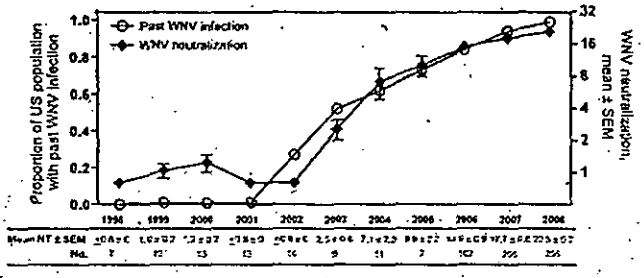

Figure 1. West Nile virus (WNV) neutralization titers of US plasma-derived immune globulin intravenous (human) (IGIV) lots by year of production and estimated percentage of the US population with past WNV infection by year. WNV neutralization titers were determined either for retention or lot release samples of 3 IGIV products produced during 1998–2005 or for a considerable proportion of Gammagard Liquid/KIOVIG lots produced during 2006–2008. Results are shown as mean ± SEM (limit of detection <0.8) by year of product release. For 5% of IGIV samples, titers were multiplied by 2 for comparison with the 10% IGIV samples at equivalent immunoglobulin concentrations. The percentage of the US donor population with past WNV infection was calculated from the number of neuroinvasive cases reported per year and the estimated ratio of neuroinvasive cases to total cases of WNV infection.

US plasma-derived IGIV lots released during 2008 showed variable WNV neutralization titers ranging from 2.8 to 69.8; mean ± SEM titer was 21 ± 1 (n = 256) (Figure 2). Compared with titers shown to be protective in an animal model of WNV infection (equivalent to >21 by the current assay) (*2*), ≈40% of the 2008 IGIV lots had higher titers.

Plasma obtained from persons with NAT-confirmed WNV infection had even higher titers; mean ± SEM titer was 208 ± 40 for 30 persons available for testing. When results were corrected for the immunoglobulin (Ig) G concentration in plasma (≈1%), compared with the 10% IGIV preparations, the mean neutralization titer of the plasma samples was ≈100× higher than that of the IGIV lots tested (2,080 vs. 21).

Conclusions

The most comprehensive collation of information about the incidence of WNV infection in the United States is available from ArboNET. When that information is combined with information obtained from the nationwide screening of the blood supply for WNV RNA by NAT (*1,4,5*), the current prevalence of past WNV in the US population is estimated to be ≈1%.

Busch et al. has noted that large-scale, community-based serologic surveys are hardly feasible because of their expense and because WNV ELISA assays are possibly biased by cross-reactions with other flaviviruses (*1*). Nevertheless, 7 seroepidemiologic studies have been performed (*6–12*). Cumulatively, 5,503 persons were tested for WNV infection by ELISA, and the results have shown highly divergent seroprevalence rates ranging between 1.9% (*6*) and 14.0% (*10*).

The use of IGIV lots, each representing the serostatus of several thousand donors in 1 sample, makes seroepidemiology practical (*13*) because it allows a large donor population to be surveyed by analyzing comparably few samples. The use of a more complex yet functional virus neutralization assay minimizes concerns about cross-reactivity with flaviviruses of other serocomplexes (e.g., dengue virus) that occasionally circulate in the US population. Also, epidemiologic considerations render interference by St. Louis encephalitis virus, a flavivirus within the same serocomplex, highly unlikely (*2*). The specificity of the neutralization assay was confirmed by testing IGIV lots manufactured from European-derived plasma against tick-borne encephalitis virus, a flavivirus closely related to WNV and circulating in Europe. Although these lots contained high neutralization titers against tick-borne encephalitis virus, only 1 of 20 had a detectable neutralization titer of 5 against WNV (unpub. data).

In this study, we determined that the mean titer of samples obtained during 2003–2008 from persons with a confirmed diagnosis of WNV infection was 100× higher than the mean titers of IGIV lots produced in 2008. This determination provides an independent experimental measure of the frequency of past WNV infection in the general US population, as reflected by the plasma/blood donor community, and the results correlate well with results of previously published theoretical extrapolations (*1*), which estimated that ≈1% of the population has already been infected with WNV.

The increasing levels of WNV neutralizing antibodies in IGIV lots from US plasma and the particularly high

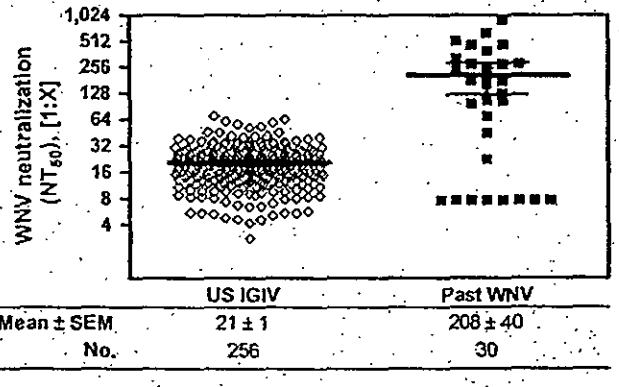

Figure 2. West Nile virus (WNV) neutralization by US plasma-derived immune globulin intravenous (human) (IGIV) released in 2008 and plasma from donors with past WNV infection (past WNV), confirmed by nucleic acid testing. WNV neutralization titers are shown as the mean ± SEM (limit of detection <0.8 for undiluted IGIVs and <7.7 for prediluted sera). NT_{50}, 50% neutralization titer.

titers in donors who have had a WNV infection suggest the possibility of preparing IGIV products with sufficiently high titers to be useful for WNV prophylaxis or treatment. Several ongoing or imminent WNV vaccine clinical trials stress the practical value of an independent confirmation of extrapolations that estimate the percentage of the US population with past WNV infection. Knowing the percentage of preexisting WNV seroprevalence as well as estimates of the mostly asymptomatic incidence rates (*14*) can be of vital importance in designing vaccine trials.

