes. Limited published data prior to 2004 suggested that a transient WNV viremia occurs within 1 to 3 days following WNV infection by mosquito bite, and lasts 1 to 11 days (with a mean of 6 days). Longer periods of viremia were noted in some patients with advanced malignancies or who were taking immunosuppressive drugs (Ref. 4). More recently, viremia in asymptomatic donors has been shown to persist for longer periods of time, including 104 days after initial detection by NAT in a single donor (see below). However, studies are ongoing. It is estimated that 1 in 150 persons infected with WNV develops a more severe form of the disease. Among individuals with severe disease, fatality-to-case ratios range from 4 to 14%, with higher ratios in older age groups.

Preliminary evidence suggests that solid organ recipients are at increased risk of neuroinvasive disease, perhaps due to their immunocompromised condition. The risk of neuroinvasive disease in persons who are immunocompromised (e.g., due to AIDS or primary immune deficiencies) is unknown. 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. Currently, treatment for WNV disease is supportive. In severe cases, this often

involves hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. Case fatalities among patients who were hospitalized in the United States with severe WNV illness have ranged from 10 to 14%. CDC has designated WNV encephalitis as a nationally notifiable arboviral encephalitides (Refs. 4 and 5).

In 2003, FDA cleared WNV antibody tests that separately detect Immunoglobulin G (IgG) or Immunoglobulin M (IgM) anti-WNV antibodies for use in the diagnosis of WNV infection (PanBio Limited and Focus Technologies, Inc.). Additionally, HHS, through FDA, encouraged the development and implementation of investigational WNV NAT for detection of WNV RNA in the blood donation setting. In June 2003, blood banks began participating in studies under FDA's Investigational New Drug (IND) regulations involving the use of investigational NATs from two test-kit manufacturers. Initial screening protocols included NAT performed on mini-pools (MP NAT) of samples from six or 16 donations, depending on the test-kit manufacturer. Reactive mini-pools were resolved by IDT NAT. In addition, selected blood banks in areas with high epidemic activity implemented IDT NAT screening during limited periods of the epidemic season. Donations that were IDT NAT reactive were not released for transfusion, and donors were deferred from donation. It is estimated that, through 2004, at least 1,017 presumptively viremic donations were removed from the blood supply as a result of blood establishment's voluntary participation in WNV NAT screening studies.

In the studies, many of the donors of NAT reactive samples identified by either screening method agreed to participate in follow-up studies to confirm WNV infection and evaluate the persistence of WNV RNA in blood samples collected subsequently. Certain studies have shown that blood donors found to be WNV-positive at the time of donation may, in rare instances, demonstrate a low level viremia in the presence of IgM antibodies for as long as 49 days after initial NAT reactivity (mean duration 20.5 days). The estimated range for duration of viremia of 6.5 to 56.4 days represented 99% of the population in one mathematical model with a time to loss of viremia of 48 days for 99% of the population following detection by MP NAT (Ref. 6). A second model, using a different donor base but including the donor detected at 49 days, estimated 31 days to negative RNA by individual donor NAT from the index reactive donation for 99% of the population. These investigational studies are ongoing. In one unpublished study, a single donor was found to be IDT NAT reactive after 104 days on one of five replicate tests. Additionally, preliminary data from FDA laboratories have indicated WNV infectivity in blood from 7 of 16 WNV NAT reactive individuals who were also seropositive for WNV antibodies, when inoculated into Vero cell and human macrophage tissue cultures. These data indicate that live virus may circulate despite the presence of antibodies to WNV, but do not clarify whether blood components obtained from individuals at this stage of infection can transmit WNV.

At this time, we believe WNV is unlikely to be transmitted through derivatives manufactured from plasma, since lipid-enveloped RNA viruses such as WNV would be removed and/or inactivated during manufacture of plasma derivatives (Ref. 7). Although direct studies on the clearance of WNV during manufacturing of plasma derivatives are limited (Refs. 7-10), 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 solvent/detergent treatment. We intend to revise these recommendations as appropriate as new scientific information about the safety of plasma derivatives becomes available.

