Plasma Protein Therapeutics Association

March 14, 2012 *Via Electronic Delivery*

Board of Governors
Patient-Centered Outcomes Research Institute
Public Comments
1701 Pennsylvania Ave. NW,
Suite 300
Washington, DC 20006

Re: National Priorities for Research and Research Agenda

Dear PCORI Board of Governors:

The Plasma Protein Therapeutics Association ("PPTA") appreciates the opportunity to comment on the Patient-Centered Outcomes Research Institute ("PCORI" or the "Institute"), January 23, 2012, draft "National Priorities for Research and Research Agenda." As the first act of prioritization by PCORI, PPTA recognizes the significance that the Institute's proposal holds for the many patients and health system stakeholders who require comparative clinical effectiveness information to make informed healthcare decisions. Accordingly, we appreciate the opportunity to provide insight into its potential effect on the plasma protein therapeutics industry.

Because plasma protein therapies almost exclusively treat patients with rare diseases, disorders, and conditions, PPTA is particularly sensitive to policies that may hinder or help patient access to the therapeutic intervention best suited for their individual needs. Thus, PPTA respectfully recommends that through the prioritization process PCORI consider the following:

- The unique and non-interchangeable nature of plasma protein therapies poses significant complexities and challenges for deriving accurate and useful data from comparative analyses;

- Because plasma protein therapies are predominantly indicated to treat rare diseases, any comparative research involving plasma protein therapies will implicate access for patients living with rare diseases, thus *any* comparative effectiveness research should trigger the appointment of the expert rare disease advisory panel;

- When appointing members to the expert rare disease advisory panel for comparative effectiveness research involving the treatment of a rare disease, disorders or condition, PCORI should consult with the patient organization representing the particular disease for recommendations for the panel's patient representative;

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- Because the unique nature of plasma protein therapies arises from the different manufacturing processes used to produce them, we urge that expert rare disease advisory panels providing guidance on comparative analyses of plasma protein therapies should include individuals with expertise in how their unique manufacturing processes affects patient outcomes; and

- Given the significance of PCORI's mandate to provide policy makers, providers, and patients with the tools necessary to make better informed health care decisions, PCORI must continue to ensure transparency at every stage of its decision making.

PPTA Background

PPTA represents human plasma collection centers and the manufacturers of lifesaving medicinal therapies, including albumin, alpha-1 proteinase inhibitor, antithrombin III, blood clotting factors, C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulins, and protein C concentrate, from this human plasma. Some of our members also use recombinant DNA technology to produce blood clotting factors. Collectively, these therapies – both plasma-derived and recombinant – are known as "plasma protein therapies." The manufacturer membership of PPTA in the United States ("U.S.") currently includes Baxter, Biotest, Cangene, CSL Behring, Grifols and Kedrion.

Many plasma protein therapies are solely approved for marketing in the U.S. by the Food and Drug Administration ("FDA") for the treatment of rare diseases, disorders, and conditions that often are chronic, genetic and life-threatening. Plasma protein therapies[1] are unique, non-interchangeable therapies that are infused or injected by patients who require them, often for the duration of their lives. In the U.S., a "rare disease or condition" is generally defined as a disease or condition that affects less than 200,000 people.[2] Given the relatively small patient populations treated with plasma protein therapies, in this clinical area, it is especially important that PCORI "considers variations in patient subpopulations." [3]

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[1] Plasma protein therapies treat alpha-1 antitrypsin deficiency, chronic B-cell lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, hereditary angioedema, hereditary antithrombin III deficiency, protein C deficiency, primary immune deficiency diseases, such as common variable immunodeficiency, X-linked agammaglobulinemia (Bruton's disease), DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, and graft-versus-host diseases, and bleeding disorders, such as hemophilia A, hemophilia B, congenital fibrinogen deficiency, Von Willebrand's disease, and factor XIII deficiency, cytomegalovirus disease associated with transplant patients, hepatitis B reinfection in liver transplant patients, idiopathic thrombocytopenic purpura, infant botulism, Kawasaki's disease, rabies, rhesus incompatible pregnancies, burns, trauma, shock and tetanus.

