August 19, 2014
The Honorable Fred Upton
The Honorable Diana Degette
Committee on Energy & Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: 21st Century Cures: Request for Comment Regarding FDA Clinical Superiority Requirements Specific to Orphan Product Designation

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to comment on potential reforms to the U.S. Food and Drug Administration’s (FDA or the Agency) current clinical superiority requirements for orphan designation as part of the Energy & Commerce Committee’s 21st Century Cures Initiative (the Initiative). PPTA represents the innovators and manufacturers of plasma-derived therapies predominantly used to treat rare, chronic and life-threatening diseases and disorders, including alpha-1 proteinase inhibitor deficiency, hemophilia, von willebrand disease, and primary immune deficiency (PID) diseases. Therapies include albumin, alpha-1-proteinase inhibitor, antithrombin III, plasma-derived and recombinant blood clotting factors, Cl esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, prothrombin complex concentrate, and protein C concentrate. Collectively, these therapies are known as “plasma protein therapies.” PPTA’s U.S. manufacturer membership includes Baxter BioScience, Bioteest, CSL Behring, Grifols, and Kedrion.

As outlined below, in furtherance of the Initiative’s objective to enhance regulations to improve the state of innovation and “accelerate the discovery, development, and delivery of promising new treatments to patients,” PPTA urges the Committee to eliminate the “clinically superior” requirement for orphan drug designation where: (1) there is no intent to break an initial product’s seven years of orphan product market exclusivity; or (2) the FDA did not grant seven years of market exclusivity to the first-to-market drug. Clinical superiority requirements should remain in cases where there is intent to break an initial product’s seven-year orphan drug market exclusivity, but should be delinked from an application to obtain FDA orphan product designation in all other circumstances. PPTA believes that this

1 Recombinant blood clotting factor therapies are those created using recombinant DNA technologies, which entail the integration of genes coding for the production of human blood clotting factor proteins into laboratory cell cultures. The cell cultures produce the blood clotting factor proteins, which are subsequently collected, purified, and further refined into safe and effective biologic medicines.
2 Human plasma is the clear liquid portion of blood that remains after the red cells, leukocytes, and platelets are removed. Due to its human origin, complexity, and richness in therapeutically useful proteins, human plasma is a unique biological material. See Thierry Burnouf, Plasma Proteins: Unique Biopharmaceuticals – Unique Economics, in 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209 (2005, 2006).
policy change would protect the original objectives of the orphan drug designation while incentivizing innovation and drug development in important therapeutic areas.

**Plasma Protein Therapies: Unique by Nature**

Plasma protein therapies comprise a unique class of biologics within the biopharmaceutical industry. From the human-derived plasma starting material, through the complex manufacturing process, to final physician-administration, plasma protein therapies and the rare disease patients that rely on these therapies for their lifesaving treatment consistently face distinct challenges. The fact that nearly all plasma protein therapies treat rare diseases, which the Orphan Drug Act of 1983 defines as US populations of under 200,000 individuals, presents additional complexities since the rare nature of the disease states targeted and treated by plasma protein therapies often presents distinct research, development, and regulatory challenges.

Plasma protein therapeutic manufacturers employ different fractionation processes to derive distinct products within each plasma protein therapeutic class. Due to these distinct manufacturing processes, products in the same class produce different therapeutic outcomes on a patient-by-patient basis, and are considered non-interchangeable, sole-source biologics. As a result of the therapies' non-interchangeable nature, patients depend on appropriate, timely, and uninterrupted access to all brands within a therapeutic class to be assured that they are able to identify and become stabilized on the therapy that best fits their health status. Yet, despite the non-interchangeable nature of many plasma protein therapies and the fact that they are typically solely indicated to treat rare diseases, many therapies do not qualify for orphan designation because they are considered the "same" drug as others in the class. As a result of not qualifying for orphan drug designation, plasma protein therapies represent a distinct class of rare disease therapies that are inappropriately subject to an increasing number of regulatory regimes that are intended for commonly indicated therapies.  

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3 FDA rarely declines from granting exclusivity. As a result, adjusting the designation requirements in this way would be narrowed to only those appropriate scenarios where designation can be granted and the potency of the orphan drug incentives are maintained.

4 Because of characteristics unique to human plasma-derivatives, which account for nearly two-thirds of the plasma protein therapeutics market, plasma protein therapies cost nearly four times more than traditional pharmaceutical products to produce. See Charles Waller, *Historical Perspective on Blood and Plasma Products*, in *7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE* 17, fig. 2 (J.L. Valverde ed., 2005) (providing a comparison of the plasma protein therapeutics industry with the pharmaceutical industry through the analysis of Smith Barney estimates from December 2003 and the 2004 Annual Reports of major pharmaceutical companies). These characteristics include the capital intensity of the facilities, equipment, and source material. See OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, *BLOOD POLICY AND TECHNOLOGY* 66 (Jan. 1985) (discussing the capital intensive nature of the facilities necessary to fractionate plasma proteins); THE MARKETING RESEARCH BUREAU, INC., *THE PLASMA FRACTIONS MARKET IN THE UNITED STATES* 2009 41 (2010) (illustrating the capital intensity of the source material required to produce plasma protein therapies).
Reforming the Orphan Designation Process for Rare Disease Therapies

Eliminating the “clinically superior” requirement for orphan drug designation in cases where an initial product’s seven-year market exclusivity is not seeking to be abridged or where the FDA did not grant seven years of market exclusivity to the first-to-market drug preserves the intent of the Orphan Drug Act (ODA) while enhancing the power of the Act to drive the innovation of therapies for rare disease patients.