B. WNV Transmission by Blood Transfusion

Between August 28, 2002 and March 1, 2003, the CDC received reports of 61 possible cases of transfusion transmitted WNV infection. Epidemiological investigations and testing of available retained donor blood samples demonstrated that blood transfusion was a confirmed source of WNV infection in 23 of these cases, with 19 cases remaining inconclusive. West Nile Virus infection was ruled out in the remaining 19 cases. Fifteen confirmed WNV post-transfusion cases had symptomatic illness, including 13 with meningoencephalitis and two with fever. Onset of illness was between 2 and 21 days (median 10 days) after the implicated transfusion. Fourteen WNV viremic donors were implicated in the 23 transfusion-associated cases. Seven instances of transmission to two or more patients occurred when the patients received different blood components 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 four instances, WNV was isolated from the withdrawn unit of frozen plasma collected as part of the suspect donation, indicating that the virus can survive in frozen blood components (Ref. 11). 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. 12).

During May to December 2003, an additional 23 suspected cases of WNV transfusion transmission were reported to CDC. Of these 23 cases, public health authorities reported 15 suspected cases of WNV transfusion transmission among patients who had WNV illness after receiving transfusions. The other eight suspected cases were in recipients of components derived from low-level viremic donations that were identified during special retrospective studies of MP NAT negative blood retested with IDT NAT by two blood organizations. Follow-up of these eight cases was performed to determine whether WNV infection had resulted from the implicated transfusions. As a result of these 23 investigations, six cases were classified as confirmed or probable WNV transmission by transfusion, 11 as non-cases, and six cases remained unresolved. Retained donation samples from four of the six confirmed or probable cases had a low viral titer (~0.11 pfu/ml) (Ref. 3).

In 2004, there was one confirmed case of WNV transmission attributed to blood screened by investigational MP NAT. The case resulted in severe WNV encephalitis in the recipient. The source of the infection was identified as a platelet transfusion for which plasma aliquot had been saved. This plasma was subsequently shown to have low level WNV viremia by an investigational IDT NAT. Seroconversion of the donor was also observed at the time of follow-up (Ref. 13). To assist in identification of other possible cases of WNV infection potentially associated with transfusion, state and local public health authorities report to CDC cases where patients with diagnosed WNV infection have received blood transfusions or organs within the eight weeks preceding the onset of symptoms. In addition, the Public Health Service has requested that cases of WNV infection in donors who had onset of symptoms within two weeks of blood or organ donation be reported to CDC through state and local public health departments. Retention by blood establishments of potentially affected blood products (e.g., frozen plasma units from donors whose red cells or platelets were given to the affected recipient), and, where available, samples of blood and tissue from the affected recipients may facilitate the epidemiological investigation in such cases.

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 procedures to screen donors for symptomatic infection. We also recommended that when cases of probable or proven WNV infection are discovered post-donation, medical directors of blood establishments carefully evaluate the potential need for component quarantine and retrieval and consult FDA if necessary.

On October 25, 2002, we issued guidance to industry, "Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection." On May 1, 2003, we issued revised guidance to industry to recommend deferral of donors who reported fever with headache in the week before donation. Additionally, we recommended that blood establishments actively encourage donors to report post-donation illnesses that could be associated with infection by WNV. Our previous guidance recommended that donors be deferred for a period of 28 days based on information from older studies of the longest known viremia.

At the time we issued the May 2003 revised guidance, investigational donor screening for WNV infection was not yet available. Limited donor interview data were available regarding possible WNV-related symptoms that occurred in a period of three weeks prior to an implicated donation. Based upon the potential for a combination of these symptoms to be predictive of early WNV infection in the absence of testing, we recommended the deferral of donors reporting fever with headache in the week prior to donation. We recognized at that time that symptoms occur in only approximately 20% of persons infected with WNV and that only a portion of the implicated donors reported symptoms prior to donation.

At the October 22, 2004, meeting, the Blood Products Advisory Committee (BPAC) heard scientific presentations that viremia associated with WNV infection rarely

extended up to 49 days following a WNV NAT-positive donation. Data presented at the October 2004, BPAC meeting (Ref. 6) also indicated that self-reported fever with headache in the past week before donation did not appear to be predictive of WNV infection and did not correlate with peak periods of WNV incidence as determined by WNV NAT prevalence in the donor pool. Based upon these data, we no longer recommend donor deferral based upon a reported history of headache with fever in the week prior to donation.

We are continuing to consult with experts on WNV at the CDC and elsewhere to ensure the safety of the blood supply from WNV infection. Epidemiological and laboratory investigations are rapidly evolving; therefore, we will evaluate promptly any new data or experiences related to this issue and provide further updates as appropriate.

