Plasma Protein Therapeutics Association

April 18, 2011
Reference No.: FDAA11008

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

SUBJECT: Draft Guidance for Industry and Food and Drug Administration (FDA) Staff on Best Practices for Conducting and Reporting Pharmacoepidemiologic (PE) Safety Studies Using Electronic Healthcare Data Sets
[Docket No. FDA-2011-D-0057]

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.

## ***Introduction***

PPTA welcomes the opportunity to discuss plasma protein therapies via written submissions. The Association would like to thank FDA for the opportunity to participate in the guidance process and is pleased to provide these written comments on the Draft Guidance for Industry and FDA Staff on Best Practices for Conducting and Reporting PE Safety Studies Using Electronic Healthcare Data Sets [hereinafter, "Draft Guidance"].[1]

[1] *See* Federal Register / Vol. 76, No. 32 / Wednesday, February 16, 2011 / Notices, pp. 9027-8

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***General comments***

The Draft Guidance provides specific recommendations to optimize FDA's review of protocols and final reports for PE safety studies designed to assess the risk attributed to drug exposures and to test specific safety hypotheses. The publication is intended for a broad audience, including industry, FDA, and other stakeholders involved in the design, conduct, analysis, and/or interpretation of observational safety studies using electronic healthcare data sets. PPTA appreciates FDA's efforts to describe best practices pertaining to conducting and documenting PE safety studies using electronic healthcare data sets and to provide recommendations for documenting the design, analysis, and results of such studies and submitting PE safety study protocols and reports to FDA.[2]

***Specific sections***

***II. BACKGROUND[3]***

Because the regulatory decision-making process described in this section excludes evidence arising from animal studies, FDA should consider revising lines 66-67:
*Initially, there is reported evidence of an association between a particular drug and an adverse event.*
to:
*Initially, there is reported evidence of an association between a particular drug and an adverse event* ***in humans****.*

Because certain drug-event combinations may not be conducive to observational studies in electronic health records databases, FDA should consider re-wording lines 89-90:

*One early aspect of regulatory decision-making* ***is*** evaluating *the evidence from [PE] safety studies that formally test drug safety hypotheses.*
to:
*One early aspect of regulatory decision-making* ***may involve*** *evaluating the evidence from [PE] safety studies that formally test drug safety hypotheses.*

Because FDA provides specific recommendations and also refers to external best practices, the Agency should consider the statement in lines 90-93:

*As described in this guidance,* ***the*** *best practices for the conduct and reporting of [PE] safety studies using electronic healthcare data are intended to facilitate a more independent interpretation of findings from these studies.*

[2] *See* Federal Register / Vol. 76, No. 32 / Wednesday, February 16, 2011 / Notices, p. 9027
[3] Draft Guidance, pp. 2-3, lines 62-93

to call out both sources of guidance:

*As described in this guidance, **FDA recommendations and related** best practices for the conduct and reporting of [PE] safety studies using electronic healthcare data are intended to facilitate a more independent interpretation of findings from these studies.*

**A. Use of Electronic Healthcare Data Sets in [PE] Safety Studies**

> *The advent of new technologies and the ability to efficiently assemble electronic healthcare data sets for use in drug safety studies have provided many new opportunities for conducting [PE] studies of drug safety issues. These technologies allow for the possibility of studying safety issues quickly (relative to alternative approaches) in real world healthcare environments involving large populations of patients. In addition, the development of innovative statistical methods has allowed investigators to study complex drug safety questions previously considered too difficult to examine outside of a clinical trial setting. **However, these developments have also precipitated a great deal of discussion over the appropriate use of electronic healthcare data and statistical methods in conducting [PE] safety studies.**[4]*

Because the potential strengths of electronic health records data for studying safety issues are described with limited reference to potential limitations in the above paragraph, FDA should consider balancing ease and quickness with real world context against known limitations:

> *The advent of new technologies and the ability to efficiently assemble electronic healthcare data sets for use in drug safety studies have provided many new opportunities for conducting [PE] studies of drug safety issues. These technologies allow for the possibility of studying safety issues quickly (relative to alternative approaches) in real world healthcare environments involving large populations of patients. In addition, the development of innovative statistical methods has allowed investigators to study complex drug safety questions previously considered too difficult to examine outside of a clinical trial setting. **While broad access and rapid turnaround of studies may be attractive for informing urgent regulatory decision-making, given the inherent complexities and known limitations of data sets and methodologies, judgment must be exercised to ensure the appropriate and scientifically-sound use of electronic healthcare data for establishing evidence on which important decision-making will rely.***

[4] Draft Guidance, p. 3, lines 98-107

## *III. BEST PRACTICES – GENERAL CONSIDERATIONS*

### B. Background

*Based on this background and the identified gaps in evidence, investigators should establish concise study objectives and specific, feasible hypotheses.*[5]
The identification of gaps in evidence are referenced in prior guidance, including ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP), where performing a review of the literature to identify knowledge gaps is noted as a critical factor for all PE studies. FDA should clarify if this is the expectation for defining knowledge gaps for inclusion in study background sections.

### C. Study Approach Considerations

*Once the pre-specified hypotheses are identified, the study approach, including the selection of data sources, study design, and analysis plan, can be developed*.[6]
Not all studies will be hypothesis testing (studies may be descriptive for purpose of identifying potential risk factors, use patterns, etc).

### D. Study Team Expertise and Credentials[7]

PPTA agrees with FDA that an experienced, balanced study team with appropriate expertise is critical to the successful execution of a safety study. However, FDA should neither encourage nor discourage the use of certain datasets that might be more or less suitable for a given drug and safety question solely on the basis of a team's dedicated experience with specific datasets.

## *IV. BEST PRACTICES – DATA SOURCES*[8]

Best Practices should pertain to safety study planning and execution, not the datasets themselves. To improve the usefulness of the guidance, FDA should consider organizing this section for study design, conduct, analysis, and interpretation highlighting the challenges posed by electronic healthcare records, *e.g.,* problem definition and amenable study designs, cohort selection, case/control selection, exposure assessment, statistical analysis planning, etc.

## *V. BEST PRACTICES – STUDY DESIGN*

### A. Study Design Considerations

[5] Draft Guidance, p. 6, lines 214-5
[6] Draft Guidance, p. 6, lines 220-1
[7] Draft Guidance, p. 7, lines 246-54
[8] Draft Guidance, pp. 8-11, lines 277-410

*2. Examples of Study Designs (Not All-Inclusive)*

Because "one size fits all" is not a recognized study design, FDA should consider restating:

*FDA discourages the use of* one size fits all *study designs. For purposes of this guidance, a* one size fits all *study design is a design employed by an investigator in a number of [PE] safety studies, irrespective of appropriateness in addressing study questions of interest and specific hypotheses.*[9]

in the affirmative:

*FDA encourages the use of appropriate, scientifically sound study designs that address specific questions of interest with pre-specified hypotheses.*

***Conclusion***

PPTA appreciates the opportunity to comment on the Draft Guidance and looks forward to continued work with FDA on its efforts to describe best practices pertaining to conducting and documenting PE safety studies using electronic healthcare data sets. PPTA welcomes from FDA any questions regarding these comments and/or requests for additional information. Thank you for your consideration.

Respectfully Submitted,

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[9] Draft Guidance, p. 12, lines 467-70