June 1, 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: A Call to Action

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to comment on the Energy and Commerce Committee’s 21st Century Cures initiative (“the Initiative”). PPTA supports the goal of enhancing regulations to improve the innovation continuum and “accelerate[ing] the discovery, development, and delivery of promising new treatments to patients,”1 and appreciates your leadership in convening and guiding this important conversation.

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, alpha1-proteinase inhibitor, antithrombin III, plasma-derived and recombinant blood clotting factors,2 C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, prothrombin complex concentrate, and protein C concentrate.3 Collectively, these therapies are known as “plasma protein therapies.” PPTA’s U.S. manufacturer membership includes Baxter BioScience, Biotest, CSL Behring, Grifols, and Kedrion.

Overview: 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 and particular regulatory treatment. For example, nearly all plasma protein therapies treat rare diseases, and certain therapies treat extremely rare diseases that feature prevalences of fewer than 100 patients. The

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1 Energy and Commerce Committee, 21st Century Cures: A Call to Action (May 1, 2014).
2 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.
3 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).
The rare nature of the disease states targeted and treated by plasma protein therapies often presents unique research, development, and regulatory challenges. Additionally, manufacturers employ different fractionation processes to derive each distinct brand within the plasma protein therapeutic class. Due to the distinct manufacturing processes used by the industry, plasma protein therapies are non-interchangeable, where each brand has unique biologics that produce different therapeutic outcomes on a patient-by-patient basis. 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.

The industry is further differentiated by the reliance on human donated plasma as the starting material for therapeutic production. The collection of human donated plasma from 430 collection centers dispersed across the United States is a time- and resource-intensive system that adds multiple layers of complexity and regulation, resulting in a 7-9 month production process. Notably, because each plasma donation only contains a fraction of the necessary proteins to produce a given therapy, there is an inherently finite supply of therapies. For example, it requires approximately 900 donations to provide enough alpha-1 proteinase inhibitor to treat one alpha-1 antitrypsin deficiency patient for one year. Importantly, however, the finite supply of therapies does not mean that therapies are in shortage or that patients are unable to access their lifesaving treatments, but rather underscores the need for regulations and reimbursement mechanisms to protect patient access to these therapies.

PPTA greatly appreciates the opportunity to provide the industry’s unique perspective on the current state of the discovery-to-delivery innovation continuum and offer solutions aimed at engendering future innovation and improving the state of patient access.

**Summary of Recommendations:**

- **Payment and Delivery**
  - Ensure that payment and reimbursement policies incentivize innovation and maintain patient access; and
  - Expand regular stakeholder engagement by the Centers for Medicare and Medicaid Services (CMS) to advance payment methodologies that keep pace with innovation and the development and commercialization of new technologies.

- **Discovery**
  - Increase and stabilize public funding for basic scientific research; and
  - Mitigate barriers that continue to impede the development of a robust body of research focused on rare diseases.

- **Clinical Development**
  - Improve regulatory predictability through timely rulemaking procedures.

PPTA strongly supports the Committee’s efforts to improve the state of innovation and patient access, and encourages the Committee to continue to engage all stakeholders.
in a transparent manner and to maintain patients, health outcomes, and quality of care at the center of the discussion.

I. DELIVERY AND PAYMENT

While the Committee’s White Paper examined the barriers to innovation on the continuum from discovery to delivery, payment plays a critical and determinative role in driving innovation and patient access to care. Importantly, even if steps are taken to increase the efficiency of pathways to bring products to market, without effective reimbursement models, innovators will face headwinds and patients will experience access challenges. Accordingly, as the Committee reviews and amends payment policies to improve the sustainability of the healthcare system, PPTA recommends that payment-related proposals also be examined for the potential to impact innovation and patient access to care.

1. Ensure that Payment and Reimbursement Policies Incentivize Innovation

PPTA recognizes and appreciates that periodically evaluating payment and reimbursement methodologies ensures the sustainability of the healthcare system and safeguards patient access. When contemplating payment and reimbursement reforms, PPTA urges policymakers to consider the rapidly changing research and development (R&D) landscape and the critical role that payment and reimbursement policies play in incentivizing early-stage exploration and advancing therapies to patients.

The plasma protein therapeutics industry is a longstanding innovative engine within the biologics sector. Currently, the industry has a robust pipeline comprising over 100 therapeutic targets, of which nearly 25% are in the preclinical stage. However, the promise of these therapies is threatened by scientific and market forces currently challenging the greater biotechnology and life sciences sector. These challenges include:

- A significant rise in the investments and resources necessary to develop safe and effective therapies due to the targeting of increasingly complex rare disease targets;
- Shrinking patient populations arising from advances in elucidation of disease etiology, pathogenesis, pathophysiology, and heterogeneity;
- Growing scientific and regulatory complexities associated with the shift to more personalized therapeutic development; and
- The inherent risks associated with developing next-generation biologic treatments.

