Plasma Protein Therapeutics Association

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Reference No. HAMB14001 **Via Email**

Dr. Margaret Hamburg
Commissioner
U.S. Food and Drug Administration
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SUBJECT: FDA Transparency Initiative – Regulations Development

Dear Dr. Hamburg:

The Plasma Protein Therapeutics Association (PPTA) would like to take the opportunity to build on its previous comments to the Agency on regulations development as part of the FDA Transparency Initiative. In particular, PPTA would like to highlight a proposed rule, "Safety Reporting Requirements for Human Drug and Biological Products" (hereinafter "Proposed Rule"), and again suggest that FDA "re-propose" the non-finalized portion of the rule as part of its ongoing efforts to foster transparency.

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma-derived products and recombinant analogues, collectively referred to as plasma protein therapies, which 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. Plasma protein 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 members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

FDA Transparency Initiative

PPTA would like to reiterate its support of FDA in its efforts to improve transparency for all stakeholders, as it is beneficial to both industry and the general public to understand how and why decisions are made. Overall, PPTA believes that FDA communicates

effectively and has made efforts to become more open and transparent. Also, PPTA appreciates the efforts of FDA to attend meetings and share information with industry. It is vital that this type of dialogue continues, which allows industry and regulators to fully communicate concerns and better understand decisions.

PPTA has been active in the FDA Transparency Initiative since its launch in 2009, when the Association attended and submitted comments to the Task Force Public Meeting docket. In 2010, PPTA submitted comments on the Task Force's Phase II Transparency Report on public disclosure and on FDA's Guiding Principle of Transparency as part of the Association's comments on the FDA FY 2011-2015 Strategic Priorities document. In 2011, PPTA commented on the Task Force's Phase III Transparency Report, "FDA Transparency Initiative: Improving Transparency to Regulated Industry" (hereinafter "Report") and suggested that FDA could revise its existing review framework through transparency as part of the Association's comments to the docket on Periodic Review of Existing Regulations; Retrospective Review under E.O 13563.

Regulations Development

A common theme in PPTA comments on transparency is the need to improve the process for publication of final regulations. PPTA recommends that FDA develop and publish a process that delineates the procedure for finalizing proposed rules. Such a procedure would state that, if a proposed rule is not finalized within a reasonable amount of time (e.g. 24 or fewer months), then the proposed rule must be re-proposed for further public comment. In the meantime, PPTA urges FDA to take such an approach to non-finalized rules, the comment periods of which have ended greater than 24 months ago.

Proposed rules remain in limbo for a number of years before being finalized. PPTA recognizes that, upon publication of a final rule, all public comments are addressed in "a concise general statement of their basis and purpose";[1] however, if the rule takes five years or more to publish, the applicability of the proposed rule and comments are questionable. When a proposed rule is published and open for comment, the comments provided are based on the science and data known at that time. If it takes a number of years for FDA to publish the final rule, then those comments may no longer be applicable, as new data and technology likely are available.

Unified Agenda

PPTA also would like to reiterate its comments on Action 14 of the above mentioned Report: "FDA, working with Department of Health and Human Services and the Office of Management and Budget, will improve the accuracy of the timetables included in the

[1] *See* 5 U.S.C. § 553 (2013).

agency's regulatory agenda published as part of the Unified Agenda."[2] PPTA encourages FDA, as part of its efforts to improve the accuracy of the timetables in the Agency's regulatory agenda, to increase the amount of detail in the timetables, particularly for Long-Term Actions. While more detailed and otherwise accurate timetables will help increase transparency, the Task Force also has recognized the importance of finalizing proposed rules as soon as possible. With that sentiment in mind, PPTA encourages FDA to explore ways to finalize proposed rules more quickly and, for proposed rules already in the Agency's regulatory agenda, by the Final Action date; if the Final Action date has passed, then the proposed rule should be finalized as soon as possible or, in some cases, should be re-proposed, as mentioned above. For Long-Term Actions in FDA's regulatory agenda, PPTA respectfully requests that the Agency provide, if not a Final Action date, then more intermediate dates; a mere Final Action date of "To Be Determined" does not provide value to industry or foster transparency.

While Unified Agendas are available on the Office of Management and Budget website, PPTA appreciates FDA's creation of Unified Agenda-TRACK as part of the Agency's Transparency Initiative and FDA-TRACK. A website with an updated agenda of FDA's upcoming rulemakings is a valuable resource; however, PPTA notes that Unified Agenda-TRACK currently does not include Long-Term Actions. PPTA suggests that all rulemaking plans are of interest to a range of stakeholders and, thus, respectfully requests that FDA expand Unified Agenda-TRACK to include all rulemaking plans.

