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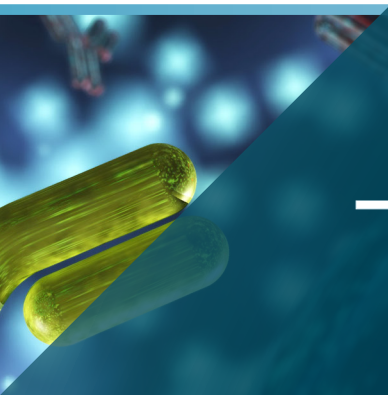

Key economic and value considerations in the U.S. market for plasma protein therapies

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February 2018

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Executive summary

Plasma protein therapies (PPTs) are biologic medicines that provide critical health benefits, especially for patients with plasma protein deficiencies. Plasma protein deficiencies are a group of chronic, serious, and mostly rare conditions that occur when a person has deficient or functionally damaged proteins in plasma—the liquid portion of blood. Plasma donated from healthy individuals is manufactured into PPTs, which replace a patient's missing proteins. Although in some cases plasma proteins can be grown using recombinant technology, therapies made using donated plasma remain an irreplaceable, and sometimes the only, lifesaving treatment for most plasma protein deficiencies. For this reason, the paper focuses on the distinct manufacturing process, economic considerations, and unique nature of products derived from donated plasma.

Plasma protein therapies are distinct from traditional prescription drugs in several important respects. Rather than being synthesized from chemicals in a laboratory, PPTs are derived from plasma obtained from human donors and manufactured into specialized therapies that treat mostly rare but serious conditions, some chronic and some acute in nature. Arguably the most important attributes of PPTs are the benefits they provide to the patients who use them. PPTs extend life expectancy, increase quality of life, and decrease complications related to conditions. Without these treatments, many patients would either not be able to survive or would have a substantially diminished quality of life and productivity.

There are other key distinctions between PPTs and other pharmaceutical products. First, because manufacturers rely on donors for their source material, PPTs are subject to even greater regulatory oversight than traditional prescription drug manufacturers. These regulations govern the safety of their products and the protection of donor health. As a result, this industry is more susceptible to unintended consequences stemming from price regulation and other government policies, such as limiting plasma resources and interruptions in production. Second, unlike many traditional prescription drugs, different versions of PPTs are commonly not interchangeable for given patients.[1] Even when products from multiple producers are approved for the same condition, a patient who responds well to one particular PPT may not respond well to another or may experience adverse side effects.[2] Imperfect interchangeability across products complicates the medical treatment of PPT-dependent patients and raises particular issues relating to access to and payment for PPTs.

The role this sector plays for the people whose health and lives depend on its products is disproportionate to its size in the overall health care system. Given the large interests and issues at play in the U.S. health care policy debate, it would be easy for the importance of this sector to be passed over and for policy solutions to be enacted that inadvertently impair the ability of the plasma products sector to meet the vital

1 Jerry Siegel, "The Product: All Intravenous Immunoglobulins Are Not Equivalent," *Pharmacotherapy* 25, no. 11P2 (2005): 78S-84S.

2 The same issue arises in the case of other biologics and biosimilars. In that setting, follow-on products that reference originators (the rough analog to generic drugs) are not considered interchangeable with the originator unless specific testing illustrates that the same patient can switch from one to another and back without experiencing therapeutic consequences.

needs of current patients and to address needs that will arise in the future. Therefore, it is important that policymakers understand the unique contributions of and challenges facing this relatively small part of the health care system. As policy proposals move forward, it is important to avoid a “one size fits all” approach that will ultimately result in higher health care costs and adversely affect patient health.