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P. Noel Barrett and Don A. Baker are acknowledged for providing unconditional support and strategic vision for the project reported. We are also indebted to John S. Finlayson for critical review of this manuscript. Critical reagents have been generously provided by Susan L. Stramer and Robert E. Shope.

Ms Planitzer is writing her PhD thesis on virus antibodies in immune globulins at the Global Pathogen Safety Group of Baxter BioScience in Vienna, Austria, in collaboration with the Medical University of Vienna, Austria. Her research focuses on determining functional antiviral properties of immunoglobulin preparations.

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研究報告の概要

このガイダンスは、輸血によるウエストナイルウイルス(WNV)伝播の可能性を最小化するために、血液採取施設が講ずる措置についての推奨である。示された全血及び血液成分のドネーションのための推奨内容は以下の通りである。、

A. 検査、ユニットの管理及びドナー管理

1. 輸注を意図して採取された全血および血液成分のドナーサンプルについて、WNVのスクリーニングを認可されたNATで1年を通じて行うことを推奨する。

2. 血液採取・取扱施設がミニプールNAT(MP-NAT)を用いてスクリーニングを行っているのならば、その施設は、陰性であったミニプールを構成している各試験サンプルのもとのユニット全てを、それらがWNV以外の点について出荷可とすることが適切であるのならば、出荷することができる。FDAは、血液採取・取扱施設がNATで陽性を示したミニプールを、それを構成する各検体に戻って個別NAT(ID-NAT)を用いて検査し、そのミニプールが陽性となる原因となったユニット(単数または複数)を同定することを推奨する。

B. MP-NATからID-NATへの切替え

1. 当該施設が採取を行う地域内で「WNVの活動性が高い」ということを定義する判断基準を設定し、バリデートすること。

2. 当該施設が採取を行う地域で「WNVの活動性が高い」際にMP-NATからID-NATへとスイッチするため、およびその地域での「WNVの活動性が高い」状態が収まったときにMP-NATへと戻すための閾値を定めること。

3. MP-NATからID-NATへのスイッチは可能な限り早期に行うべきだが、定めた閾値に達してから48時間以内に行うこと。

4. このような決定のプロセスについてSOP(標準作業手順書)を制定し、それに従うこと。

C. 検査実施報告書

1. 血液採取・取扱施設が認可を得ている施設であって、かつ、血液製剤の感染症検査を行うことがすでにFDAによって承認された施設では、認可を得ているWNV NAT検査を製造者の使用説明書に従って当該施設で用いることができ、その場合には21 CFR 601.12(d)に従って、検査法の変更について、その施設のFDAへの年次報告中に記載してFDAに知らせなければならない。

2. 血液採取・取扱施設が認可を得ている施設であってWNVのNAT検査を行うために新たな契約ラボを利用する場合であって、かつ、そのラボがすでに血液製剤の感染症検査を行っている場合には、その血液採取・取扱施設はその変更についてFDAに報告しなければならず、またそのことは21 CFR 601.12(c)(1)および(5)に従って"Supplement-Changes Being Effected"の申請を行うことによって報告しても良い。

D. 輸血を目的とした全血及び血液成分の表示

21 CFR 606.122(h)は、輸注を意図した血液製剤用の使用案内書("Circular of Information"としても知られている)には、安全でかつ有効な使用のために必要であれば、実施した検査名と結果を全て含めることを求めている。この21 CFR 606.122(h)に準拠するために、WNVのNATとして認可を受けた検査を実施するに際しては、認可を受けた血液採取・取扱施設、認可を受けていない施設のどちらでも、そのような使用案内書を改訂して、WNVについてのNAT検査が陰性であったとの結果を含めるようにしなければならない。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意

(1) 本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-I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人ハプトグロビンを濃縮・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ろ過膜処理(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	
ウエストナイルウイルスの伝播リスクを低減するための核酸検査（NAT）の使用に関する業界ガイダンスである。 FDA は、2005 年 6 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。万一、原料血漿に WNV が混入しても、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ものと考えるので、特段の措置はとらない。	

ハプトグロビン

Guidance for Industry

Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (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/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2009

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Contains Nonbinding Recommendations

Guidance for Industry

Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion

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

We, FDA, are issuing this guidance to provide you[1] with recommendations for testing donations of Whole Blood and blood components for West Nile Virus (WNV) using an FDA-licensed donor screening assay[2]. We believe that the use of a licensed nucleic acid test (NAT) will reduce the risk of transmission of WNV, and therefore recommend that you use a licensed NAT to screen donors of Whole Blood and blood components intended for transfusion for infection with WNV.

The recommendations in section III of this guidance apply to all donations of Whole Blood (as defined in Title 21 Code of Federal Regulations (CFR) 640.1) and blood components for transfusion[3].