The prevalence of WNV seropositivity among blood donors in 2003 and 2004 indicates that WNV NAT testing of donated blood in response to annual epidemics is likely to continue for the foreseeable future. The Public Health Service has worked with device manufacturers and blood organizations to facilitate the availability of investigational tests and to develop more focused testing strategies for areas of high infection incidence, and we are working with manufacturers to make licensed tests available in the near future.

III. RECOMMENDATIONS FOR DONOR DEFERRAL

Donors must be in good health at the time of donation and free of diseases transmissible by blood (21 CFR 640.3 and 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.

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 a 14 day asymptomatic incubation period and a 120 day potential viremic period, which includes all known observations of prolonged viremia plus an additional margin of safety.

A. Diagnosed or Suspected Acute WNV Illness or Infection

In the course of routine medical screening, donors may volunteer symptom histories that reflect WNV infection. We recommend that you defer a potential donor with a medical diagnosis or suspicion of WNV infection (based on symptoms and/or laboratory results)

for 120 days following diagnosis or onset of illness, whichever is later. At your discretion, you may reenter such donors after the 120 day deferral period.[1]

In the absence of a WNV compatible illness in the previous two weeks, an IgM positive WNV antibody test result alone should not be grounds for deferral provided that the donor was tested and found to be negative for WNV by MP or IDT NAT at the time of collection.

B. Presumptive Viremic Donors

We recommend that you defer a donor who has tested reactive for WNV infection using the investigational WNV NAT donor screening tests. At your discretion, you may reenter such donors after 120 days from the date of their reactive donations (see footnote 1).

C. Suspected WNV Illness in a Donor

We recommend that donors who report 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) within two weeks after donation during the typical WNV season (or at other times when your Medical Director determines that there is evidence of local WNV activity), be deferred for 120 days following the onset of illness.

D. Donors Who May Have Transmitted WNV Infection

We recommend that blood donors whose blood or blood components were potentially associated with a transfusion-related WNV transmission be deferred for 120 days following the date of donation. At your discretion, you may reenter such donors after 120 days from the date of donation (see footnote 1). The following sites provide information that may be helpful to blood establishments in counseling blood donors:

http://www.cdc.gov/ncidod/dvbid/westnile/clinical_guidance.htm
http://www.cdc.gov/ncidod/dvbid/westnile/city_states.htm

[1] As discussed in the introduction to this guidance, we are not at this time recommending additional testing of the donor during the recommended 120 day deferral period. However, we encourage you to perform IDT NAT for WNV on a follow-up sample obtained from such donors during the 120 day deferral period because of the additional scientific information that might be obtained on the duration of WNV viremia in donors. If a follow-up sample is reactive for WNV, we recommend that the donor be deferred for an additional 120 days from the date the sample was collected.

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

As a prudent measure to address the possible risk of transmission of WNV by blood transfusion, we are providing revised recommendations for component retrieval and quarantine related to reports of post-donation illnesses in the donor, or association with WNV infection in recipients of blood.

During a typical WNV season, we recommend that you actively encourage donors to report unexplained post-donation febrile illnesses 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 two weeks after blood donation.

A. Diagnosed WNV Infection or Illness in a 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 an asymptomatic incubation period of 14 days prior to onset of illness and up to and including 120 days after diagnosis or onset of illness, whichever is later. Absent a recent compatible illness, a positive WNV antibody test result alone should not be grounds for product quarantine and retrieval provided that the donor did not test positive for WNV by MP or IDT NAT at the time of collection.

B. Presumptive Viremic Donors

We recommend that in-date components from relevant collections be quarantined and retrieved promptly if a donor has tested reactive for WNV infection using the investigational WNV NAT donor screening test. Relevant collections include those occurring between 120 days prior to the date of the reactive test and 120 days after the date of the reactive test.

C. Donors Who May Have Transmitted WNV Infection

Based on the observation that time to development of illness may be prolonged in some blood recipients, we consider a donor 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 from the donor within the 120 days before the onset of symptoms in the recipient. The collections from which the infected recipient received a blood component are regarded as “suspect” donations. We recommend that you conduct prompt product quarantine and retrieval for in-date components collected from the donor of a suspect donation in the period between 120 days before the suspect donation and up to and including 120 days after the suspect donation.