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4 For a description of the discovery and development of the modern plasmapheresis process used to separate blood and plasma, giving rise to the availability of therapeutically useful plasma, and ultimately establishing the foundation for future innovations that led to plasma protein isolation and therapeutic development, see Production of Plasma Proteins for Therapeutic Use, Bertolini J., Goss N., Curling J, Wiley & Sons (2013).
5 See Member company product portfolio and pipeline reports.
While these challenges are positive in the sense that they reflect the rapid advancement of R&D technologies and the biomedical community's growing understanding of disease state pathophysiology (thereby enabling the discovery and development of more effective and targeted therapies), they have contributed to a significant growth in R&D costs\(^6\) and a rise in the number of research and development projects that fail before reaching patients.\(^7\)

While the plasma protein therapeutics industry is working on ways to reduce the risks and costs associated with developing the next generation of biologic therapies, downward pressure from public payers is amplifying the impact of these challenges. Across the life sciences industry, this economic pressure is contributing to earlier therapeutic candidate terminations by innovators, and by extension, reducing the number of potential lifesaving therapies that will be available to patients in the future.\(^8\) Accordingly, it is imperative that the increasingly complex, risky, and costly nature of therapeutic development be taken into consideration as payment and reimbursement methodologies are reformed. In particular, policymakers should avoid policies that indiscriminately reduce payment and reimbursement rates without consideration for the evolving R&D landscape, as this can result in a chilling effect on upstream innovation and impede future patient access to lifesaving therapies.

2. Ensure that Payment and Reimbursement Policies Maintain Patient Access

As the 21st Century Cures initiative progresses, PPTA urges the Committee to keep patients at the center of the discussions. The plasma protein therapeutics industry makes this recommendation based on the experience of the industry and patients during the implementation of reimbursement changes enacted as part of the Medicare Modernization Act of 2003 (MMA), which demonstrated the unintended consequences of well-intentioned payment reforms.

Beginning in 2003, the MMA mandated that reimbursement for intravenous immune globulin (IVIG) under Medicare Part B change from average wholesale price (AWP) to average sales price (ASP). This resulted in a significant reduction in how physicians were reimbursed by Medicare for administering therapies. At these reimbursement levels, many physicians could no longer afford to purchase and administer IVIG, and

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\(^7\) KMR Group, R&D Performance—Pharmaceutical Benchmarking Forum (2012) (observing that 3% of R&D projects that successfully progress from the preclinical stage to phase I clinical testing will succeed in the remaining stages of clinical development to be approved by the FDA).

\(^8\) Bruce Booth & Rodney Zemmel, Prospect for Productivity, 3 Nature Review Drug Discovery 451, 456 (2004) (Highlighting that "as health care cost containment becomes an increasingly important issue for payers and governments, the pressure on the current R&D model will probably make [continued productivity] unsustainable for the industry"); see also Carmelo Giaccotto, et al., Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry, 48 J. L. Econ. 195, 212 (2005) (conducting a simulation study predicting that "the capitalized value of pharmaceutical R&D spending would have been about 30 percent lower if the federal government had limited drug price increases to the same rate of growth as the general CPI during the period 1980-2001").
therefore discontinued providing in-office infusion services. An unintended consequence of the MMA’s change to reimbursement was that between 2003 and 2006, IVIG treatment in the physician office setting fell from 54% to 31%, and by 2010, 64% of Medicare IVIG, immune compromised, patients were treated in hospital outpatient departments versus 33% in physicians’ offices. This example demonstrates that changes to reimbursement have the potential to immediately and dramatically affect patient access to care, resulting in long-term, irreversible adverse events.

Access issues can be especially devastating for patients living with chronic and rare diseases, such as patients treated with plasma protein therapies. For example, many IVIG patients are living with an immune deficiency or are immune-compromised. As a result, the most appropriate and safest — and presumably most cost-effective — site of care is often in the home, where these patients are not exposed to potential infections. Forcing IVIG patients to travel to hospital outpatient departments for infusions can not only be a significant hardship, but can lead to worse health outcomes (and resultant costs to Parts A and B from unnecessary hospital admissions and physician care).

Additionally, prior to being properly diagnosed and gaining access to treatment, many rare disease patients who rely on plasma protein therapies are often misdiagnosed for multiple years and sometimes decades. Ensuring that these patients have insurance coverage that allows for uninterrupted access to the dispersed networks of specialists who best understand their rare conditions, and appropriate and timely access to the best possible therapies is critical to maintaining and improving patient health outcomes.

