TESTIMONY

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BEFORE THE

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AND

COMMITTEE ON GOVERNMENTAL AFFAIRS

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Jesse Goodman, an Infectious Diseases physician and scientist, and Deputy Director of the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to appear today to discuss FDA's response to the emerging threat of transmission of West Nile virus (WNV) through blood and tissue. One of FDA's primary responsibilities is to help ensure the safety of the nation's blood supply. Within FDA, CBER is responsible for regulating blood and blood-related products. Our goal is to help ensure the safety of the nation's blood supply by minimizing the risk of infectious disease transmission and other hazards, while maintaining an adequate supply.

The Department of Health and Human Service's (DHHS or the Department) Coordination

In 1995, DHHS created the Blood Safety Committee to ensure coordinated activities across the Department. Chaired by the Assistant Secretary for Health, the Committee

includes the Commissioner of FDA, the Director of the Centers for Disease Control and Prevention (CDC), and the Director of the National Institutes of Health (NIH). There have been periodic meetings to discuss important safety and availability issues concerning the blood supply. On September 13, 2002 , the issue of West Nile virus was discussed with the Chair of the Blood Safety Committee. DHHS also established the Advisory Committee on Blood Safety and Availability (Advisory Committee) to look at broad issues including global public health, legal, ethical, and economic matters related to the blood system. On September 5, 2002 , the issue of West Nile virus was discussed at this Advisory Committee meeting so that the public and blood industry would be informed of the latest CDC and FDA efforts. In addition to these activities at the Department, the current status of the West Nile virus epidemic was presented as an information item at FDA's Blood Products Advisory Committee (BPAC) on

September 12, 2002 . The BPAC considers scientific technical issues related to regulation of blood and tissue.

FDA'S ROLE

In recent years, tremendous steps have been taken that have greatly enhanced the safety of our blood supply. While we now face a new challenge, the American public can be assured that FDA is vigilant in its efforts to keep blood as safe as possible. In July 1997, CBER initiated a Blood Action Plan to increase the effectiveness of our scientific and regulatory actions and to ensure greater coordination with other parts of the Public Health Service (PHS). We recognized then, and recognize now, that potential threats to the blood supply will continue to emerge and we believe that helping to ensure blood safety requires timely action and a coordinated approach. Consequently, FDA works closely with CDC and NIH, and seeks input from consumers and the blood, diagnostic, and biomedical industries, to develop strategies that lead to appropriate studies, risk assessment, communication, and any other prevention strategies or regulatory controls needed to protect the blood supply.

Over a period of years, we progressively strengthened overlapping safeguards that protect patients from unsuitable blood and blood products. FDA's blood-safety system includes the following five measures; all of which are relevant as we address the threat of

West Nile virus:

- **Donor screening:** Donors are provided educational materials and asked specific questions by trained personnel about their health and medical history. Potential donors whose blood may pose a health hazard are asked to exclude themselves. Donors also undergo medical screening to ensure that they are in good health at the time of donation.

- **Blood testing:** After donation, each unit of donated blood undergoes a series of tests for blood-borne agents such as HIV-1, HIV-2, HBV (hepatitis B virus), HCV (hepatitis C virus), HTLV-1 and HTLV-II (Human T-Cell Lymphotropic Viruses), and the agent of syphilis.

- **Donor lists:** Blood establishments must keep current a list of individuals who have been deferred as blood or plasma donors and check all potential donors against that list to prevent use of units from deferred donors.

- **Quarantine:** Donated blood must be quarantined until it is thoroughly tested

and the donation records have been verified.

- **Problems and deficiencies:** Blood establishments must investigate any failures of these safeguards, and correct system deficiencies that are found by the firms or through FDA inspection. Firms must report to FDA any manufacturing problems, e.g. biological product deviations that may affect the safety, purity, or potency of their products.

If any one of these safeguards fails, affected blood products are considered unsuitable for transfusion and subject to recall.

WEST NILE VIRUS

Background

WNV is the most recent emerging infectious disease threat to public health and, potentially, to the safety of our blood supply. WNV primarily infects birds but can be transmitted to humans and other animals by mosquitoes. The majority of humans who become infected never develop symptoms. Approximately one in 150 of those people infected develop serious and life-threatening nervous system infection.