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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 first appeared in the United States in 1999, and has become endemic with high viral activity during the warm months of the year. WNV is a mosquito-borne agent that is maintained

[1] This guidance is intended for establishments that collect Whole Blood and blood components intended for transfusion.

[2] This guidance finalizes the recommendations for donations of Whole Blood and blood components in the draft guidance titled, *Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*, dated April 2008 (April 28, 2008, 73 FR 22958).

[3] This guidance does not apply to Source Plasma or plasma derivatives.

in nature primarily between birds and mosquitoes but can also infect other animals, including humans. The potential for WNV transmission by blood transfusion during the acute phase of infection, when infected individuals are viremic and asymptomatic, was first recognized in 2002 (Ref. 1). At that time, test kit manufacturers and blood organizations, with input from the Public Health Service (National Institutes of Health, FDA, and Centers for Disease Control and Prevention (CDC)), actively pursued development of NAT systems for WNV. Retrospective studies have subsequently confirmed human-to-human transmission of WNV by blood transfusion and by organ transplantation (Refs. 2, 3).

Nationwide clinical studies to evaluate a NAT for the detection of WNV were initiated in 2003, under FDA's Investigational New Drug Application (IND) regulations (21 CFR Part 312). Such large-scale studies were necessary to help ensure blood safety and to determine the efficacy of investigational assays to prevent the transmission of WNV through blood transfusion, because at that time there was no FDA-licensed screening assay available to detect WNV infection.

Since 2005, FDA has approved biologics license applications for two NAT assays for detecting WNV ribonucleic acid (RNA) using plasma specimens from human donors of blood. The assays are intended for use in testing individual donor samples and in testing pools of human plasma comprised of equal aliquots of not more than either 6 or 16 individual donations (minipools) of whole blood and blood components, depending on the manufacturer.

As explained below in section III, if the result of a licensed minipool NAT (MP-NAT) is reactive, and subsequent testing of the individual donation(s) (ID-NAT) comprising the tested minipool is reactive, then FDA would recommend treating the reactive unit(s) as though they are infectious.

Evaluation of additional testing performed on specimens that were reactive on screening by ID-NAT has shown that a repeat ID-NAT on index donation specimens (i.e., the same or an independent specimen from the index donation, which is the donation for which the test result was reactive), using either the same screening assay or an equally sensitive alternate NAT, together with a test result for antibody to WNV, has a positive predictive value of 98% (Ref. 4).

Data show that up to 10% of donors who have a reactive ID-NAT that fails to be reactive on repeat testing by ID-NAT actually are infected, based on the presence of antibodies to WNV either in the index donation (ca. 8%) or on a follow-up test (ca. 2%) (Ref. 4). Therefore, additional testing that would include repeat testing by ID-NAT along with testing for antibody to WNV may be of value in donor counseling.

A. Whole Blood and Blood Components

In 2002, there were 23 confirmed cases of WNV transmission by blood or blood components (Ref. 3). Only six transmissions of WNV by transfusion were documented in 2003 (Ref. 5) following nationwide implementation of screening for WNV by MP-NAT under an IND in July 2003. Retrospective studies using ID-NAT to test MP-NAT non-reactive specimens collected during that season identified additional reactive donations and indicated that up to 25% of viremic units were not detected by MP-NAT, presumably due to low viral load (Ref. 6). Results

of these studies show that for detecting WNV, ID-NAT has greater sensitivity than MP-NAT.

As a result, ID-NAT may identify reactive donations not detected by MP-NAT. However, limitations in reagent availability, and personnel and logistical issues related to blood donor screening may not allow full implementation of ID-NAT. During the development and implementation of the ID-NAT test under IND, MP-NAT of plasma samples (pools of 6 or 16 samples), rather than ID-NAT, was the only feasible format for performing the test. In addition, testing using the MP-NAT format was similar to the assay platforms being used for human immunodeficiency virus type 1 (HIV-1) NAT and hepatitis C virus (HCV) NAT at that time. As reagent availability increases, technology advances, and personnel and logistical issues related to blood donor screening diminish, year-round ID-NAT testing of all donations of blood and blood components, using a licensed NAT, may become feasible and practical.

Although year-round ID-NAT testing of all blood and blood components may not be currently feasible, we believe that using ID-NAT instead of MP-NAT on a limited basis during periods of high WNV activity to maximize the benefit to the public health is more practicable. Statistical analyses were performed on the data from the retrospective studies described above to establish criteria for defining high WNV activity in a particular geographic region (Ref. 7). These criteria were used as a "trigger" for ID-NAT implementation and for reversion to MP-NAT testing when the high WNV activity in that region subsided. Since 2004, ID-NAT screening replaced MP-NAT screening in those geographic regions of high WNV activity during epidemic periods (Refs. 7, 8) when a threshold was reached. The threshold was usually based on the number of MP-NAT-reactive screening test results obtained during a one-week interval or on a cumulative rate for ID-NAT reactive screening test results in a particular region (Ref. 4).

