Plasma Protein Therapeutics Association

Date: June 24, 2016
Reference No.: FDAA16010 VIA EMAIL

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

SUBJECT: **Comments to Docket No. FDA-2009-D-0539**, "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products; Revised Draft Guidance for Industry; Availability"

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) thanks FDA for the opportunity to participate in the guidance development process and is pleased to provide these comments on the revised draft guidance for industry "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products" dated April 2016 (hereinafter "Revised Draft Guidance").

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. Plasma protein therapies are used mostly in the treatment of a number of rare diseases. These 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. These therapies include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with severe autoimmune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult-onset emphysema and substantially limits life expectancy, and albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

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Comments

Section	Page	Lines	Current language	Suggested revision	Comments
VI.A.	23	903-05	"Critical method parameters, for example, incubation times and temperatures, should be validated to demonstrate that the assay performs as expected within predetermined ranges for these parameters. Generally, the low, middle, and high values of the allowed range are tested in the validation exercise."	PPTA suggests that assay robustness be removed from the validation section. Alternatively, wording could be incorporated similar to the 2009 draft guidance for industry, "Assay Development for Immunogenicity Testing of Therapeutic Proteins," at lines 568-70: "The applicant should examine robustness during the development phase and if small changes in specific steps in the assay affect results, specific precautions should be taken to control their variability."	Robustness testing is normally done as part of method development. Adding additional robustness testing to the validations will greatly increase the amount of work and the complexity of these validations. ICH Q2(R1), "Validation of Analytical Procedures: Text and Methodology" (2005) at page 13 suggests that: "The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study." Keeping the robustness with the method development in the Revised Draft Guidance would be consistent with ICH Q2(R1). Suggestions for the parameters to be examined for robustness could be incorporated elsewhere in the document; there is already some text regarding robustness testing in section

					IV.G. (Assay Design Elements, Robustness and Sample Stability) at lines 401-16.
VI.E.	26	1011-13	"Additional parameters that should be validated are assay performance when cells at the low, middle, and high range of the allowed passage numbers, cell density, and cell viability are used (see section IV.G)."		These parameters should be evaluated as part of assay development, and should not need to be repeated in validation (see comments to lines 903-05).
VII.A.	26	1040-42	"If therapeutic protein product-free samples cannot be obtained during the treatment phase of the trial, the sponsor should take additional samples after an appropriate washout period (e.g., five half-lives)."	"If therapeutic protein product-free samples cannot be obtained during the treatment phase of the trial, the sponsor should take additional samples after an appropriate washout period (e.g., five half-lives <u>or until the concentration of circulating drug is below the level for interference with detection of ADA</u>)."	Five half-lives may not be sufficient to achieve levels of circulating drug that would not interfere in the ADA assays.
VII.A.	27	1066	"The concentration of high-positive QC samples should be set to monitor prozone effects."		Please clarify the practical approach being suggested with this language.
VII.A.	27	1071-72	"This issue is not a problem for antigen bridging assays because labeled antigen is used for detection."	"This issue is not a problem for ~~antigen~~ <u>ADA</u> bridging assays because labeled antigen is used for detection."	

Conclusion

PPTA appreciates the opportunity to comment on the Revised Draft Guidance and looks forward to continued work with FDA in developing and validating immune assays for assessment of the immunogenicity of therapeutic protein products during clinical trials. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully submitted,

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Plasma Protein Therapeutics Association