Although FDA was concerned about the possibility of West Nile virus being transmitted by blood transfusions, until three weeks ago available evidence suggested that any risk was likely to be very low. We knew that such transmission was plausible because the virus is believed to be present in the blood for a period of a couple of days to weeks early in infection, including in patients who never develop symptoms of infection. Thus, a donor could feel well but, after mosquito exposure, could have the virus present in the blood for a short time and, while unaware of this, could donate blood. However, the risk of such an infected donor transmitting infection was believed to be very low because, unlike classic transfusion-transmitted viruses such as HIV and hepatitis B and C, where individuals may be infected for life, in West Nile infection there is no known chronic carrier state. Persons infected with WNV develop a rapid immune response, which clears the virus from the blood stream. Thus, to pose a risk to recipients, a donor would need to donate blood precisely during the days in which the virus is present in the blood.

In addition, levels of virus in the blood, when present, are low compared with HIV or hepatitis. Finally, despite three previous years of reported WNV cases in the

United States , and many years of epidemic infections in other nations, no cases of transfusion transmission had been reported.

Risk to the Blood Supply

FDA has been working closely with CDC, state health departments, and blood organizations as part of the ongoing investigations of the recent WNV cases where patients had received organ transplants or blood transfusions. Based on the preliminary results of these investigations, we believe that it has been shown that organ transplantation can transmit WNV and that it is very likely that blood transfusion also has done so. Thus, there is a newly recognized threat to blood safety.

It is important to recognize that the true dimension of the risks of either blood transfusion or transplantation spreading West Nile virus is not defined at this time and more

information is critically needed. The risk could be higher or lower than the case reports suggest. Our investigations continue and new information, which shapes our understanding of the risk, comes to light almost daily. We are working closely with CDC, NIH, the Health Resources and Services Administration (HRSA), and with colleagues in the blood transfusion community to address this evolving situation, and to share new knowledge. We are communicating with Congress, the public, the media, the blood industry, and health professionals. As we have much to learn, we strive to present a clear picture of our evolving understanding of this potential risk.

To better define the risk and to determine what interventions are needed will require more knowledge. We are investigating case reports as they are received. We are also working with CDC, the blood community, and NIH to design and help implement studies that will give us a better idea of what proportion of donors may be infected in areas of differing intensity of disease transmission. We are hopeful that additional studies can provide information as to the degree to which such infection of donors then translates into risk for blood recipients. FDA also believes that studies are needed to confirm that long-lived blood stream infection (viremia) does not occur in persons who are potential blood donors. In addition, we are encouraging further studies of the effects on the virus on various conditions of blood product storage and manufacturing. We also are working with our partners to study the incidence of infection in frequently transfused individuals or those receiving plasma derivatives, such as patients with thallassemia, hemophilia, and immune deficiencies, even though existing information indicates that steps normally taken in the manufacturing of plasma derivatives are expected to kill this virus, thus protecting recipients. All of this knowledge, as it becomes available, will help us, not only to better understand the nature and the degree of any risk, but also to shape effective policy and better protect the public.

While it is true that transfusion has not yet been conclusively proven to transmit infection to any patients, we now believe, based on the aggregate of recent reports and laboratory testing, that it is likely that this has occurred, and can occur in the future. We are particularly concerned that in 1 of the cases under study, 3 different donors, among 15 tested, may have carried the WNV at the time of donation. This would obviously represent a far cry from the predicted likelihood of something like 1-2 in 10,000.

This estimate is from a CDC modeling study based on the density of infection during the 1999 epidemic in Queens , New York . Unanswered questions include: Is the West Nile virus persisting longer than expected in the bloodstream of some patients? Is there something unusual about the donors to this recipient? These possibilities are under investigation. Regardless of the answers, we now have a very heightened level of suspicion and concern about all such reports, even if some may represent coincidental occurrence of transfusion and infection. Such coincidences can be expected to occur because the same individuals who need transfusions--the elderly, the chronically ill, and the immunosuppressed--are also most likely at higher risk to develop severe West Nile infection.

FDA Response

Based on the growing distribution and increased number of cases of WNV in this year's epidemic, FDA, working with CDC and NIH, decided it would be prudent to issue an alert on August 17, 2002, to the blood banking community about the possibility of transfusion-transmitted WNV, and to emphasize the need for careful attention to screening procedures for blood donors, especially the exclusion of donors with even mild symptoms that could represent early or mild WNV infection. In addition, where there have been reports suggesting that recipients of blood transfusions may have been infected

by donated blood, we have worked with the blood banks and state health departments involved to take a precautionary approach. In these cases, the blood banks, at FDA's request, have withdrawn any untransfused blood components to protect other potential recipients while we investigate whether the donor(s) may actually have been infected.