After selective implementation of ID-NAT during epidemic seasons, there were three additional transmissions of WNV by transfusion between 2004 and 2006: one in 2004 and two in 2006. The WNV transmission in 2004 resulted from a donation of red blood cells which tested non-reactive in a MP-NAT assay, but which was subsequently found to be reactive in an ID-NAT test. Plasma from the donation retrospectively tested reactive by ID-NAT. However, ID-NAT had not yet been implemented (Ref. 9). The two WNV transmissions in 2006 resulted from a non-reactive MP-NAT donation from which red blood cells and fresh frozen plasma were transfused to two immunosuppressed recipients (Ref. 10). Investigation of the 2006 cases showed that: 1) there were no established methods of communication linking WNV MP-NAT data from multiple collecting and testing facilities serving overlapping or adjacent geographic areas; and 2) if efficient communication mechanisms had been in place, the corresponding collection area would have reached the threshold for switching to ID-NAT screening, and the WNV-contaminated components would likely have been detected and removed from the blood supply (Ref. 4).

At this time, there is insufficient data to support recommendation of uniform threshold criteria for switching from MP-NAT screening to ID-NAT screening. Pending development of suitable uniform threshold criteria, we consider it appropriate for each blood establishment to define its own threshold criteria for switching from MP-NAT to ID-NAT screening and for reverting to MP-NAT screening. Each blood establishment should follow an established standard operating procedure (SOP) for this decision process. Voluntary industry practice of switching from MP-

NAT to ID-NAT screening during seasonal activity has been useful in increasing the effectiveness of the WNV screening process.

III. RECOMMENDATIONS FOR DONATIONS OF WHOLE BLOOD AND BLOOD COMPONENTS

Testing donations of Whole Blood and blood components for WNV using NAT involves the use of defined pooling and testing systems. We recognize that licensed testing technology in a semi-automated or fully automated format is not universally available, and that if you are currently performing NAT for WNV under an IND you would need time to fully implement a licensed system with all approved components, including the supporting software cleared as a device. If you are therefore using some, but not all, of the licensed or cleared components, you should continue your existing IND and report the use of the licensed assay or the related cleared components as an amendment to your existing IND. When you implement all licensed or cleared components of the test system, you may withdraw the IND in accordance with the procedures provided in 21 CFR 312.38.

A. Testing, Unit Management, and Donor Management

1. We recommend that you screen year-round for WNV using a licensed NAT on donor samples of Whole Blood and blood components intended for transfusion. In general, you may use either MP-NAT or ID-NAT for screening (see Figure 1 and Table 1), except that we recommend that you use ID-NAT screening during high WNV activity in your region (using a previously defined geographic area). See section B.

2. If you perform screening using MP-NAT, you may release all units whose test samples comprise a non-reactive minipool, if those units are otherwise suitable for release.

   We recommend that you resolve a NAT-reactive minipool using ID-NAT to test each specimen in the minipool in order to identify the unit(s) that led to the reactivity of the minipool. Based on the ID-NAT results, we recommend the following:

   a. You may release all ID-NAT non-reactive units if they are otherwise suitable for release.

   b. If one or more individual donation(s) is (are) reactive, we recommend that you discard the unit(s), defer the donor(s) for a period of 120 days and retrieve and quarantine in-date products from prior collections dating back 120 days prior to the donation that is ID-NAT-reactive. We recommend that you notify the donor of his or her deferral and counsel the donor. Further testing on the index donation using the same ID-NAT or an alternate NAT with sensitivity equal to or greater than that of the screening assay, in addition to testing the

specimen using a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

3. If you perform screening using ID-NAT, we recommend that you follow the steps in 2.a. and 2.b. for testing, unit management, and donor management.

B. Switching from MP-NAT to ID-NAT

We recommend that you:

1. Establish and validate criteria that define high WNV activity in your geographic area of collection.
2. Define a threshold for switching from MP-NAT to ID-NAT screening during high WNV activity in your geographic area of collection, and for reverting to MP-NAT screening when the high WNV activity in your geographic area has subsided.
3. Switch from MP-NAT to ID-NAT screening as soon as feasible, but within 48 hours of reaching that threshold.
4. Establish and follow an SOP for this decision process.

NOTE: To define the geographic area for which the threshold criteria would apply, you may consider using the donor's residential zip code or county, or other well-specified region of comparable size that includes the donor's residence. Although exposure to WNV may occur in any location, it is reasonable to assume that exposure most likely occurred while the donor was near his or her residence, because mosquito activity is highest at dawn and dusk, times when many donors are at home. Mechanisms for switching to ID-NAT screening that utilize defined geographic areas based on residential zip codes, counties, or other comparable well-specified regions provide a standardized method for collecting data on the number of NAT-reactive donations and the number of donations tested.

Consideration of other epidemiological data may be useful in defining a threshold for switching from MP-NAT to ID-NAT screening, if such data are available.

Examples include the number of clinical cases, the number of positive birds or mosquito pools reported in a particular geographic area, and prior ID-NAT implementation history.

You should switch from MP-NAT to ID-NAT screening when the WNV case threshold has been met or exceeded in your defined geographic area. Blood establishments that share geographic collection areas should consider a communication plan so that data from overlapping and adjacent collection areas may be shared and used to assess WNV activity in a defined geographic area. You may use this data to determine whether your defined threshold for switching to ID-NAT screening has been met.

