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**TO:** PPTA North American Board  
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**CC:** Global Board of Directors  
Global Management Committee  
Source Board of Directors  
Regulatory Policy and Compliance Steering Committee  
Health Policy Steering Committee

**FROM:** Christopher P. Healey, Executive Director PPTA North America

**SUBJECT:** Summary of West Nile Virus Meeting with FDA

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PPTA staff and member company representatives recently met with officials from the Food and Drug Administration (FDA or the Agency) to explore a path forward for the plasma therapeutics industry to address West Nile Virus (WNV). A copy of the meeting agenda is attached. In general, the meeting was very productive. Industry presented a three-part approach to addressing WNV that includes: (1) risk assessment, (2) viral clearance verification studies, and (3) continued surveillance. Agency officials expressed a willingness to consider alternatives to Source Plasma donor testing for WNV that draw on the approach industry presented. Further, FDA officials outlined specific data that might support a change in the Agency's current position with respect to donor testing for WNV. Background information and a more detailed summary of the meeting follows.

### Background

As you may be aware, the FDA's Blood Products Advisory Committee (BPAC) met in March 2003 to consider, among other things, precautionary measures to address the potential risk of WNV to blood and blood products. At this meeting, the BPAC recommended the following steps to address plasma therapeutics: (1) industry validation of viral inactivation measures, and (2) donor testing for WNV. Industry

argued against the need for donor testing based on the presentation of robust viral inactivation data from verification studies using WNV and model viruses.

Following the BPAC recommendation PPTA expressed to FDA its significant concerns about the public process that led to the BPAC vote. More specifically, PPTA expressed concern about the fact that industry had not been forewarned about the questions being put to BPAC regarding donor testing and process validation and the conduct of the Committee deliberations. More important, PPTA strongly expressed its position that donor testing is not warranted for WNV given the epidemiology of the disease and significant margin of safety demonstrated through viral inactivation studies. As a result of PPTA's initial exchanges with FDA, the agency agreed to meet with industry experts to discuss a potential path forward to address WNV.

### Industry Paradigm for WNV

Through a series of meetings with industry viral safety, quality and regulatory experts, PPTA developed a three-part approach for addressing WNV in plasma therapies. First, this approach includes performing a risk assessment to establish worst-case and likely-case scenarios for the possible contribution of WNV positive donations to a manufacturing pool. Second, the approach calls for the performance of viral clearance verification studies to demonstrate the margin of safety over and above the worst case and likely case risk assessment.

Third, the industry approach calls for ongoing surveillance of the WNV epidemic to assure continued accuracy of the facts underlying the risk assessment. Surveillance focuses on the disease prevalence as reported by the Centers for Disease Control and Prevention (CDC) and viral titers in known WNV positive individuals. This latter element would be based on testing performed on blood donors; a sampling of positive donors would be further tested to determine the virus titer in their plasma. In the event that either the disease prevalence or the viral titers were to significantly change, the industry risk assessment could be revisited and further action could be considered.

### Industry Presentations

During the meeting with FDA, industry representatives presented a WNV risk assessment. A copy of the two risk assessment presentations is attached. In general, the risk assessment calculated the worst-case and likely-case of the potential WNV titers in a Source Plasma preproduction pool. Based on maximum donor WNV titers of  $2 \times 10^5$  PCR copies/ml and a worst-case prevalence of 10.4/10,000 donors for an outbreak area, the calculated potential pool load could be a maximum of 1 iu/ml. This risk assessment was then discussed in the context of industry clearance data that demonstrate WNV log reduction factors of between >5.5 and >8.2 logs for a single process step; additional clearance steps would provide for an ever larger margin of safety.

Representatives from the participating PPTA member companies (Aventis Behring, Baxter Bioscience, and Bayer Biologicals) presented supporting information for their company clearance studies. This proprietary information included data regarding the specific assays used, study set-points, and details regarding the inactivation methods employed in the study. During this portion of the meeting only representatives from the presenting company remained in the room.

The final part of the industry presentations included the introduction of the PPTA paradigm for addressing WNV as discussed above. It was noted that the foregoing presentations address the risk assessment and verification study parts of the industry paradigm. Thus, PPTA representatives discussed the potential for conducting epidemiological surveillance based on CDC reported data and collaboration with the blood industry once blood donor testing commences. A copy of this presentation is also attached.

#### Industry – Agency Dialogue

Agency officials initiated the dialogue by acknowledging the substantial work that industry has done to address WNV. Nonetheless, Agency officials stated that donor testing and validation of viral clearance with the virus of interest are a *de facto* policy for addressing transfusion transmitted pathogens. Importantly, FDA indicated that alternative approaches might be considered when sufficient data demonstrate the absence of risk.

The ensuing discussion between FDA and industry centered around the types of data that would support an alternative approach to donor testing and validation of viral clearance. Although no formal Agency position was stated, FDA representatives indicated that the following data would be necessary in order to adequately consider alternative approaches to addressing WNV:

- ?? testing of plasma pool retention samples from August 2002 demonstrating viral titers consistent with those calculated in the WNV risk assessment,
- ?? data for two independent process steps showing WNV clearance with a >4 log margin of safety over known viral titers, and
- ?? prospective surveillance of viral titers in known positive donors during the anticipated 2003 WNV epidemic.

Although the Agency did not endorse the industry paradigm for addressing WNV, the types of data requested generally comport with the industry approach. In essence, FDA has requested additional data to support the current WNV risk assessment and industry verification studies. Further, the Agency has articulated the types of data industry should monitor as part of its proposed surveillance.

During the discussions, the Agency and industry explored various possibilities for developing clearance data on two process steps. FDA officials suggested that industry

might want to develop a so-called “master file” through which companies could cross reference clearance data for process steps shown to be sufficiently similar. Industry representatives proposed a limited verification study for a second step that would test only a single set point rather than a range of process parameters. It was noted that one process step studied must be inactivation and a second step may be removal.

With respect to surveillance, FDA expressed a preference for surveillance of viral titers among Source Plasma donors through an investigational new drug (IND) process. However, Agency officials appeared open to the possibility of utilizing samples from known WNV positive blood donors to monitor maximum viral titers. The Agency also appeared willing to engage in further discussion about the need to conduct surveillance through the IND process.

Other comments indicated that the Agency expects the results of clearance verification studies to be submitted as a license supplement to existing biologics licenses. It was also noted that the industry risk assessment should be revised to include the possibility of multiple donations from a single infected donor. Finally, the Agency expressed a desire for industry to perform surveillance in a fashion that would allow for the collection of data on viral kinetics over time.

### Conclusion

As noted above, the Agency did not endorse the industry paradigm for addressing WNV but indicated openness to considering alternatives to donor testing if data demonstrate the absence of risk. The key data elements FDA identified track the three elements of the industry paradigm. In essence the Agency has asked for further refinement of the proposed paradigm through the collection of additional data and information. Nonetheless, substantial questions remain about precisely what types of data are needed, how such data should be collected, and what regulatory mechanisms must be employed. Notwithstanding these open questions, the meeting was productive and offered the possibility of developing an alternative approach to addressing WNV.

Attachment(s)