Safety Reporting Requirements for Human Drug and Biological Products

As in previous comments on transparency, PPTA points to the abovementioned Proposed Rule as illustrative of the need for FDA to improve the regulations development process. First published on March 14, 2003, the Proposed Rule's initial 120-day comment period was extended an additional 90 days to close on October 14, 2003. PPTA submitted comments on October 13, 2003, which were limited to the proposed requirements for reporting safety information related to Source Plasma donation. PPTA recognizes that FDA finalized the Proposed Rule in part in a rule, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans" (hereinafter "Premarketing Rule") on September 29, 2010, and plans to finalize the rest of the Proposed Rule a separate rule, "Postmarketing Safety Reporting Requirements for Human Drug and Biological Products" (hereinafter "Postmarketing Rule"), including requirements for blood and blood component safety reports under 21 CFR § 606.170. The proposed Postmarketing Rule was most recently published in the Spring 2011 Unified Agenda as a Long-Term

[2] PPTA notes that, as of January 25, 2012, FDA's updates to its Phase III Progress Report do not indicate that Action 14 has been completed and encourages FDA to continue to work diligently to implement it.

Action with a Final Action date of "To Be Determined"; however, PPTA understands that the final Postmarketing Rule will be published this year.

In previous comments to FDA on transparency, PPTA has questioned whether the final Premarketing Rule is applicable, as it is based on comments from seven years prior, and has suggested that it would have been more transparent for FDA to re-propose the Premarketing Rule before finalizing it. In 2014, the applicability of a final Postmarketing Rule is even more questionable, as it will be based on comments from over 10 years ago. PPTA again suggests that it would be more transparent to re-propose the Postmarketing Rule before it is finalized. PPTA questions whether, at this point, FDA has provided adequate notice and comment on the Postmarketing Rule.

The language of the "notice and comment" procedures of § 553 of the Administrative Procedure Act, as well as the subsequent development of § 553 procedures by the judiciary, suggest that FDA is required to re-propose the Postmarking Rule and re-open the comment period.[3] Notice and comment procedures have been converted into what are commonly known oxymoronically as a "paper hearing," in which agencies are required "to incorporate data and information that they relied on in formulating a rule into the notice of proposed rulemaking so that affected parties could comment on it."[4] Further, agencies have been prevented "from adopting rules that are not a 'logical outgrowth' of the initial notice of proposed rulemaking without issuing a new notice and providing a new opportunity for comment."[5] Both FDA and stakeholders should have an opportunity to consider current science and data, as well as legislation, regulatory activities, and industry initiatives since 2003, and revise the Postmarking Rule and comments accordingly.

Significant Changes in Circumstances since 2003

FDA has acknowledged that, if the Agency determines that circumstances have changed significantly since the publication of a proposed rule, FDA may reopen the comment period to allow the public to submit additional comments before finalizing the proposed rule.[6] PPTA suggests that significant changes since publication of the Proposed Rule warrant not only a reopening of the comment period but also a re-proposal of the Postmarketing Rule.

Passage of legislation

While, in 2003, PPTA was primarily concerned with the Proposed Rule's requirements for reporting safety information related to Source Plasma donation, the passage and

[3] *See supra* note 1.
[4] Sidney A. Shapiro & Richard E. Levy, *Administrative Procedure and the Decline of the Trial*, 51 U. Kan. L. Rev. 473, 489 (2003).
[5] *Id*. n.73.
[6] *See* FDA Transparency Initiative: Improving Transparency to Regulated Industry at 33-34.

implementation of the Food and Drug Administration Amendments Act of 2007 (FDAAA) has brought into question the implications of the Postmarketing Rule for biological products as well. For instance, FDAAA added new provisions to the Federal Food, Drug, and Cosmetic Act ("FDCA") authorizing FDA to require certain drug and biological product application holders to make safety-related labeling changes based upon new safety information that becomes available after the drug or biological product is approved under FDCA or the Public Health Service Act.

The safety-related labeling change authority granted to FDA under FDAAA has particular relevance to the plasma protein therapeutics industry. Citing § 505(o)(4) of FDCA, last June, FDA required manufacturers "to add information on thrombosis to the current boxed warning in the labels of all intravenous human immune globulin products and to add a boxed warning to the labels of all subcutaneous and intramuscular human immune globulin products to highlight the risk of thrombosis and to add information on its mitigation" (so-called "black box" warning). FDA asserted that a "retrospective analysis of data from a large health claims-related database, as well as continued postmarketing adverse event reports of thrombosis have strengthened the evidence for an association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis" and have necessitated a boxed warning for the entire class of products. PPTA understands that FDA considers this information to be "new safety information."[7]

In addition, section 905 of FDAAA directed FDA to develop methods to obtain access to disparate data sources and to establish a postmarket risk identification and analysis system; the law set a goal of access to data from 100 million patients by July 2012. In response, in May 2008, FDA launched the Sentinel Initiative to create and implement a nationwide electronic system for monitoring medical product safety, the Sentinel System, which is currently in pilot as Mini-Sentinel. FDA met its goal of 100 million patients early, in December 2011, and in FY 2013, expanded surveillance to 149 million patients. FDA and PPTA have discussed the implications of the Sentinel Initiative on the plasma protein therapeutics industry at recent Liaison Meetings, and Mini-Sentinel activities of FDA's Center for Biologics Evaluation and Research (CBER) have begun to impact plasma protein therapies. In particular, PPTA understands that the "data from a large health claims-related database" cited by FDA in support of the black box warning was from Mini-Sentinel. Following the black box warning, last September, Mini-Sentinel posted a protocol for a surveillance assessment of thromboembolic events after immunoglobulin administration, on which PPTA commented in October; posting of the final report is pending. The project is one of the first two protocol-based assessments of blood products in Mini-Sentinel.