C. Reporting Test Implementation

1. If you are a licensed blood establishment and are already FDA-approved to perform infectious disease testing of blood products, you may use at your facility a licensed WNV NAT according to the manufacturer's product insert, and you must notify us in your annual report of the testing change in accordance with 21 CFR 601.12(d). Also, if you have already filed a supplement to your Biologics License Application to use a contract laboratory to perform infectious disease testing of blood products, and the contract laboratory will now perform a NAT for WNV, you must report this change in your annual report, in accordance with 21 CFR 601.12(d).

2. If you are a licensed blood establishment and you use a new contract laboratory to perform a NAT for WNV and the laboratory already performs infectious disease testing for blood products, then you must report this change to FDA, and may do so through submission of a "Supplement – Changes Being Effected" in accordance with 21 CFR 601.12(c)(1) and (5), also known as changes being effected immediately (CBE). If your contract laboratory previously has not performed infectious disease testing for blood products, then you must submit this change in a prior approval supplement (PAS) in accordance with 21 CFR 601.12(b).

D. Labeling of Whole Blood and Blood Components Intended for Transfusion

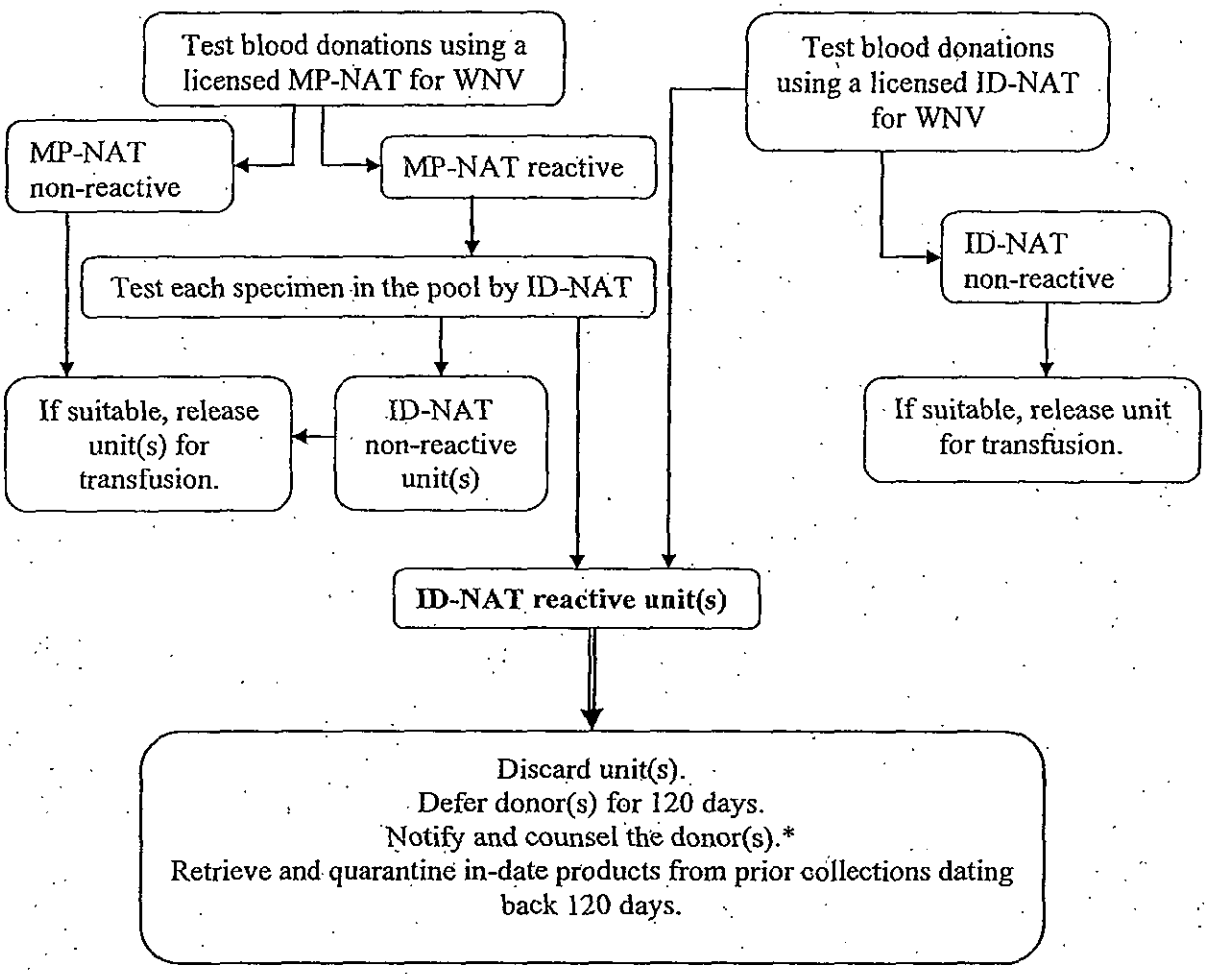
Title 21 CFR 606.122(h) requires that an instruction circular, also known as the "Circular of Information," for blood products intended for transfusion include the names and results of all tests performed when necessary for safe and effective use. To comply with 21 CFR 606.122(h), upon implementation of a licensed NAT for WNV, both licensed and unlicensed blood establishments must revise such instruction circular to include the non-reactive results of a NAT for WNV. If you are a licensed blood establishment, you may submit this labeling as a CBE (21 CFR 601.12(c)(1) and (5)), provided the revision is identical to the following statement:

"A Licensed Nucleic Acid Test (NAT) for West Nile Virus (WNV) RNA has

been performed and found to be non-reactive."