I. Plasma protein therapies provide medical, economic, and personal value

Plasma protein therapies (PPTs) are a unique set of biologic therapies that treat chronic life-threatening conditions, such as alpha-1 antitrypsin deficiency (alpha-1), primary immunodeficiency diseases (PI), chronic inflammatory demyelinating polyneuropathy (CIDP), hereditary angioedema (HAE), and bleeding disorders such as hemophilia.[3] These therapies are not widely known because they typically treat rare conditions and have orphan designations.[4] Congress has recognized the importance of meeting the needs of rare disease patients through mechanisms such as the Orphan Drug Tax Credit, the Rare Pediatric Disease Priority Review Voucher, and, most recently, with the rare disease provisions in the 21st Century Cures Act. PPTs provide immeasurable value by increasing survival rates, bolstering patient health, and enabling individuals to participate as productive members of society. Each of these contributions improves patient lives while reducing direct and indirect costs to society.

The lifesaving benefit of PPTs is evident in the improved life expectancies and survival rates of various treated patient populations. PPTs allow patients to live an additional 60 years in some populations. For example, at the beginning of the 20th century, individuals with severe hemophilia rarely lived past 13 years of age, yet they now approach a normal life expectancy due to both plasma-derived and recombinant therapies.[5] In 1971, only 37% of individuals with common variable immune deficiency (CVID), the most common PI, survived ten years. Due to treatment with PPTs, that survival rate increased to 90% by 2008.[6]

One way to measure the benefit of PPTs is to place it in monetary terms. It is common for policymakers to compare the value of one therapy versus another by assuming an amount a patient would be willing to pay for an additional year of life and then comparing how much additional value the competing therapies provide relative to their cost. For example, suppose there were two drugs being considered for congestive heart failure. Further suppose that Drug A offers patients three additional years of life and that Drug B offers patients five additional years of life but costs $150,000 more than Drug A. Policymakers and other stakeholders vary on the threshold used, but often assume that patients are willing to pay $100,000 for an additional year of life. Using this assumption, since Drug B confers two additional years of life over Drug

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3 More information on plasma, plasma protein deficiencies, and other uses for PPTs is provided in the Appendix.

4 In the U.S., a rare disease is defined as affecting fewer than 200,000 individuals. https://rarediseases.info.nih.gov/diseases.

Some PPTs are also used for acute conditions; a description of these is provided in the Appendix. This paper focuses on the chronic use of therapies for plasma protein deficiencies.

In the U.S., the Food and Drug Administration may grant a special "orphan drug designation" for products that treat diseases or disorders that affect fewer than 200,000 individuals. This designation, which provides temporary regulatory exclusivity for these products, is aimed at spurring the development of products that treat rare diseases. https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/.

5 L. Alecort, "The evolution of comprehensive haemophilia care in the United States, perspectives from the frontline," *Haemophilia*, 22(2) (2016): 676-683.

6 H. Chapel, M. Lucas, M. Lee, et al. "Common variable immunodeficiency disorders: Division into distinct clinical phenotypes," *Blood*, 112(2) (2008): 277–286.

A, it offers patients $200,000 in additional value over Drug A. It would also be considered cost-effective because the economic benefit conferred (assuming that patients are willing to pay $100,000 for each additional life year) outweighs the incremental cost of $150,000 it has over Drug A.

For many disorders treated by PPTs, there are no alternative treatments available. This means that the economic benefits associated with PPTs are simply the assumed patient's willingness to pay for each additional life year. As noted above, individuals with severe hemophilia are expected to live close to normal life expectancy, or an additional 66 years, due to the availability of PPTs and recombinant treatments. This means that every new patient effectively receives nearly $3 million in economic benefits from treatment if one assumes their willingness to pay is $100,000 for each additional year of life.[7] For the 480 severe hemophilia patients diagnosed each year, the economic benefits total nearly $1.4 billion. For every 1,000 newly diagnosed patients with CVID in a given year, the present value of PPTs over a twelve-year period after the initial diagnosis exceeds $300 million.[8]

The World Health Organization recognizes the importance of PPTs, having added immunoglobulins and coagulation factors to its List of Essential Medicines. Essential Medicines are those that the WHO views as providing the minimal needs for a basic health care system and for the treatment of priority diseases.[9] The inclusion of PPTs on this list reinforces the importance and cost-effectiveness of these unique treatments.

