Plasma Protein Therapeutics Association

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Reference: EPST11002 **VIA E-MAIL**

Jay S. Epstein, MD
Director, Office of Blood Research and Review (HFM-300)
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852

SUBJECT: Blood Products Advisory Committee [Docket No. FDA-2011-N-0002]: HBV NAT clinical sensitivity

Dear Dr. Epstein:

More than 10 years ago, PPTA launched two voluntary standards programs to complement established regulatory requirements: the International Quality Plasma Program (IQPP) which covers the area of plasma collection, and the Quality Standards of Excellence and Leadership (QSEAL), which is a manufacturer-based standard. As part of the standard, QSEAL-certified manufacturers are required to perform Nucleic Acid Technology (NAT) testing for HCV, HIV and HBV either on single units, mini pools and/or the fractionation pool. Within the PPTA membership, mini pool NAT testing in conjunction with production pool testing is the preferred algorithm for all three of these viruses.

At the April 2011 meeting of the FDA Blood Products Advisory Committee (BPAC) the Committee advised FDA that scientific data support the concept that testing Source Plasma for HBV DNA by NAT increases the margin of safety of plasma protein therapies and that testing of donors contributes to overall public health.

Clinical Sensitivity

During the course of the meeting, the BPAC recommended a sensitivity of at least 500 IU/mL for the individual Source Plasma collection unit (clinical sensitivity) for HBV NAT when testing mini pools of Source plasma. While not mandatory, FDA usually accepts the recommendations of its advisory committees. Prior to your accepting the BPAC recommendations relating to clinical sensitivity, PPTA would like to provide some additional considerations concerning the establishment of such a stringent threshold for HBV NAT clinical sensitivity.

Influence of Standards

Benchmarking clinical performance to recognized standards ensures a common expectation concerning potential variations in performance among multiple test platforms. The development of the WHO International Standards to use with NAT testing for viral pathogens has provided the means to improved confidence in the

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establishment of common expectations related to clinical performance. However, recent experiences with replacement WHO International Standards indicate that continuity to the original standards may be elusive. Collaborative studies that include a range of laboratories using different tests are the basis for the establishment of International Standards. As replacement standards are established, bias and inconsistent quantitation due to different mixes of laboratories, qualitative and quantitative tests may lead to a 'drift' in the International Unit which is the basis for quantitation. Coupled with the accuracy and precision of current NAT test, this could potentially lead to perceived inaccurate quantitation by existing tests.

The discussions at the BPAC concerning the establishment of a threshold of 500 IU/mL for HBV NAT clinical sensitivity did not take into account the potential loss of continuity when the current HBV International Standard is replaced. Indeed, the stringency of a threshold at 500 IU/mL could place once-compliant NAT test systems in default when a new standard for HBV is introduced. A mere shift of 1-2 IU/mL in analytical sensitivity could raise concerns about sample pool sizes where none existed previously. Such shifts could readily result due to changes in matrix constituents, stability profile, or standardization protocol. In light of this emerging awareness concerning the variation among replacement standards, the PPTA urges FDA to consider a less stringent threshold for HBV NAT (which could be set after further discussions with stakeholders).

NAT testing of Source Plasma is one of several measures that increase the margin of safety of the final medicinal products. The responsibility for testing lies with the individual manufacturer of these products. Safety and availability are of key importance to patients using these products. NAT testing of the manufacturing pool is accepted as the crucial point before manufacture to ensure that only non-reactive materials are processed. This testing strategy has proved to be efficient and reliable over more than a decade of testing.

The Association looks forward to continued work with FDA on efforts to solicit advice and recommendations from BPAC on the Agency's regulatory issues. PPTA welcomes from FDA any questions regarding the above comments or requests for additional information.

Respectfully Submitted,

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Vice President, Global Regulatory Policy
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cc: Dr. Susan Zullo