If you are a licensed blood establishment and you wish to use a different statement, then you must submit the labeling change as a PAS (21 CFR 601.12(b)). If you are an unlicensed blood establishment, you must revise the instruction circular under 21 CFR 606.122(h), but you are not required to submit the revision as a supplement.

Figure 1. Recommendations on Testing, Unit Management, and Donor Management for Whole Blood and Blood Components



* Additional testing on the index donation using the same ID-NAT assay or an alternate NAT of comparable sensitivity in addition to a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

Table 1. Recommendations on Testing, Unit Management, and Donor Management for Whole Blood and Blood Components

MP- NAT	ID-NAT	Actions
Reactive	Reactive unit(s)	Discard the unit(s).
		Defer the donor(s) for 120 days.
		Notify and counsel the donor(s).*
		Retrieve and quarantine in-date products from prior collections dating back 120 days.
	Non-Reactive unit(s)	If suitable, release units for transfusion.
Non-Reactive	Not needed	If suitable, release units for transfusion.

* Additional testing on the index donation using the same ID-NAT assay or an alternate NAT of comparable sensitivity in addition to a cleared test for antibodies to WNV may be of value in donor counseling.

Note: In the event that the NAT screening assay does not discriminate between WNV and other Flaviviruses that belong to the Japanese Encephalitis (JE) serogroup (namely, Saint Louis Encephalitis virus, Japanese Encephalitis virus, Murray Valley Encephalitis virus and Kunjin virus), the donor should be counseled that he or she tested positive for a JE serogroup virus, most likely WNV. Alternatively, the use of a NAT assay that discriminates WNV from other members of the JE serogroup may be of value in donor counseling.

Note: Antibodies to viruses of the JE serogroup may cross-react on the test for antibodies to WNV (Refs. 11, 12). Therefore, reactivity in a WNV antibody test may not be conclusive for WNV infection.

IV. IMPLEMENTATION

We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than six months after the guidance issue date.

V. REFERENCES

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番号：2

別紙様式第２－１

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 平成22年1月5日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ヨウ化人血清アルブミン（^{131}I）		研究報告の公表状況	Google News Dec 18, 2009 （追加情報：The New York Times December 19,2009）	公表国 米国	
販売名（企業名）	放射性ヨウ化人血清アルブミン注射液（富士フイルムＲＩファーマ株式会社）					
研究報告の概要	要約：米国においてアメーバ性髄膜脳炎の初めてのヒトからヒトへの伝播が報告された： 米国にて、臓器ドナーから腎移植を受けたレシピエント２例がアメーバ性髄膜脳炎に感染し、患者は重篤な状態にあることが保健当局により報告された。これは、おそらく初めてのヒトからヒトへのアメーバ性髄膜脳炎の伝播であると思われる。レシピエント２例は重症であるが、同患者からの別の臓器の移植を受けたその他の患者は症状を呈していない。後に検査により、ドナーと腎移植を受けたレシピエント２例から髄膜脳炎の原因とされる「Balamuthia mandrillaris」というアメーバが検出され、感染が確認された。					使用上の注意記載状況・その他参考事項等 特になし
報告企業の意見			今後の対応			
初めての人から人への感染報告であり、新たな感染経路かつ重大な感染症に関するものであるため、感染症定期報告の対象と判断する。			本研究報告は、ヒト血液を原料とする血漿分画製剤とは直接関連しないことから、現時点で当該生物由来製品に関し、措置等を行う必要はないと判断する。			

MedDRA/J Version(12.1)

8

CDC: Rare infection passed on by Miss. organ donor

By HOLBROOK MOHR (AP) – Dec 18, 2009

JACKSON, Miss. — An extremely rare infection has been passed from an organ donor to at least one recipient in what is thought to be the first human-to-human transfer of the amoeba, medical officials said Friday.

Four people in three states received organs from a patient who died at the University of Mississippi Medical Center in November after suffering from neurological problems, said Dave Daigle, a spokesman for the Centers for Disease Controls and Prevention.

Organs are routinely tested for HIV, hepatitis and other more common infections, but occasionally rare ones slip through.

"We test for the known harmful diseases, but there's not a test for every single pathogen out there," said Dr. Kenneth Kokko, medical director of kidney transplants at UMMC.

Two of the recipients are critically ill, but the others haven't shown symptoms, Daigle said. The CDC confirmed the presence of the organism, known as Balamuthia mandrillaris, in one of the recipients.

Dr. Shirley Schlessinger, a UMMC doctor and medical director of the Mississippi Organ Recovery Agency, would not say which states had patients receiving the organs.

The public should not be concerned, both Schlessinger and Daigle said.

Balamuthia mandrillaris is a microscopic parasite found in soil that causes encephalitis in humans, horses, dogs, sheep and nonhuman primates. Scientists think people get infected by breathing it in, but it can also pass into the blood through a cut or break in the skin. It can be especially dangerous to people undergoing organ transplants, whose immune systems are purposely weakened so their bodies don't reject their new organs.

Human infections are very rare: Only about 150 cases have been reported worldwide since the disease was first identified in 1990. But it can be hard to diagnose because few laboratories test for it and many doctors don't know about it. Some cases are not identified until autopsy, according to the CDC.