As outlined above, under 21 C.F.R. § 316.20, the manufacturer or sponsor of a drug that is otherwise the “same” as an already approved orphan drug and seeking “orphan designation” for the same rare disease or condition as that drug must submit with its request plausible evidence that it may be “clinically superior” to that already approved drug. The purpose of the “clinically superior” threshold is to strike an appropriate balance between protecting the value of the seven years of market exclusivity that FDA is authorized to grant under the ODA for the first FDA approved brand for a specific rare disease or condition in a particular therapeutic class and encouraging continued innovation in treating that rare disease. However, under present law, a manufacturer seeking orphan designation for a subsequent product must demonstrate clinical superiority even if FDA has not granted seven years of market exclusivity for the first-to-market drug or, if granted, after the exclusivity period has expired for that drug. PPTA believes that requiring a demonstration of clinical superiority when there is no exclusivity period to protect is inconsistent with the purpose of the ODA and also places a significant financial burden on drug manufacturers, patients, and the health care system as a whole.

Because there are multiple brands in most therapeutic classes, plasma protein therapies are acutely affected by the “clinically superior” requirement: despite the fact that the brands within each respective therapeutic class of plasma protein therapies are non-interchangeable, unique biologicals, FDA generally defines two drugs with the same active ingredient (E.g. immunoglobulin G protein for immunoglobulin therapies) as the “same” for the purpose of the ODA regulations; thus, well-established classes like alpha-1-proteinase inhibitor, factor VIII, factor IX, and immune globulin which have numerous second-to-market brands of therapies are disproportionately affected by how the FDA awards orphan product designation. Accordingly, delinking clinical superiority from orphan exclusivity would represent a significant step forward in meeting the Committee’s goals to, “accelerate the discovery, development, and delivery of promising new treatments to patients.”

Expeditures in these areas are due in part to the direct and indirect costs of compliance with stringent FDA regulations and rigorous voluntary industry standards by both plasma collectors and fractionators.

This issue is compounded by the Affordable Care Act’s (ACA) provisions that expanded the 340B Drug Pricing Program\textsuperscript{6} and established an annual pharmaceutical fee on certain branded prescription drug sales.\textsuperscript{7} In both these provisions, Congress excludes “orphan drugs” to prevent any unnecessary economic harm that could hinder research and development of rare disease targets.\textsuperscript{8} However, most plasma protein therapies will not qualify for these exclusions because they have not received orphan designation for their FDA approved indications, despite meeting the “rare disease or condition” threshold of affecting less than 200,000 patients in the U.S.\textsuperscript{9}

The plasma protein therapeutics industry prides itself on being the drug industry’s leader in the shift toward the personalized medicine paradigm. The alpha\textsubscript{1}-proteinase inhibitor, factor VIII, factor IX, and immune globulin classes of therapies are among the most well-established therapeutic classes in medicine due in large part to the industry responding to patient directives urging the development of brand diversity. Access to a full range of plasma protein therapies in each therapeutic class ensures that patients will be treated with a therapeutic intervention best suited for their individual needs, which will prevent avoidable costs in unnecessary physician visits, hospitalizations, and surgical interventions. Unfortunately, the “clinically superior” requirement creates a situation where many promising therapies may not receive orphan designation because they were not first to market. The result of this regulatory framework is a chilling of innovation of personalized medicines for rare disease patients.

PPTA believes it is vital to reward past and encourage future innovation in developing therapeutic interventions for the treatment of rare diseases, disorders, and conditions. The financial incentives Congress created under the ODA are responsible for over 400 orphan designated drugs receiving FDA marketing approval since its enactment. PPTA generally supports the regulatory framework that FDA created to implement the ODA, but believes that it should be improved to accelerate the research and development required to adequately serve the rare disease patient populations.

With more than 30 million patients in the U.S. suffering from a rare disease or condition, the Committee should remove any policies that create barriers to rare disease innovation. PPTA’s recommendation to eliminate the “clinically superior” requirement for orphan drug designation in cases where the agency did not grant seven years of market exclusivity to the first to market drug or in cases where there is no intent to break an initial product’s seven years of orphan product market exclusivity, will move the pharmaceuticals and biologicals industries closer to developing therapies for the more than 7,000 identified rare diseases, and provide relief from the newly created economic pressures for established

\textsuperscript{6} See Patient Protection and Affordable Care Act (ACA) 42 U.S.C. § 256b(a)(4)
\textsuperscript{7} Id.
\textsuperscript{8} 42 U.S.C. § 256b(e)
\textsuperscript{9} For example, hemophilia A afflicts approximately 14,218 patients, according to the National Hemophilia Foundation. There are ten unique factor VIII therapies currently available to treat hemophilia A in the U.S., yet FDA has only granted orphan designation to one of the ten brands. An 11th brand, ReFacto, is no longer available in the U.S as of May 31, 2009, as it was phased out in favor of Xyntha. Interestingly, FDA had approved ReFacto for an orphan designated indication, but did not grant it the seven years of market exclusivity.
classes. PPTA further asks that its recommendation be applied retrospectively so that the more than 30 plasma protein therapies, all of which exist within therapeutic classes where the first-to-market therapy’s exclusivity was never given or has already expired and yet still currently lack orphan designation, are appropriately classified.

**Conclusion**

Thank you for your time and consideration of PPTA’s comments on the 21st Century Cures Initiative, and the current regulatory framework for orphan designation. PPTA greatly appreciates the Committee’s outreach to interested stakeholders, and we look forward to continuing to engage in the initiative as it progresses.

Best regards,

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