Plasma Protein Therapeutics Association

Date: February 15, 2016
Reference No.: FDAA16001 **VIA EMAIL**

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

SUBJECT: Safety Assessment for Investigational New Drug Application Safety Reporting; Draft Guidance for Industry [Docket No. FDA–2015–D–4562]

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for the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance for industry "Safety Assessment for IND Safety Reporting."[1] PPTA understands that the draft guidance provides recommendations to sponsors on developing a systematic approach to IND safety reporting for human drugs and biological products and follows the guidance for industry and investigators "Safety Reporting Requirements for INDs and BA/BE Studies," which provides recommendations to sponsors on identifying and evaluating important safety information that must be submitted to FDA and all participating investigators.[2] In particular, FDA recommends that sponsors develop a safety assessment committee and a safety surveillance plan as key elements of a systematic approach to safety surveillance.[3]

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 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 immune 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 in emergency-room settings to treat individuals with 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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[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM477584.pdf accessed February 1, 2016
[2] *See* FR Notice, 80 Fed. Reg. 78743 (December 17, 2015)
[3] *See id.* at 78744

I. Safety assessment committee

A safety assessment committee would be a group of individuals chosen by the sponsor to review safety information in a development program and tasked with making a recommendation to the sponsor regarding whether the safety information must be reported in an IND safety report. The description of the committee in the draft guidance, while not precise, does include a discussion of the composition and roles of the committee and a section that is helpful to understand the differences between the committee and a data monitoring committee (DMC).

The challenge would be to form such a committee in a mid to small size organization where it may not be possible to create a multi-disciplinary internal team (mainly clinical and safety) with clinical expertise who are not directly involved in the program. This challenge may potentially be overcome with consultants, feasibility/affordability questions in smaller organizations, and/or rate limiting for study start-up activities and be unnecessary in many circumstances considering the specialty and expertise already existing within the project teams. The rationale for such a committee is to review unblinded data and facilitate IND reporting, while maintaining the integrity of the trials, but that is a limited rationale to support such a committee when the existing benefit-risk team (BRT) or safety sub-teams within industry have been facilitating similar matters with an external DMC when needed. FDA's proposal may generate some redundancies in the operating systems for some companies, as most will have safety review teams/BRTs in place with similar but different principles and mandates/dictates.

Aggregate analyses for comparison of adverse event rates across treatment groups: The draft guidance recommends unblinding of aggregate data for comparison of event rates and numerical imbalances across treatment groups to identify safety information. An alternative proposal in the draft guidance is limited unblinding of event rates for serious adverse events pre-specified in the safety surveillance plan. Either way, the draft guidance is recommending the aggregate review of safety data at pre-specified intervals and by the safety assessment committee with IND safety reports if a safety matter is identified. This overlaps with a DMC; if a DMC already is place, then the recommended safety assessment committee is potentially redundant.

Planned unblinding of safety data: The draft guidance discusses that unblinding of single or small numbers of serious and unexpected adverse reactions will not compromise the integrity of the study. The draft guidance also states that such unblinding would be infrequent and those patients may potentially be withdrawn from the study. PPTA does agree that to ensure patient safety unblinding would be needed for serious, unexpected adverse reactions for the continuation of the study patient. However, such unblinding can be deemed to have a major impact for small sample size trials and rare disease area trials, particularly, if such unblinded data were to be known by the team conducting the trials. PPTA recognizes that the safety assessment committee is the proposed solution to maintain integrity of the trial, the redundancy of which already has been discussed above.

Recommendation: Instead of a multi-disciplinary safety assessment committee, a well-rounded, consultant safety expert would perform the required unblinded review and bring the summarized blinded data back to the multi-disciplinary BRT or safety review committee that most companies already have in place.

II. Safety surveillance plan

A safety surveillance plan would describe processes and procedures for assessing serious adverse events and other important safety information. The need of a safety surveillance plan mentioned seems redundant with or similar to that part in the Safety Risk Management Plan.

Clinical trial projects are already implementing a plan, i.e. benefit-risk (BR) document, to facilitate ongoing safety surveillance. However, from the draft guidance, a cross reference to the safety surveillance plan or BR document would need to be included in the protocol; also, a summary would need to be submitted to the IND before initiating phase 2 or phase 3 studies. The additional recommendation of adding elements in the protocol would need a future update of the protocol template.

Recommendation: FDA should explain the relationship between the safety surveillance plan and the Safety Risk Management Plan and if the intention is to create yet another document.

Conclusion

In summary, it would be beneficial for industry to have the lack of clarity and the redundancies in the draft guidance, particularly the questions regarding the safety assessment committee and the safety surveillance plan, addressed in the final guidance. PPTA appreciates the opportunity to comment on the draft guidance and looks forward to continued work with FDA on IND safety reporting for human drugs and biological products. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully submitted,

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