医薬品
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化粧品

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研究報告の概要

本ガイダンス案は 2003 年 5 月発行の最終ガイダンスの改訂版であり、輸血用血液製剤（全血、血液成分）および注射用又は非注射用製剤の製造に用いられる血液成分（回収血漿、原料白血球、並びに原料血漿を含む）に適用されるが、組織の採取業者又は人の血液以外の細胞及び組織には適用されない。

・主な変更点は次のとおり。

①供血禁止及び再登録

・供血前 1 週間以内に「発熱を伴った頭痛」がする血液ドナーを供血禁止とはしない（この項目は次回問診表から削除される）。

・WNV 感染又は WNV 感染の疑いがあると医学的に診断された血液ドナーは、診断時点又は発症時点のどちらか遅い方から 120 日間は供血禁止される。

・NAT により供血禁止された血液ドナーは、陽性のドネーションの 120 日以降、120 日の供血停止期間の間又は後に採取された追跡サンプルについて個別 NAT による再検査が陰性であれば再登録できる。

・追跡サンプルが個別 NAT 陽性であった血液ドナーは、その採血日から更に 120 日間は供血禁止される。2 回目の供血禁止された血液ドナーの再登録は、再登録前に個別 NAT が陰性でなければならない。

・追跡検査を行わない場合は、WNV NAT 陽性に基づいて供血停止されたドナーは無期限に供血禁止とし、将来の科学的データにより供血禁止期間が明白となるまでは保留とする。.

・WNV シーズン中に供血後に他には説明できない WNV 感染を示唆する発熱を報告した血液ドナーは症状発生から 120 日間は供血禁止される。血液ドナーは、供血後 2 週間以内に起こった原因不明の WNV 感染を示唆する頭痛を伴う発熱又は他の症状を積極的に報告することが推奨される。

・当該供血日から 120 日後に個別 NAT 陰性に基づいて再登録されることを条件として、輸血後 WNV 伝播と潜在的関係がある血液ドナーは供血禁止される。

②有効期限内血液成分の回収及び隔離

・もし血液ドナーの WNV 感染の医療診断が後に報告されたなら、関係する供血からの有効期限内血液成分は速やかに回収及び隔離しなければならない。
関係する供血とは、WNV 発症の 14 日前から、WNV 診断時点又は発症時点のどちらか遅い方から 120 日間までの間の供血と定義される。

・もしレシピエントが発症前 120 日以内に血液ドナーからの血液製剤を受け、WNV 感染と診断されたなら、その血液ドナーは WNV 伝播に潜在的に関与していると考えられる。この供血からの関係する血液成分はすべて疑い有りとみなされる。疑い有りとされたドネーションの 120 日前と 120 後（120 日を含む）までの間に疑いドナーから収集された有効期限内血液成分は速やかに回収及び隔離しなければならない。

③輸血レシピエントへの通知

・もし血液ドナーの WNV 感染の医学的診断が後に報告されたなら、レシピエントへの通知を目的に採血所は、血液ドナーの発症 14 日前から発症後 120 日の全てのユニットについて記録の遡及調査を行わなければならない。

・特定の血液ドナーがレシピエントへの WNV 伝播源と考えられる場合には、輸血サービス、レシピエント、治療担当医師への通知のために採血所は、WNV 伝播が示唆されたドネーションの供血日前後 120 日間のすべてのユニットについての記録の遡及調査を行わなければならない。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリンーIH の記載を示す。

2. 重要な基本的注意

(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の破傷風抗毒素を含有する血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

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報告企業の意見	今後の対応	
米国でのWNV感染した血液ドナーにおけるFDAのガイダンスの改訂版である。 今回のガイダンス案では前回のガイダンスにおいて供血禁止とされた「発熱を伴った頭痛」を有するドナーは供血禁止とはされず、また一度供血禁止されたドナーの再登録には個別NAT陰性が確認されなければならないなどが変更されている。 FDAは、2003年5月の業界向けガイダンス改訂版において、「FDAは全ての血漿分画製剤について現在行われているウイルス低減工程を再調査した。現在行われている方法は、WNVと分類上関連しているフラビウイルスを不活化することがバリデートされている。」と評価し、CPMPもまたポジションステートメントにおいて、血漿分画製剤の製造工程でWNVは不活化・除去されると評価している。 弊社への米国の原料血漿供給元では、2003年6月よりWNVの問診を開始している。万一、原料血漿にWNVが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (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*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, 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 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
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Guidance for Industry

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

This draft guidance, when finalized, will represent 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 draft guidance document provides revisions to our previously published final guidance entitled, "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. Our current thinking is that these revised recommendations should 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 draft guidance revises the final 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. The 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, provided that they are retested and found negative by individual donation testing (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, FDA, 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 reactive 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.

This draft 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 "WNV season" to mean either (a) May 1 to November 30, or

(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

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).

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.

Contains Nonbinding Recommendations

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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

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.

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 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.

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.

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

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.

IX. REFERENCES

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