A 2008 study conducted by the Immune Deficiency Foundation (IDF) found that on average 14 percent of patients diagnosed and living with primary immune deficiency (PID) discontinue utilization of IVIG replacement therapy due to a lack of insurance coverage. The findings of the 2008 study also demonstrate that such discontinuance increases the risk for those patients of permanent impairment of lung function, mobility, digestive function, and vision and hearing. Once PID patients begin or resume treatment the functional impairments arising from non-treatment suppress the effectiveness of IVIG. Accordingly, not only do discontinuances and gaps in insurance coverage undermine the health of already immune-compromised patients, but they also serve to increase the overall costs of treatment and care to the healthcare system. An estimated 4,000 PID patients who are under the age of sixty-five receive Social Security Disability Insurance payments due to the functional impairments arising from their disease.

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10 Id.
11 See, e.g., Vogelmeier C., et al., Alpha-1-antitrypsin deficiency. Summary of a scientific symposium at the conference of the Swiss Pneumologic Society on April 16th, 2009, 63 Pneumologie 12, 718-25 (2009) (Noting the clinical findings that the “time delay between the start of respiratory symptoms and the correct diagnosis of alpha-1-antitrypsin (AAT) deficiency is often 6 to 8 years”).
12 Marcia Boyle, Christopher Scalchunes, Impact of intravenous immunoglobulin (IVIG) treatment among patients with Primary Immunodeficiency diseases, Pharmaceuticals Policy and Law 10 (2008) 133–146.
Based on the industry’s experiences with changes in reimbursement, PPTA urges policymakers considering payment and reimbursement reforms to incorporate strict safeguards for patient access to all sites of care, and to ensure that changes to reimbursement do not present a barrier to timely and appropriate patient access of the therapy prescribed by their physician. For example, in 2013, recognizing the potential for improved health outcomes and savings to Medicare, Congress passed the Medicare IVIG Access Act (P.L. 112-242), enacting a three-year demonstration project that allows for the payment of home infusion services for Medicare primary immune deficient (PID) patients. The passage of the IVIG Access Act will not only benefit patients living with chronic and rare diseases, but stands as a model for patient-centered policymaking that should be applied through the 21st Century Cures initiative.

3. Consistently Engage Stakeholders to Ensure Payment and Reimbursement Methodologies Advance In Parallel to Technological Improvements

Recognizing the logarithmic trajectory of biomedical innovation, PPTA urges policymakers to expand opportunities for stakeholders to inform consistent advancement of payment methodologies through regular public meetings with CMS aimed at preparing the agency for next-generation technologies. For example, diagnostics and gene therapies are experiencing rapid innovation and will present distinct new challenges, including appropriate patient identification, therapeutic delivery and administration, effective treatment regimens, and unique pharmacoeconomics. As policymakers evaluate payment methodologies, it is vital to appreciate these evolving advances and challenges.

Compounding the importance of consistently and predictably advancing payment and reimbursement methodologies are the complex and hard-to-treat disease states that many of these medical technologies are targeting. Lifelong, genetic diseases such as hemophilia and alpha-1-antitrypsin deficiency, which are currently effectively treated with coagulation factors and plasma-derived alpha-1 proteinase inhibitor, are seeing significant advances in promising next-generation therapies and diagnostics. As exciting as these advances are, without effective reimbursement rates and models, innovation will falter and patient access will suffer.

Accordingly, PPTA recommends Congress authorize and CMS implement a “public workshop” approach to stakeholder engagement on complex scientific issues, similar to that employed by FDA. FDA’s public engagement procedures, while still progressing and improving, offer a model worthy of replication by other agencies that must maintain a cutting edge understanding of scientific advancements to ensure innovation and patient access do not suffer. FDA regularly holds public workshops to bring together a broad range of stakeholders to discuss current and future standards development

13 Patricia Danzon, and Adrian Towse, The Economics of Gene Therapy and of Pharmacogenetics, 5 Value in Health 1 (2002).
activities for next-generation medicines and medical technologies. These workshops serve to transparently communicate FDA's intended approach to regulating next-generation medical technologies, while also providing stakeholders opportunities to provide expert advice and inform the advancement of regulatory science. Similar engagement efforts by CMS would advance predictability and transparency in payment policymaking, while also providing CMS access to stakeholder expertise and perspectives. Importantly, improving public engagement by CMS in this way will allow the agency to maintain the relevancy and effectiveness of payment and reimbursement policies in parallel to advances in therapies and treatments.

II. DISCOVERY

The success of the discovery stage of innovation – as measured by the advancement in the scientific community's understanding of the underlying genetics and pathophysiology of diseases and the identification of possible treatment targets – is primarily determined by stable funding for what are often long-term projects as well as the availability of disease and patient-related data. Accordingly, PPTA urges the committee to consider ways in which the state of basic research funding and data availability can be improved.

