Plasma Protein Therapeutics Association

January 27, 2012
Reference No.: FDAA12003

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

VIA WEB

SUBJECT: Draft Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components, including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus [Docket No. FDA-2011-D-0799]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is the international trade association and standards-setting organization for the world's major producers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA member companies are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

General Comments

In the Draft Guidance, FDA implies that it is meeting a previously unmet need by recommending that establishments use Agency-licensed nucleic acid amplification technology (NAT) tests to screen donors for hepatitis B (HBV) deoxyribonucleic acid (DNA). However, FDA's recommendation reflects the status quo in the plasma protein therapeutics industry; in fact, Source Plasma collectors have performed HBV NAT testing on donations for over a decade. As PPTA described during the April 2011 Blood Products Advisory Committee (BPAC) meeting, the Association's Quality Standards of Excellence, Assurance and Leadership (QSEAL) include a NAT standard, which requires NAT testing for HBV, hepatitis C (HCV), and HIV. While the Standard allows flexibility in where the test is performed (donation mini-pool or manufacturing pool), HBV NAT testing in the US has been performed under INDs at the donation mini-pool level, following the paradigm of HCV/HIV NAT testing. Voluntary testing would continue whether or not FDA recommends the testing. As such, PPTA respectfully requests that FDA revise the Draft Guidance to acknowledge the implementation and current practice of testing as part of the

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Association voluntary standards. The FDA recommendation furthers current practices by recommending the use of FDA-licensed HBV NAT tests.

It is noted that the construction of the recommendation for HIV and HCV NAT testing and the construction of this draft guidance for HBV NAT testing differ in structure and content, specifically regarding labeling and lookback. We note that the current draft guidance, unlike the 2010 guidance, does not include lookback recommendations. We recommend a lookback of no longer than six months as that is consistent with the recommended donor re-entry time. FDA may wish to align the two recommendation documents before issuing the final guidance.

When the final guidance issues, we suggest a 12-month implementation time frame to allow transition from testing under an approved IND to testing with a licensed test. The transition to another NAT test platform is difficult and must be completed in a compliant manner.

Detailed comments

I. Introduction

Page 1: The 1st paragraph describing recommendations should include a reference to plasma establishments to be consistent with FDA Guidance for Industry: "Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry," issued May 2010.

II. Definitions

Page 2: The following definitions should be added in order to be consistent with FDA guidance noted above for HIV and HCV NAT:

- Definitions for HBsAg, anti-HBc and anti-HBs
- Definition for Deconstruction
- Definition for Subpool

III. Background

Page 3: The 4th paragraph indicating the licensed tests referenced should also include plasma donors since some of the tests are licensed specific to Source Plasma.

Page 4: The description of the Roche COBAS AmpliScreen HBV NAT fails to include the 96 donation pooling option for Source Plasma.

Page 5: The description of Roche COBAS TaqScreen MPX test fails to include the 96 donation pooling option for Source Plasma.

IV. Recommendations

Page 8: "lower limit of detection"

In general, the development of the WHO International Standards for use in benchmarking NAT test performance has facilitated the establishment of common expectations related to long-term clinical performance of such tests in the early detection of chronic viral pathogens. A case in point is found in the release of FDA's recent draft concerning the use of NAT on pooled and individual samples for the detection of HBV.

The PPTA member companies agree with the overall recommendation for the implementation of HBV NAT testing and, as stated earlier, have been testing for over a decade. However, there is still some concern over the stringency of the proposed detection limit of <500 IU/mL in Source Plasma minipools. The draft guidance is thorough in its survey of commercially available test systems, including expectations concerning the basic performance of these during high-throughput testing of donor samples. Never the less, the draft guidance does not account for anticipated variation in HBV NAT test performance that may arise over time as the WHO transitions through multiple issues of the HBV NAT Standard.

Indeed, it is noted that the performance of all of the HBV NAT test systems cited within the draft guidance has been benchmarked against the 1st WHO International Standard for HBV DNA NAT assays (97/746), whereas only 2nd WHO International Standard for HBV DNA NAT assays (97/750) is currently available for the calibration of laboratory working standards and controls. Comparison of the first and second standards indicated that a difference of 0.08 $\log_{10}$ was detected. [1] This is not surprising considering the fact that these materials have been derived from the same source and were prepared in parallel.[2] Never the less, it is conceivable that laboratories using 96- or 512-pooling algorithms may find themselves drifting slightly above a 500 IU/mL cut-off for clinical sensitivity.

When thresholds are tightly set against the statistical limits of assay performance, even the slightest variation can be magnified across a large dilution scale. For example, the 95%LOD of an HBV NAT assay may be benchmarked at 5 IU/mL. When used to test 96-sample mini-pools an allowable clinical detection level of 480 IU/mL is calculated. However, it could be argued that any variance below 0.3 $\log_{10}$ between an established standard and a proposed new standard would likely be accepted in the issuance of the new standard. Given the example of very limited variance cited above (0.08 $\log_{10}$) and a theoretically acceptable limit of <0.3 $\log_{10}$, it can be anticipated that the apparent 95%LOD of the same HBV NAT assay could drift upward from 5 IU/mL to somewhere within the range of 6-10 IU/mL. Calculation of clinical detection in a minipool of 96 samples immediately suggests that the test system is in default of the prescribed limit, falling somewhere between 576 and 960 IU/mL (note: this assumes a standard issued at 5.70 $\log_{10}$ IU/mL, or 5.5 x 105 IU/mL, with a variance of 0.08 to 0.30 IU/mL relative to the 1st International Standard [97/746]).

Fryer of NIBSC has recently addressed plans to develop a third WHO HBV standard to replace the dwindling supplies of the second standard.[3] Whether the original source

materials can continue to be utilized for new HBV standards remains to be determined. For example, different source materials have been used over the years to develop the WHO HCV standards, and Baylis et al. (2007) identified some loss in the continuity of the performance parameters between the 2nd and 3rd WHO HCV standards.[4]

In light of the potential for some variation in materials, methodologies, and analyses to occur in the establishment of future standards, PPTA proposes that the recommended target should be 1,000 IU/mL, which is comparable to the clinical sensitivities of HIV and HCV.

V. Labeling

Section B: We suggest that FDA include the recommended combined labeling statement when NAT testing is performed for HBV, HIV and HCV. Additionally, we suggest that FDA include that exceptions are allowed for labeled units to be shipped pending test results in some circumstances.

We hope that you will find our comments constructive and remain at your disposal for further discussions.

Respectfully Submitted,

Mary Gustafson
Vice President, Global Regulatory Policy
Plasma Protein Therapeutics Association

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[1] Baylis, S. A., A. B. Heath, M. Chudy, G. Pisani, A. Klotz, S. Kerby5 & W. Gerlich; *Vox Sanguinis* (2008) 94, 358–362

[2] Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A, The WHO Collaborative Study Group; *Vox Sanguinis* (2001) 80, 63 – 71

[3] J. Fryer;
http://www.nibsc.ac.uk/sogat/sogatxxii/3%20%20J%20Fryer%20HBV%20HAV%20IS%202011.pdf

[4] Baylis SA, Heath A, the collaborative Study Group; WHO ECBS Report 2007; WHO/BS/07.2055