Indeed, improved health due to PPT treatment can ease burdens on the health care system. For example, PPT treatment of newly diagnosed patients with Primary Immunodeficiency Disease (or PI) reduces illness and health care utilization and results in overall annual per-patient savings of about $56,000.[10] Unfortunately, it can still take up to seven years to appropriately diagnose and treat a patient with a PI.

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7 Even though $100,000 per year for 66 years yields $6.6 million dollars, economists discount the future value of accrued benefits to account for the opportunity costs associated with valuing a life year gained now versus in the future. At a 3% discount rate, the present value of $6.6 million is approximately $3 million.

8 This value is calculated based on the differences in survival for each year after the initial diagnosis between a 1972 cohort of common variable immune deficiency patients and survival described for patients analyzed in the 2008 Chapel et al. paper. We assume that there are 1,000 newly diagnosed patients per year, but current U.S. estimates only describe a prevalence of 1 in 25,000. Survival rate calculations are available from the authors upon request.

9 The WHO defines essential medicines as "those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford." World Health Organization, *WHO Model List of Essential Medicines* (Geneva: World Health Organization, 2017), http://www.who.int/topics/essential_medicines/en/.

10 Vicki Modell, Jessica Quinn, Grant Ginsberg, Ron Gladue, Jordan Orange, and Fred Modell, "Modeling strategy to identify patients with primary immunodeficiency utilizing risk management and outcome measurement," *Immunol Res* 65 (2017): 713-720.

Delays in diagnosis of plasma protein deficiencies not only cost the health care system but can cause disease progression and poorer patient health outcomes.[11]

In addition to directly quantifiable benefits, PPTs improve patient outcomes by reducing disease-related disabilities. Individuals with a plasma protein deficiency can suffer from moderate or severe activity limitations such as physical immobility and other nerve system disorders. Physical limitations affect a person's productivity and ability to work or attend school. For example, 80% of individuals with hemophilia reported that their condition had a negative impact on their employment, and 40% of patients were forced to select their job/training based on specific needs related to their condition.[12] On average, an undiagnosed individual with a PI misses 20 days of work or school per year.[13] Because individuals often cannot perform normal activities, caregivers are affected as well. Caregivers reported an average of 19.1 days of low productivity and/or missed work or school per year.[14] PPTs improve patient outcomes and reduce costs for families, employers, and the health care system. Treatment with PPTs has been shown to reduce the number of unproductive days by 75%. Thus, PPT treatment adds nearly $3,000 of wages per patient per year.[15] PPTs substantially diminish condition-related limitations; in fact, nearly three-quarters of individuals with a PI reported their overall health to be good to excellent when using a PPT treatment.[16] Plasma protein therapies allow otherwise debilitated individuals to actively contribute to their schools, workplaces, and communities.

In addition to the medical and economic benefits, at a personal level, PPTs enable patients to lead healthier and more normal lives. These intangible benefits are difficult to quantify and are perhaps best described in patient testimonials on the personal impact of treatment:

> "[Immune globulin treatment] significantly made my life more normal. … Once on [IG], I noticed the episodes of illness much less frequent and less severe. … My immunoglobulin levels were much more consistent and prevented more infections. … Peace of mind and some normalcy has returned to my life. … I quickly found different immunoglobulin products unique; there are no generics or therapeutic equivalents."

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11 Vincenzo Graziano, Antonio Pecoraro, Ilaria Mormile, Giuseppe Quaremba, Arturo Genovese, Claudio Buccelli, Mariano Paternoster, and Giuseppe Spadaro, "Delay in diagnosis affects the clinical outcome in a cohort of CVID patients with marked reduction of IgA serum levels," *Clinical Immunology* 180 (2017): 1-4.

See also Bharat Srinivasa, Reza Alizadehfar, Martin Desrosiers, Joseph Shuster, Nitika Pant Pai, and Christos Tsoukas, "Adult Primary Immune Deficiency: What Are We Missing?" *American Journal of Medicine* 125 no. 8 (2012): 779-786.