1. Increase and Stabilize Public Funding for Basic Scientific Research

Patients are currently realizing the dividends of past investments made by the government in basic scientific research. PPTA recognizes the important role that basic research plays in the innovation continuum, and supports increasing and stabilizing basic research funding for National Institutes of Health (NIH). The history of the plasma protein industry demonstrates the importance of this investment: the industry’s genesis can in part be traced to government-funded research during World War II that aided the early-stage development of fractionation technologies, which act as the first step in isolating therapeutic proteins from human-donated plasma.\textsuperscript{15} As such, PPTA is keenly aware that basic scientific research can play a pivotal role in laying the groundwork for future medical innovation, and potentially, spark the formation of entirely novel industries. Accordingly, PPTA encourages the committee to increase funding for basic research, particularly as it relates to rare diseases where research is more difficult and costly to conduct\textsuperscript{16} and funding levels are traditionally lower relative to common disease states.\textsuperscript{17}

2. Mitigate Barriers that Impede the Development of a Robust Body of Research Focused on Rare Diseases

\textsuperscript{15} Roger Lundlud, \textit{Biotechnology of Plasma Proteins}, CRC Press (2013) (detailing the defense department's role in aiding the early-stage development ethanol fractionation).

\textsuperscript{16} Institute of Medicine Report, \textit{Rare Diseases and Orphan Products, Accelerating Research and Development} (2013).

As leading innovators targeting rare diseases, plasma protein therapeutics manufacturers have identified certain barriers to research related to rare diseases, which could in part be mitigated by collaboration between the public and private sectors. These challenges include:

- Difficulties developing fundamental incidence, prevalence, and outcomes-focused data among dispersed rare disease patient populations, which challenge researchers seeking to identify the genetic and pathophysiological underpinnings of rare diseases; and
- A lack of centrally organized and publicly accessible databases providing rare disease-focused animal models and pathobiology and pathophysiology information generated by researchers from public, academic, and non-profit institutions, as well as industry, which impedes the translational capacity of rare disease researchers and clinicians.

Accordingly, PPTA encourages the committee to require prioritization of rare disease research efforts as part of the growing number of collaborations between FDA, NIH, the Centers for Disease Control and Prevention (CDC), the Patient Centered Outcomes Research Institute (PCORI), and other federal agencies that are focused on improving basic research. For example, the National Patient Centered Research Network (PCORnet), a promising partnership between PCORI, NIH, and multiple other academic institutions, features a task force on rare diseases that aids researchers across the country overcome research barriers that are unique to rare disease research. The PCORnet model of collaboration and rare disease prioritization is a paradigm worthy of replication; yet, integration of a rare disease focus in PCORI’s efforts required special advocacy by patients and stakeholders. Given the power of these collaborations to overcome the specific barriers facing rare disease researchers, PPTA recommends that as collaborations and cross-agency partnerships focused on improving basic research expand and grow in number, rare disease-focused functions be a required element of the collaboration.

III. CLINICAL DEVELOPMENT

1. Improve Regulatory Predictability Through Timely Rulemaking Procedures

In recent years, the FDA has successfully leveraged increased funding and new congressional authority to develop new review pathways and accelerate lifesaving therapies to patients. PPTA applauds these efforts, and supports the goal of advancing a collaborative regulatory environment that ensures that safe and effective therapies reach patients at the fastest possible rate. However, we believe that more can be done, particularly in the areas of consistency and predictability.

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To help realize the promise of these new review pathways, PPTA urges Congress and the FDA to examine ways to increase the timeliness of agency rules. Too often, proposed rules linger for years before finalization. For example, a 2003 proposed rule, Safety Reporting Requirements for Human Drug and Biological Products, was published on March 14, 2003, and its comment period closed in October 2003; however, the rule was not finalized (and then, only in part) until 2010.19

Given the rapid pace of innovation in the biomedical sector, large gaps between rule proposal and finalization deprives the agency of the most recent data and accumulated industry experience on the subject at issue. This practice also makes it extremely difficult for industry to anticipate and adjust business practices ahead of new rules, and arguably deprives the public and stakeholders of a true opportunity for notice and comment.

More generally, these types of delays by the agency undermine regulatory predictability, an integral factor for ensuring the stability and efficiency of the innovation continuum. Accordingly, PPTA suggests that the Committee collaborate with the FDA to develop a process that delineates procedures for finalizing proposed rules. Such a process could reflect that, if a proposed rule is not finalized within a reasonable amount of time after the closing of the comment period, (e.g., 24 or fewer months), then the proposed rule must be re-proposed for further comment.

IV. CONCLUSION

Thank you for your time and consideration of PPTA’s comments on the 21st Century Cures initiative. PPTA greatly appreciate the Committee’s outreach to interested stakeholders, and we look forward to engaging in the initiative as it progresses.

Best regards,

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19 Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (21 CFR Parts 312 and 320) (2010).