[7] To better understand FDA's application of § 505(o)(4) of FDCA to require the black box warning, last August, PPTA submitted a FOIA request for any and all information regarding the "new safety information" referenced by the Agency.

The regulatory implications of adverse event reports created by the passage of FDAAA in 2007, and by FDA's implementation thereafter, including its safety labeling guidance, the Sentinel Initiative, and increased staffing capabilities, represent significant changes in circumstances since the Proposed Rule's comment period closed in 2003. In light of these changes, FDA should re-propose the Postmarketing Rule to delineate the relationship between the requirements of the rule and the implications of FDAAA. Further, had FDAAA been in place before the closing of the Proposed Rule's comment period, PPTA likely would have broadened its comments beyond the requirements for reporting safety information related to Source Plasma donation to include also those related to biological products. As such, PPTA and other stakeholders should have an opportunity to submit revised and/or new comments on the Postmarketing Rule.

Development of definitions

In the Proposed Rule, 21 CFR § 606.170 points to § 600.80(a) to define suspected adverse reactions (SARs) and serious SARs and to § 600.80(c)(4) to require a reporting format for serious SARs and for SARs that result in a fatality. In other words, the same definitions and reporting format, including MedDRA, would be used for biological products and blood or blood component collection or transfusion. However, as PPTA noted in its comments on the Proposed Rule in the Source Plasma context, the definitions of "SARs" and "serious SARs" present a lack of clarity that opens the door to wide variation in regulatory interpretation; similarly, "medical intervention" is not clearly defined. PPTA recognizes that the changes to § 606.170 were not based on any International Conference of Harmonization guidance, as were some of the other changes in the Proposed Rule. However, since 2003, steps have been taken, at the urging of regulators and through industry initiatives, both domestically and internationally, to develop adverse event definitions specific to blood and blood component collection and transfusion. PPTA suggests that these steps represent significant changes in circumstances warranting a re-proposal of the Postmarketing Rule and an opportunity to submit revised and/or new comments in light of the changes.

Continued safety

PPTA's primary concern about the requirements as described in the Proposed Rule for reporting safety information related to Source Plasma collection remains that the requirements will increase the burden without yielding tangible benefit. Source Plasma collection continues to have a proven record of safety, which is being enhanced by PPTA's PlasmaVigilance efforts. More than 10 years after PPTA's comments on the Proposed Rule, automated collection procedures, the advent of which has greatly improved donor safety, now have been in place for approximately 30 years. PPTA suggests that donor safety efforts over the last 10 years also represent significant changes in circumstances warranting a re-proposal of the Postmarketing Rule and an opportunity to submit revised and/or new comments.

Additional burden

PPTA continues to disagree with FDA that "[t]his proposed safety reporting requirement would not impose significant new burdens on blood establishments" and to believe that FDA should have forecasted IT costs for blood facilities. At the same time, changes in technology, procedures, and other organizational considerations since 2003 likely are significant and necessitate updates by FDA to its Tables in the Proposed Rule estimating benefits and burdens. Similarly, stakeholders likely can update their comments based on such changes; thus, a re-proposal of the Postmarketing Rule and reopening of the comment period would be appropriate.

Conclusion

The length of time since the Proposed Rule's comment period closed in 2003, alone, is significant; changes in circumstances in the intervening years, particularly development of definitions and passage of legislation, add to the need for FDA to re-propose the Postmarketing Rule and reopen the comment period. FDA's failing to do so risks the Agency not providing adequate notice and comment to stakeholders nor fully meeting its goal to strengthen its ability to monitor the safety of human drugs, biological products, and blood and blood products.

For this reason, and as part of FDA's on-going efforts to foster transparency through the Agency's Transparency Initiative, PPTA respectfully requests that the Postmarketing Rule be re-proposed and the comment period be reopened to allow the public to submit additional comments before finalization. More broadly, PPTA recommends that FDA develop and publish a process that delineates the procedure for finalizing proposed rules, including a statement that, if a proposed rule is not finalized within a reasonable amount of time (e.g. 24 or fewer months), then the rule must be re-proposed for further public comment. Finally, PPTA respectfully requests that FDA provide, if not a Final Action date, then more intermediate dates for Long-Term Actions in the Agency's regulatory agenda and that FDA expand Unified Agenda-TRACK to include all rulemaking plans.

If you have any questions regarding these comments or would like more information, please contact me at 443-433-1115 or mgustafson@pptaglobal.org.

Thank you for your consideration.

Sincerely,

Mary Gustafson
Vice President, Global Regulatory Policy