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(b) a wider band of time encompassing the full period during which your medical director is aware of reports of epizootic activity or human transmission of WNV in your local area. We developed the recommendations in this guidance in consultation with other Public Health Service Agencies of the Department of Health and Human Services. 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. 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.

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, 4156 cases of human illness were reported, including 2946 neuroinvasive disease cases and 284 fatalities. In 2003, a total of 9862 cases of human illness, including 2775 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

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diagnostic tests, and the wide spread use of investigational WNV NAT tests 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 – 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 in 2000 and 2001, May in 2002, and April in 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 2–14 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 1-3 days following WNV infection by mosquito bite, and lasts 1–11 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 as long as 49 days (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 4-14%, 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).

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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 tests 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 1017 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. These 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.

At this time, we believe WNV is unlikely to be transmitted through derivatives manufactured from plasma, since lipid-enveloped RNA viruses such as WNV should 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.

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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 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 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-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 4 of the 6 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 a 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, patients with diagnosed WNV infection who have received blood transfusions or organs within the 8 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.

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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, “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 include deferral of donors who reported fever with headache in the week before donation. Additionally, we advised blood collection centers to 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 October 22, 2004, meeting, the Blood Products Advisory Committee (BPAC) heard scientific presentations that viremia associated with WNV infection has now been observed to rarely extend up to 49 days following a WNV NAT-positive donation. We have modified our previous recommendations to incorporate this new information and we now recommend that donors with diagnosed or suspected WNV infection be deferred for 120 days following diagnosis or onset of illness, whichever is later. We also recommend that you defer donors who are reactive on an investigational screening test for WNV. You may reenter such donors after 120 days from the date of their reactive donation, provided that they are retested and found negative by IDT NAT for WNV on a follow-up sample obtained during or after the 120 day deferral period. If the 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, and that the donor be retested and found negative by IDT NAT for WNV before reentry after the second deferral period. We recognize that follow-up testing by IDT NAT of donors deferred based on positive NAT for WNV may not be feasible or practical at all blood centers. In cases where follow-up testing is not performed, we recommend that donors deferred on the basis of positive NAT for WNV remain deferred indefinitely, pending future scientific data to clarify the necessary period of deferral in the absence of further testing.

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, 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 percent of persons infected with WNV and that only a portion of the implicated donors reported symptom prior to

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donation. At this time, based upon a review of the available information about the performance of the donor screening question at the October 22, 2004, BPAC, we are removing the recommendation for donor deferral based upon a reported history of headache with fever in the week prior to donation.

As a prudent measure to address the possible risk of transmission of WNV by blood transfusion, we are providing revised recommendations for product retrieval and quarantine related to reports of post-donation illnesses in the donor, or association with WNV infection in recipients of blood. Our quarantine and retrieval recommendations related to WNV infection in a donor are now based on the interval from 14 days prior to WNV illness onset in a donor up to and including to 120 days after WNV diagnosis or illness onset, whichever is later. Our quarantine and retrieval recommendations related to implication in a WNV transmission are based upon the identification of suspect donations received by an infected recipient within the 120 days prior to the appearance of WNV symptoms in the recipient. 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 prior to the suspect donation and 120 days after the suspect donation.

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.

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 be needed for the foreseeable future. The PHS has worked with device manufacturers and blood organizations to facilitate test availability 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

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.

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 longest known viremic period, plus an additional margin of safety.

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A. Diagnosed or Suspected Acute West Nile Virus Illness or 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.

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 by MP or IDT WNV 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 choose to reenter such donors after 120 days from their reactive donation, provided that they are retested and found negative by IDT NAT for WNV on a follow-up sample obtained during or after the 120 day deferral period. If the 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, and that the donor be retested and found negative by IDT NAT for WNV before reentry after the second deferral period.

C. Suspected West Virus Illness in a Donor

We recommend that donors who report during WNV season (at least between May 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 120 days following the onset of illness.

D. Donors Who May Have Transmitted West Nile Virus Infection

We recommend that blood donors whose blood or blood components were potentially associated with a transfusion-related WNV transmission be deferred with a provision for re-entry 120 days following the date of donation, based upon negative test results with IDT NAT. 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

Contains Nonbinding Recommendations*Draft – Not for Implementation***IV. RECOMMENDATIONS FOR RETRIEVAL AND QUARANTINE OF BLOOD AND BLOOD COMPONENTS INCLUDING RECOVERED PLASMA, SOURCE PLASMA, AND SOURCE LEUKOCYTES**

During WNV season (at least between May 1 and November 30), 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 West Nile Virus 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 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 tested negative by MP or IDT WNV NAT at the time of collection.

B. Donors Who May Have Transmitted West Nile Virus Infection

Based on the observation that time to development of illness may be prolonged in some blood recipients, a donor is considered to be potentially associated with transmission of WNV if a recipient of blood or transfusable 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.

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

We recommend that medical directors exercise judgment in assessing whether a donor's febrile illness may represent infection by WNV, in particular, during WNV season (at least between May 1 and November 30). 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.

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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 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 Source Plasma, recovered plasma or Source Leukocytes have been pooled for fractionation, quarantine and retrieval are not recommended. 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 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 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 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 at 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

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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. We believe that the receipt of post donation information concerning donor illness would be reportable under this section, since 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 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, when final, as soon as feasible, but not later than 30 days after issuance of a final guidance. Consistent with 21 CFR 601.12, licensed establishments implementing these recommendations must 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.