More recently, we learned that the Mississippi blood donor, who likely transmitted WNV to a transfusion patient, became ill four days after donating blood. FDA policies encourage reporting by patients and resultant evaluation by blood banks of such so-called "post-donation" events. We have alerted blood banks to this finding and plan to issue guidance shortly to emphasize the importance of soliciting and investigating post-donation reports of illness. In cases of serious illness, quarantine of blood products and investigation of the donor illness should provide an additional safeguard to reduce the risk to possible blood recipients. With regard to donors who never develop symptoms, we need to continue to investigate and collect information so that we can develop appropriate policies to further reduce the risk of transfusion-transmitted infection.

Some have raised the question whether not allowing anyone who reports mosquito bites to donate blood would be appropriate. This would likely be both inefficient and ineffective. Most people living in areas where WNV is spread will have had recent mosquito bites and we would exclude a large number of safe donors for every one donor with actual WNV infection. In addition, some individuals with WNV infection will not recall mosquito contact. These factors suggest that such measures could create serious blood shortages with the potential to hurt far more people than might be helped.

If areas of intense WNV transmission can be identified, another measure that could be considered is excluding donors from those areas. This approach could potentially reduce risk, but the ever-expanding map of transmission makes it likely that this approach could likewise cause blood shortages, yet may still fail to exclude a significant number of infected donors. Nonetheless, if an unexpectedly high risk is identified in a specific area, such measures could be considered, particularly if no other effective interventions might be immediately available. It is also possible that a greater use of autologous blood collections could be encouraged in areas of intense infection.

The most effective means of reducing the risk of WNV transmission by blood transfusion, if confirmed to be significant, would be to test donor blood samples for the presence of the virus. Such testing could be performed generally (e.g., on all blood donors nationally), which is most likely, or, if transmission is more restricted, during seasons where transmission is occurring, or, in donors from selected regions. If specific populations (e.g., transplant or other immuno suppressed individuals) were to be identified as being at special risk for severe disease from receiving WNV infected blood products (and other populations not), donor screening could be performed to target blood intended for such individuals. It is unlikely, however, that an approach focused on specific recipients would be either desirable or practical, except perhaps as an interim measure were one needed until testing methods for broader use were made available. All individuals exposed to WNV are at risk for infection, and the elderly, who appear most at risk for severe disease, also need transfusions more frequently than other populations.

What are the prospects for availability of a good blood screening test for this disease? In short, the prospects are encouraging although it cannot happen overnight and significant challenges will need to be addressed. Classic tests for infectious agents involve looking for the human's immune response to the agent, in the form of antibodies. However, in the case of this virus, the WNV is present in the blood during the time period before antibodies develop. Therefore, direct methods to detect the virus itself will be needed.

These methods are more complex, more expensive, and more difficult to implement on a broad scale than antibody tests. On the positive side, state and academic labs, some diagnostic companies, and the CDC, have developed sensitive tests that can amplify and detect the genetic material of this virus.

Tests based on similar technologies, called NAT (for nucleic acid amplification test), are now universally used in the U.S. to test all donated blood for the presence of early HIV and hepatitis C infection. These tests have helped make our blood supply very safe from these infections, with risks of transmission of these agents in the 1/1,000,000 range for hepatitis C and in the 1/2,000,000 range for HIV. The medical diagnostics industry, the blood industry, and FDA have significant expertise in the development, implementation, and evaluation of NAT testing. Such experience will be useful in adapting WNV test methodologies currently in use in diagnostic laboratories to more widespread and automated use for blood screening. There are many challenges, including the need to achieve high levels of reliability when used in populations with very low frequencies of infection, the lower levels of virus compared to those currently tested, the difficulties involved in scale-up, and time needed for test development and wide implementation. For testing organ donors, special challenges would be added, including timing, logistics, and determination of whether screening blood samples can rule out infection in tissues and organs. While we do not yet know if screening of blood will be needed, we believe it is likely, and therefore most prudent, to move forward to facilitate its availability as soon as possible.

To this end, we are working with our partners in the blood and diagnostics industries, including the American Association of Blood Banks and AdvaMed. Recently, they hosted an important meeting with FDA, CDC, and state health departments with potential WNV diagnostics methodologies to discuss the development of assays of potential utility, to stimulate interest in testing, identify barriers and approaches to resolve them, and foster technology transfer and sample sharing, all in an effort to get all partners the information and materials needed to be as prepared as possible to meet the potential need for testing. This meeting was quite successful and we plan a follow-up public workshop at FDA co-sponsored by CDC, NIH, and HRSA in the near future. Further development and implementation of effective screening tests for WNV will depend in large part on the efforts and innovation of our public health and blood and diagnostic industry partners. It is important to note, however, that FDA can use its regulatory authority to make such tests available even before licensure under an investigational new drug (IND) application. Again, while we hope that this will not turn out to be needed, we must be prepared.