[2] *See* 21 U.S.C. § 360bb(a)(2) (2006).

[3] Social Security Act ("SSA") § 1181(c).

As representatives of a niche segment of the biologics industry with considerable experience in treating rare diseases, disorders, and conditions, PPTA emphasizes that the diverse clinical characteristics of these diseases and the products used to treat them translate into unique policy needs that demand special consideration.

Plasma Protein Therapies Raise Specific Challenges for Comparative Analyses

The unique non-interchangeable nature of plasma protein therapies, the patient populations they serve, and the often unique and very rare diseases they treat present challenges for comparative effectiveness analyses of plasma protein therapies. Of chief concern is that because plasma protein therapies give rise to varying pharmacokinetics and pharmacodynamics on a per patient basis,[4] it is difficult to ensure the accuracy and utility of comparative data when that data is scaled to entire patient populations. Also, the extremely small patient populations served by certain plasma protein therapies can challenge researchers' capacity to provide meaningful and comprehensive comparative data.[5] Adding to these challenges are considerations that inherently arise for researchers studying plasma protein therapies because patients may face serious adverse events if they discontinue therapeutic treatment or are administered a different therapy or treatment regimen from one in which they have been stabilized.[6]

Another significant challenge involves the per patient variances in tolerance and adverse event rates exhibited from brand to brand.[7] In 2002, Dr. Basil Golding,

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[4] Plasma protein therapy patients exhibit varying clinical responses to plasma protein therapies depending on the brand they are administered. These variances arise on a per patient basis and are determined by how an individual's biologic makeup interacts with the biologic characteristics that are specific to each brand. *See, e.g.*, R. Ameratunga et al., Increased Risk of Adverse Events When Changing Intravenous Immunoglobulin Preparations, 136 Clin Exp Immunol 111-113 (2004); M. Turf, IGIV: Contents, properties, and methods of industrial production—evolving closer to a more physiologic product, 6 Intl Immunopharmacology 517-522 (2006); L. Feldmeyer et al., Not All Intravenous Immunoglobulin Preparations Are Equally Well Tolerated, 90 Acta Derm Venereol 494-497 (2010); M.H. Tsai et al., Clinical Responses of Patients with Kawasaki Disease to Different Brands of Intravenous Immunoglobulin, 148 J. Pediatrics 38-43 (2006); *see also* Letter from Jordan Orange, M.D., and Kathleen Sullivan, M.D., to Anne Jacques, Dir. Clinical Pharmacy Servs., Highmark (Feb. 28, 2011) (on file with author) (describing the clinical differences among the brands of immune globulin).

[5] FDA has long dealt with the challenges associated with gleaning clinically meaningful data from very small sample sizes. At the 2005, FDA public meeting, *Biological Therapeutics for Rare Plasma Protein Disorders*, Agency officials described the difficulties that the Agency experiences in approving as clinically meaningful, data from small sample sizes, stating, "[a]dequate and well-controlled . . . one of the definitions for the evidence to support effectiveness, is very difficult in this [small patient population], again because of the limited sample size. . . .If the patient population is quite small we are extremely limited in the trials that we can conduct." *See,* N. Jaine, FDA Perspective: Current Clinical Trial Designs Review by OBRR for Very Small Populations with Rare Plasma Protein Disorders; P. Lachenbruch, FDA Perspective: Statistical Considerations for Very Small Clinical Trials, FDA Public Meeting, *Biological Therapeutics for Rare Plasma Protein Disorders* (June 13, 2005). Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/TranscriptsMinutes/UCM054435.pdf (last accessed Feb. 27, 2012).