"The thing we don't want to happen is for people to take this rare and extraordinary anomaly and think it speaks to a lack of safety," she said. "It's very rare so the likelihood that this will happen again (is small), I mean, it's rarer than rabies."

There are risks to transplants and doctors can't test for everything, but the potential benefits far outweigh the risks, she said.

AP Medical Writer Mike Stobbe in Atlanta contributed to this report.

On the Net:

- CDC details on Balamuthia mandrillaris: http://bit.ly/7swHMV
- University of Mississippi Medical Center: http://www.umc.edu/

Related articles

CDC: Rare infection passed on by Miss. organ donor
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The Associated Press - Dec 18, 2009

The New York Times

December 19, 2009

2 Kidney Recipients Contract Brain Disease From Donor

By DENISE GRADY

Two transplant patients are critically ill with a rare brain infection that was transmitted to them by kidneys taken from a donor at the University of Mississippi Medical Center in Jackson, health officials reported on Friday.

The same infection probably killed the organ donor, but it was not diagnosed; his doctors thought he had an autoimmune disease. Two other patients also received heart and liver transplants from the donor, but neither has become ill. The transplants took place in November, in three states. A spokeswoman for the university declined to say where the recipients were, citing patient confidentiality.

Three weeks after their transplant surgeries, the kidney recipients became ill abruptly, within hours of each other, with seizures, a change in mental status and fever, said Dr. Eileen Farnon, an epidemiologist at the Centers for Disease Control and Prevention, which is investigating the cases. A doctor noted that both were transplant recipients, and immediately suspected that they might have contracted an illness from the donor.

Subsequent tests of tissue left from the deceased donor found the infection, which was also diagnosed in the patients. The patients are being treated with a mixture of antimicrobial drugs.

The infection is caused by an amoeba, Balamuthia mandrillaris, which lives in soil and water. Only about 70 cases have ever been identified in the United States. Nearly all have been fatal. The current cases are the first to have been found in transplant recipients. Although infections from transplants are uncommon, there have been cases in which recipients contracted West Nile virus, rabies and other infections.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 10. 14	該当なし	

一般的名称	人赤血球濃厚液	研究報告の公表状況		公表国
販売名(企業名)	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)		水野泰孝, 氏家無限, 竹下望, 加藤康幸, 金川修造, 工藤宏一郎, 林昌宏, 高崎智彦. 第58回日本感染症学会東日本地方会学術集会・第56回日本化学療法学会東日本支部総会合同学会; 2009 Oct 30-31; 東京.	日本

研究報告の概要

○遷延する関節痛を主訴に来院したチクングニヤ熱の3例

チクングニヤ熱(Chikungunya fever;CHIKF)は発熱、関節炎、発疹を主症状とする熱性疾患であり、臨床症状や検査所見はデング熱に類似するが、遷延する関節症状が特徴的である。本年になり東南アジア地域を中心に再びCHIKF流行が拡大しており、2009年5月から6月にかけての2ヶ月間で、東南アジアから帰国後に遷延する関節痛を主訴に来院した3例を血清学的にCHIKFと診断したのでその概要を報告する。(症例1)52歳日本人男性。2009年3月26日から4月5日までインドネシア・スマトラ島へ蝶の採集目的で滞在。3月31日に39.5度の発熱、関節痛(両手足首、両膝)が出現。翌日には解熱したものの関節痛は持続したため、帰国後5月上旬に近医整形外科受診。関節リウマチ、痛風検査を実施されるも陰性であったため、精査目的で当センターを受診した。(症例2)30歳日本人男性。2009年4月16日より6月14日までインドネシア・ジャワ島へ舞台公演目的で滞在。5月13日に発熱、関節痛(右足首、左膝、右肩)、頭痛、発疹が出現。4日後に解熱したものの関節痛は持続したため6月22日に当センターを受診した。(症例3)39歳日本人女性。2009年4月4日より6月28日までマレーシア・クアラルンプール郊外に帯同家族として滞在。5月12日に39.5度の発熱、関節痛(両手足首)、発疹、歯肉炎が出現。現地の病院で膠原病スクリーニング等の精査を受け、異常所見は認められなかったものの関節痛が持続するため、6月30日に当センターを受診した。いずれの症例も来院時の検査でチクングニヤウイルスIgM抗体及び中和抗体陽性であり、血清学的にCHIKFと確定診断した。流行地から帰国した後、遷延する関節症状を訴える患者を診療する場合には、リウマチ性疾患との鑑別の上でもCHIKFの可能性を考慮に入れた正確な血清診断を行うべきである。

報告企業の意見	今後の対応
2009年5月から6月にかけて、東南アジアから日本へ帰国後に、遷延する関節痛を主訴に来院した3例を血清学的にチクングニヤ熱と診断したとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