One final approach that could be used in helping to address the WNV threat, as well as other future and potential infectious risks to the blood supply, is called “pathogen inactivation.” In pathogen inactivation, a chemical and/or physical treatment of blood products is used that is capable of killing many infectious agents. FDA recently held a workshop on this promising and innovative strategy. Several approaches are currently under study and may be effective at inactivating viruses such as WNV. Although promising, it is important to realize that preventive treatment of blood products affects the products given to all recipients. In other words, if only 1 in 5,000-blood units had an infectious agent present, for every patient protected from the disease, 4,999 would receive a product that may be altered in some ways that could affect its other characteristics and, perhaps, its safety. For these reasons, these approaches must be, and are being, carefully evaluated for their immediate and long-term safety. However, should WNV risk prove significant in degree, or blood screening be difficult to implement in a timely manner, pathogen inactivation may prove valuable as an approach to reducing risk in blood either from high risk areas and/or potentially for blood being

given to recipients at highest risk of developing severe disease. Such approaches could also be initiated and evaluated in pre-licensure pilot studies under an IND application. FDA is also currently planning to specifically address the inactivation of WNV by such methods in conjunction with its upcoming workshop on WNV donor blood testing.

Treatments for WNV and Vaccine Development

Most people who become infected with WNV will have either no symptoms or only mild ones. More severe disease occurs in approximately 1/150 of those infected and is manifested as encephalitis, meningitis, or meningoencephalitis. Encephalitis refers to an inflammation of the brain; meningitis is an inflammation of the membrane around the brain and the spinal cord, and meningoencephalitis refers to the combination of both. There are currently no drugs on the market to treat this virus. There are currently six IND applications involving two products in effect at FDA for the treatment of WNV. The National Institute of Allergy and Infectious Diseases (NIAID) has also supported promising research to identify and develop potential treatments for this disease.

While there is currently no licensed vaccine available to prevent WNV infection, FDA is aware of several promising approaches to vaccine development and believes that this is a potentially viable strategy to address this increasing public health threat. Because of the increased presence of WNV in the U.S., NIAID has supported research in this area. NIAID announced that in 1999 it funded a fast-track project to develop a candidate WNV vaccine with Acambis PLC. Scientists at CBER are also engaged in studies, which may hold promise for developing a vaccine effective against WNV.

Given the important and increasing public health impact of WNV infection, including the potential threat to blood safety, and the lack of available vaccines and therapeutic measures, FDA places a high priority on facilitating the development and review of such products.

CONCLUSION

As we act on our current knowledge of the risk of WNV to the blood supply, and share information with the public as it becomes available, it is also important that we keep the risk, even a risk that is not yet well understood, in perspective. There has been a remarkable decrease in the transmission of viral diseases through blood in recent years. We believe that our experience in dramatically reducing the risk from HIV and hepatitis will serve us well in addressing whatever needs to be done with respect to the challenges we now face with the WNV. Thousands of individuals' lives are saved or transformed every year by organ transplants. Millions of lives are enhanced by transfusion of blood and related products. It is essential that we keep these medical procedures and related products as safe as possible.

We will continue to work closely with our partners in CDC, NIH, HRSA and the states, and to engage the blood and diagnostics industries to harness their capabilities to help make a sensitive blood test a reality. We will continue to share information with and seek input from the public and from experts outside of government, as we recently did with both FDA's Blood Products Advisory Committee and the DHHS Advisory Committee on Blood Safety and Availability. We will continue to engage the highest levels of attention with the Department, including discussion of major blood safety policy issues with the Assistant Secretary's Blood Safety Committee.

As a final note, FDA would like to encourage the public to continue donating blood because supplies are low and the need is great. Blood remains in short supply, in part,

because of the extensive safety measures already in place. Some people are concerned that they might get an infection by donating blood. We want to assure you and the public that donating blood is a safe procedure. We also want to take this opportunity to thank blood donors and to emphasize that the cornerstone of our blood safety system is the volunteer blood donor. Thank you very much for the opportunity to testify today.

I welcome your ideas and your questions.

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