[6] *See, e.g.,* K. Fischer et al., The Effects of Postponing Prophylactic Treatment on Long-term Outcome in Patients With Severe Hemophilia, 99 Blood 2337-2341 (2002). (Demonstrating that the longer prophylaxis is postponed after a pediatric patient's first joint bleed, the higher the risk is for that patient to develop arthopathy).

[7] *See, supra* note 2.

Associate Director FDA Office of Blood Research and Review described these per patient variances as an inherent clinical characteristic of protein therapeutics.[8] Expounding on the extent of these per patient variances, in 2010, Laurence Feldmeyer et al. published the results of their retrospective clinical study in the article, *Not All Intravenous Immunoglobulin Preparations Are Equally Well Tolerated*, demonstrating that patients exhibit different tolerance and adverse event rates depending on the brand of IVIG that is administered for their treatment.[9] The adverse events catalogued by Dr. Feldmeyer and his colleagues ranged in severity, including fever, chills, nausea, anaphylaxis, acute renal failure, and thromboembolic complications such as stroke and myocardial infarction.[10] Similarly challenging for comparative effectiveness research is the need to ensure that data from PCORI apprises patients and physicians in a clearly understandable manner of both effectiveness and safety. The need to clearly communicate all safety concerns associated with its effectiveness data is especially important for patients being treated for hemophilia who face the potential to develop inhibitors if they choose to change products based on PCORI data.[11] With the development of inhibitors comes an increased risk of hemophilia-related morbidity, including "uncontrollable hemorrhage, devastating joint damage, and subsequent disability."[12]

The variances in immunogenic profiles of plasma protein therapies mean that the results of comparative trials involving one plasma protein patient population may not be applicable to all patients. Therefore, for PCORI's comparative analyses to be useful for physicians seeking to provide their patients with the safest and most effective treatment, physicians must be able to predict immunogenicity based on each patient's individual biology. Currently, this capacity to predict the immunogenic profile of a plasma protein therapy for a particular patient does not exist.[13] Accordingly, plasma protein patients

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[8] Dr. Golding specifically stated, "[a]ntibody responses to proteins require T cell help, and this help is related to MHC Class II expression and T cell receptor repertoire. . . . Because these genes are different in different animal species and are, in fact, different from one human to another and any outbred species, you cannot predict from a response in one species that there is going to be a response to the same protein in another species. The same goes for humans. One human may respond and another human may not respond." *See*, FDA Public Meeting *Comparability Studies For Human Plasma-Derived Therapeutics* (May 30, 2002).

[9] L. Feldmeyer et al., *supra* note 2.

[10] *Id*.

[11] *See* Jenny Goudemand, et al., *Influence of the Type of Factor VIII Concentrate on the Incidence of Factor VIII Inhibitors in Previously Untreated Patients with Severe Hemophilia A*, 107 BLOOD 46, 48-49 (2006); Pipe, *supra* note 15 at 1696; Press Release, The European Medicines Agency, EMEA Completes Review of Recombinant Factor VIII Products and Inhibitor Development (July 31, 2007), http://www.ema.europa.eu/pdfs/human/press/pus/31022507en.pdf (describing the European Medicines Agency's study of recombinant factor VIII ("rFVIII") that revealed cases of recurring inhibitors are especially prevalent after switching from one rFVIII therapy to another in previously treated patients) (last accessed Feb. 27, 2012).

[12] Helen Platokouki, et al., *First Attempt at Immune Tolerance Induction with Factor VIII/von Willebrand Factor Concentrates in Hemophilia A Children with High-Titer Inhibitors*, 2 J. OF COAGULATION DISORDERS 35 (Feb. 2010).