D. Undiagnosed Post-Donation Illness in Potentially Exposed Individuals

We recommend that you conduct quarantine and retrieve in-date prior collections only if your medical director concludes that a donor's febrile illness represents likely infection by WNV, taking into account whether the illness occurs during the typical WNV season, or following donor exposure in an area with an extended outbreak of WNV. Current information on WNV activity in different geographical areas can be found at http://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 http://www.npic.orst.edu/wnv/states.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 an asymptomatic incubation period of 14 days prior to the onset of symptoms in the donor and 120 days after onset of symptoms. We do not recommend that quarantine or retrieval of blood or blood components 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 you decide to conduct quarantine and retrieval of Source Plasma, recovered plasma or Source Leukocytes, we do not recommend quarantine and retrieval of those products once they have been pooled for fractionation. We have 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 an asymptomatic incubation period of 14 days prior, through 120 days after, the onset of illness in the donor. If a post-donation illness is not diagnosed as WNV infection, we do not recommend that you consider 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 (e.g., WNV infection was later confirmed in the donor, and the donor was the sole source of blood received by the affected recipient; or multiple blood component recipients developed WNV infection and had the donor in common), 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 120 days prior, to 120 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 do not recommend that you consider notifying 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 in 21 CFR 606.171. Under these regulations, you must submit biological product deviation reports when you distribute a product and an event occurred while the product was in your control. An event is reportable if it is associated with product manufacture and it either represents a deviation from current good manufacturing practice or specifications that may affect the safety, purity, or potency of the product, or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product. The receipt of post donation information concerning a diagnosed or suspected WNV infection would be reportable under this section, because collection from a donor who may have been infectious at the time of donation would be an unexpected event that may affect the safety, purity, or potency of the product. Additionally, if a suspect donation results in fatality in a transfusion recipient, you must report the fatality to the FDA (21 CFR 606.170(b)).

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

We recommend that quarantined components 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 issuance of this guidance. Consistent with 21 CFR 601.12(d)(3)(ii), licensed establishments implementing these recommendations must submit a statement in their annual reports indicating the date that the revised standard operating procedures were implemented. These changes do not require our prior approval.

IX. REFERENCES

1. Possible West Nile Virus Transmission to an Infant Through Breast-Feeding–Michigan, 2002. MMWR Morb Mortal Wkly Rep 2002; 51:877-8.
2. http://www.cdc.gov/ncidod/dvbid/westnile/index.htm
3. Update: West Nile Virus Screening of Blood Donations and Transfusion-Associated Transmission – United States, 2003. MMWR Morb Mortal Wkly Rep 2004; 53:281-284.
4. Petersen, L.R., Marfin, A.A. West Nile Virus: A Primer for the Clinician. Ann Intern Med 2002; 137:173-179.
5. http://www.cdc.gov/epo/dphsi/nndsshis.htm
6. Blood Products Advisory Committee meeting, October 22, 2004. http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4074t2.htm
7. Kreil, T.R., Berting, A., Kistner, O., Kindermann, J. West Nile Virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. Transfusion 2003; 43:1023-8.
8. Mather, T., Takeda, T., Tassello, J., et al. West Nile Virus in blood: stability, distribution, and susceptibility to PEN110 inactivation. Transfusion 2003; 43:1029-37.
9. Jakubik, J.J., Vicik, S.M., Tannatt, M.M., Kelley, B.D. West Nile Virus inactivation by the solvent/detergent steps of the second and third generation manufacturing processes for B-domain deleted recombinant factor VIII. Haemophilia 2004; 10:69-74.
10. Mohr, H., Knuver-Hopf, J., Gravemann, U., et al. West Nile Virus in plasma is highly sensitive to methylene blue-light treatment. Transfusion 2004; 44:886-90.
11. Pealer, L.N., Marfin, A.A., Petersen, L.R., et al. Transmission of West Nile Virus through blood transfusion in the United States in 2002. N Engl J Med 2003; 349:1236-45.
12. Update: Investigations of West Nile Virus Infections in Recipients of Organ Transplantation and Blood Transfusion – Michigan, 2002. MMWR Morb Mortal Wkly Rep 2002; 51:879.
13. Transfusion-Associated Transmission of West Nile Virus – Arizona, 2004. MMWR Morb Mortal Wkly Rep 2004; 53:842-844.