041

在日ラテンアメリカ人の慢性シャーガス病キャリアーと2次感染予防

慶應義塾大学医学部熱帯医学寄生虫学

○三浦 左千夫, 竹内 勤

我が国の在日ラテンアメリカ人は既に40万人に達する勢いで増加している。そのうちブラジルからの滞在者が80%を占めており、その8万人が既に定住永住権を取得している。こうした中で、南米特有の風土病シャーガス病患者も散見されるようになった。近年各地医療機関から依頼のあった心疾患患者41名についてシャーガス病病原体*Trypanosoma cruzi* (*T.cruzi*) 血清抗体検査を行った。その結果15名 (36.59%) が明らかに陽性と判定され、シャーガス病が示唆された。更に、抗体陽性者について血液を材料にしたPCRを行った結果4名に*T.cruzi*－DNA産物を検出した。病原体の血液内生残が強く示唆されたので、更に血液培養を試みた結果2名 (抗体陽性者の13.3%) から*T.cruzi*虫体を分離することが出来た。即ち慢性の病原体キャリアーが日本に現存することが明らかとなった。ECGでは不整脈、心エコーで拡張型心筋症を示した。ブラジル、ボリビアの生活歴がある者に関しては、我が国では臨床経験の少ないシャーガス病感染を検討すべきである。

一方、消化器系の症状を訴える患者の検査依頼は皆無であったが、心室拡張症で通院している同一患者は消化器症状 (飲み込み困難、排便困難) をも訴えているものの、検査を受けていない。

本疾患の特徴は感染者の70%は病型が定まらない慢性感染で、一見健常者とみえることである。本人、家族もその感染を認知するものは少ない。

媒介昆虫の存在しない日本国内で感染が起こるとすれば、それは輸血感染、臓器移植による2次感染であると思われる。肝要な点は、事前の抗体チェックでこのような2次感染が防げることである。ラテンアメリカ人の多くを抱える地方自治体は健康保健支援環境を整備し、シャーガス病の2次感染を阻止すべく啓蒙監視活動を強化すべきであり、全国的に行われている善意の献血現場で抗体スクリーニングを実施すべく、体制の整備を行う必要がある。

042

遷延する関節痛を主訴に来院したチクングニヤ熱の3例

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チクングニヤ熱 (Chikungunya fever; CHIKF) は発熱、関節炎、発疹を主症状とする熱性疾患であり、臨床症状や検査所見はデング熱に類似するが、遷延する関節症状が特徴的である。本年になり東南アジア地域を中心に再びCHIKF流行が拡大しており、当センターにおいても2009年5月から6月にかけての2ヶ月間で、東南アジアから帰国後に遷延する関節痛を主訴に来院した3例を血清学的にCHIKFと診断したのでその概要を報告する。(症例1) 52歳日本人男性。2009年3月26日から4月5日までインドネシア・スマトラ島へ蝶の採集目的で滞在。3月31日に39.5度の発熱、関節痛 (両手足首、両膝) が出現。翌日には解熱したものの関節痛は持続したため、帰国後5月上旬に近医整形外科受診。関節リウマチ、痛風検査を実施されるも陰性であったため、精査目的で当センターを受診した。(症例2) 30歳日本人男性。2009年4月16日より6月14日までインドネシア・ジャワ島へ舞台公演目的で滞在。5月13日に発熱、関節痛 (右足首、左膝、右肩)、頭痛、発疹が出現。4日後に解熱したものの関節痛は持続したため6月22日に当センターを受診した。(症例3) 39歳日本人女性。2009年4月4日より6月28日までマレーシア・クアラルンプール郊外に帯同家族として滞在。5月12日に39.5度の発熱、関節痛 (両手足首)、発疹、歯肉炎が出現。現地の病院で膠原病スクリーニング等の精査を受け、異常所見は認められなかったものの関節痛が持続するため、6月30日に当センターを受診した。いずれの症例も来院時の検査でチクングニヤウイルスIgM抗体及び中和抗体陽性であり、血清学的にCHIKFと確定診断した。流行地から帰国した後、遷延する関節症状を訴える患者を診療する場合には、リウマチ性疾患との鑑別の上でもCHIKFの可能性を考慮に入れた正確な血清診断を行うべきである。

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 9. 16	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		ProMED 20090831.3065, 2009 Aug 31. 情報源:Thanhnien News.com, 2009 Aug 29.	ベトナム

研究報告の概要

○デング/デング出血熱 最新情報
[1]ベトナム
ベトナムの首都ハノイの保健当局は、年初～8月下旬のデング熱患者数が2500名近くに達したと報告した。これは、2008年の同時期の10倍以上となり、ここ数年で最悪の状態である。国立感染症・熱帯医学研究所の医師によると、患者の大半は市内のHoang Mai、Thanh Xuan、Dong Daなどの地区で発生しており、2008年に隣接の地区を合併して人口が増えたために患者が増加したという説を否定した。
南部のホーチミン市では、2009年の症例数は大きく増えてはいないものの、重症化・死亡する患者が多くなっている。市の保健当局によると、年初～現在までの症例数は7100例で2008年の同時期と比べて5%多く、死亡患者は現時点で7名となっている。同市の第一小児病院では治療を受けている80名以上の子供のうち、1/4は循環器障害、神経学的問題、出血などを発症するステージ3か4である。毎日20～25名の子供が入院しており、70%はホーチミン市の患者である。「症状が出て1～2日の間は、手足口病やH1N1インフルエンザと区別がつきにくい。H1N1では様々な症状が現れるため、デングへの警戒がおろそかになっているが、子供は死に至る危険性がある」と第一小児病院の医師は警告した。

報告企業の意見	今後の対応
ベトナムの首都ハノイで、デング熱患者が2008年の同時期の10倍以上に達し、南部のホーチミン市では重症化・死亡する患者が多くなっているとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

(10)