[13] In the article, *Not All Intravenous Immunoglobulin Preparations Are Equally Well Tolerated*, Laurence Feldmeyer et al. spoke to the lack of this necessary diagnostic technology stating, "[t]here are currently no tests or markers available to predict adverse reactions in a given patient and guide the choice of a particular IVIG product," L. Feldmeyer *supra* note 2*;* Providing clinical recommendations based on his retrospective study Javier Carbone, also states, "[i]n view of the inability to predict which patients are likely to react and the seriousness of such reactions it is prudent to use an IVIG preparation with low concentration of IgA in patients with high titers of anti-IgA antibodies." J. Carbone, Adverse Reactions and Pathogen Safety of Intravenous Immunoglobulin, 2 Current Drug Safety 9-18 (2007).

may only realize the value of PCORI's recommendations once the diagnostic technology has been developed to allow physicians to determine whether a given PCORI recommendation will provide added benefit without also stimulating an adverse reaction. Recognizing PCORI's mandate to provide patients and providers with the information necessary to make better informed healthcare decisions, PPTA urges the Institute to ensure that its research initiatives and recommendations do not outpace the diagnostic technologies currently available to practitioners.

Deriving clinically meaningful data from comparative effectiveness analyses of certain plasma protein therapies will also be significantly challenged by the very rare nature of the diseases often treated by plasma protein therapies.[14] The rare diseases treated by these important medicines include: Factor XIII deficiency affecting approximately 60 people,[15] hemophilia B with inhibitors affecting approximately 52 people,[16] hemophilia A with inhibitors affecting approximately 1,163 people,[17] and congenital fibrinogen deficiency affecting approximately 300 people.[18] Comparative studies designed to demonstrate superiority would likely be precluded by the small patient populations of many rare diseases because the required sample size would be larger than the disease prevalence.[19] For plasma protein therapies in particular, comparative analyses involving very small patient populations will face significant obstacles to producing clinically meaningful data that effectively accounts for the potential for plasma protein therapy immunogenicity.[20] Given the significant risks associated with immune-responses to plasma protein therapies, PPTA urges PCORI to limit the Institute's comparative analysis initiatives to those studies wherein the Institute can be assured that clinically meaningful data accounting for all safety concerns can be statistically substantiated. These risks also underscore the need for a rare disease advisory panel (discussed below) to be involved when PCORI is pursuing research involving plasma protein therapies.

Also, active comparator trials are equally challenged by the availability of multiple non-interchangeable brands within each therapeutic class of plasma protein therapies. Because of these multiple brands and their non-interchangeable nature, it is difficult for PCORI to ensure that any comparative analyses using active comparators to examine

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[14] *Supra* note 3.
[15] *See,* Factor XIII Deficiency, National Hemophilia Foundation. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=71&contentid=58 (last accessed Feb. 27, 2012).
[16] *See,* Hemophilia B (Factor IX), National Hemophilia Foundation. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=181&contentid=46 (last accessed Feb. 27, 2012).
[17] *See, Hemophilia A (Factor VIII), National Hemophilia Foundation. Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=180&contentid=45&rptname=bleeding* (last accessed Feb. 27, 2012).
[18] *See, K. Tziomalos et al.*, Treatment Of Congenital Fibrinogen Deficiency: Overview and Recent Findings, 5 Vasc Health Risk manag 843-848 (2009).
[19] *See, e.g.,* M. Hoeper et al., End Points and Clinical Trial Designs in Pulmonary Aterial Hypertension, 43 J Am Coll Cardiol. 48-55 (2004) (Demonstrating that small sample sizes may preclude certain comparative trial designs).
[20] Because the immunogenic profiles of plasma protein therapies vary per patient, developing a usable sample within a rare disease population will likely require narrowing participation to a sample size that is too small to produce clinically meaningful data.

effectiveness between plasma protein therapies and non-plasma protein therapies will be applicable beyond the exact brand, dosage, and infusion rate of plasma protein therapies used in the trial.[21] Therefore, PPTA urges PCORI to limit the Institute's comparative analysis initiatives to those studies wherein the Institute can be assured that broadly useful data is gathered with the upmost consideration for patient safety.

The PCORI Rare Disease Panel Must Operate to Protect Patients with Rare Diseases

A. Plasma protein therapies are predominantly indicated to treat rare diseases, therefore any comparative trials involving plasma protein therapies should trigger the appointment of a rare disease advisory panel.

The statute requires PCORI to establish an expert advisory panel when a comparative analysis is conducted for a rare disease. The statute describes the purpose of the panel as, "assisting in the design of the research study and determining the relative value and feasibility of conducting the research study."[22] Based on the language of the statute, it seems clear that Congress intended the rare disease advisory panel to be established on an ad hoc basis to ensure the unique interests of patients living with rare diseases are fully understood and considered by researchers. Fulfilling the intent of the rare disease advisory panel is especially important for plasma protein therapies, which are predominantly indicated to treat rare diseases. When analyzing plasma protein therapies, PPTA urges PCORI to consider that these unique therapies are finitely sourced from the collection of human plasma, therefore *any* comparative analysis of plasma protein therapies, notwithstanding a particular analysis' non-rare disease focus, will have implications for rare disease patients. Recognizing the implications that comparative analyses of plasma protein therapies can have for patients with rare diseases, PPTA further urges PCORI to follow the intent of the statute and establish an expert rare disease panel for any study of plasma protein therapies. When appointing members to the expert rare disease advisory panel for comparative effectiveness research involving the treatment of a rare disease or condition, PCORI should consult with the patient organization representing the particular disease for recommendations for the panel's patient representative.

Further, PPTA recommends PCORI transparently implement clear guidance that outlines the Institute's intended process for establishing rare disease advisory panels. PPTA additionally recommends that this guidance include predictable timelines for receiving stakeholder input preceding the panel's establishment, during the panel's deliberations, and in response to the panel's recommendations. PPTA believes that it is important to move forward on providing guidance on rare disease advisory panels quickly since, once established, those panels can provide important input on research that would and would not be feasible, as PCORI further identifies national priorities for research.

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[21] Clair Foster, The Ethics of Medical Research On Humans 95 (Cambridge University Press 2001).
[22] SSA § 1181(d)(4)(A)(iii).

B. Rare disease panels focused on plasma protein therapies should include individuals with expert knowledge of the effects of varying manufacturing techniques on patient outcomes.

In addition to requiring the inclusion of patients, the statute allows PCORI to, "include a technical expert of each manufacturer or each medical technology that is included under the relevant topic, project, or category for which the [rare disease] panel is established."[23] PPTA urges PCORI to include individuals with expert knowledge of the effects that varying manufacturing techniques used by the plasma protein therapeutics industry have on patient outcomes. Including an expert with knowledge of the process-patient outcome link on the rare disease panel will provide necessary insight into how the non-interchangeable nature of plasma protein therapies arises, and what that non-interchangeable nature means for the value of the proposed study and participant safety. We encourage PCORI to reach out to PPTA for recommendations on a manufacturing representative with the expertise to provide the appropriate technical knowledge to guide PCORI in comparative research.

Conclusion

PCORI is well positioned to provide significant and positive benefit to physicians and other health care providers and patients. While PPTA supports the Institute's endeavors, we believe it is of upmost importance that PCORI's research initiatives fully account for the unique health concerns that arise when plasma protein therapies are the subject of comparative analyses. PPTA believes that PCORI can operate in cognizance of these health concerns by following the recommendations described in this comment. Finally, PPTA encourages PCORI to continue to operate with transparency and to regularly engage plasma protein therapy stakeholders in open dialogue, as this will ensure the Institute is consistently apprised of the information and expertise necessary to inform its research decision making.

We look forward to working with PCORI and welcome the opportunity to discuss the unique needs of rare disease patients who require plasma protein therapies throughout the evolution of the Institute's research and priorities.

Sincerely,

Julie Birkofer
Senior Vice President, North America, PPTA

[23] SSA § 1181(d)(4)(B).