12 Sheh-Li Chen, "Economic Costs of Hemophilia and the Impact of Prophylactic Treatment on Patient Management," *American Journal of Managed Care* 22 no. 5 (2016): 126-133.

13 Marcia Boyle and Christopher Scalchunes, "Impact of intravenous immunoglobulin treatment among patients with primary immunodeficiency diseases," *Pharmaceuticals Policy and Law* no. 10 (2008): 133-146.

14 Sheh-Li Chen, "Economic Costs of Hemophilia and the Impact of Prophylactic Treatment on Patient Management," *American Journal of Managed Care* 22 no. 5 (2016): 126-133.

15 This is based on assuming an average salary of $49,000 and 270 days worked per year, or $49,000/270 x 15 = $2,722.

16 Marcia Boyle and Christopher Scalchunes, "Impact of intravenous immunoglobulin treatment among patients with primary immunodeficiency diseases," *Pharmaceuticals Policy and Law* no. 10 (2008): 133-146.

"After the first infusion there was a sparkle in Isaac's eyes that we had never seen. Within a couple of months, Isaac could run and play! One summer day he announced, 'Mom, look at me! I'm just like a normal kid now!'… And today he continues to be a normal kid! He is an excellent student who is looking forward to attending college and being a contributing member to society." [17]

"When I had a swelling episode in my hand, it would get so big, it looked like an inflated surgical glove! Then the swelling would travel all the way up to my shoulder. A foot swelling would become so painful, I couldn't walk, or even wear a shoe. I had excruciating stomach episodes and frightening throat swellings as well. The smallest pressure or slightest muscle-pull could set me off. I lived in a world of complete uncertainty. … Not only do I now have a choice of outstanding, effective treatments, but my children, and my children's children, don't have to deal with emergency room egos, pain, shame, or the fear of seeming 'odd.'"[18]

"Augmentation therapy saved my life. No hospitalization since I've been on augmentation. I can honestly say that the difference from having no augmentation therapy to having augmentation therapy is monumental. Before therapy, I knew I wasn't going to be long on this earth. Granted, it took a bit of time, but my quality of life had improved tremendously. I have a life again. It gives us a fighting chance."[19] [20]

"As a child, I was expected to live into my early 30s, and I think for many of us, we are still stuck in that definition of normal. Normal is surviving a normal life that everybody else has. And to me, normal is so much more than just a life expectancy. My goal isn't to survive, but my goal is to actually have a high quality of life. ... We've really moved from that generation of treating the disease to the opportunity now to treat the individual, and ... about what are those life goals, those aspirations, and what are the things the individual wants." [21]

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17 "Testimonies to the Minnesota Senate Committee on Health, Housing and Family Security," Accessed 30 June 2017, https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjY98qKyObUAhVEcz4KHaFBCIEQFggoMAA&url=https%3A%2F%2Fprimaryimmune.org%2Fidf-advocacy-center%2Fidf-advocacy-center-activity%2F%3Faid%3D2281%26sa%3D1&usg=AFQjCNELHDfGhDuwq9kSykukG9tJLjoDnw.

18 U.S. Hereditary Angioedema Association, "Linda's Story," accessed Dec. 19, 2017, https://www.haea.org/Linda.php.

19 Testimony at the U.S. Food & Drug Administration Public Meeting on Patient-Focused Drug Development for Alpha-1 Antitrypsin Deficiency, September 29, 2015.

20 Augmentation therapy is treatment with alpha-1 proteinase inhibitor.

21 Testimony at the U.S. Food & Drug Administration Public Meeting on Patient-Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease, and Other Heritable Bleeding Disorders, September 22, 2014.

II. PPT production provides macroeconomic value

Although PPT manufacturing is a niche industry, it makes a valuable contribution to the U.S. and local economies. The industry employs highly skilled and well-educated people in every state in the U.S. Across the country, the industry directly employs more than 25,000 U.S. workers who earn an average of $45,000 per year.[22] These workers are employed in a variety of settings, some of which include:

- 2,000 people in manufacturer headquarters, including positions in sales, marketing, and medical affairs
- Over 3,000 individuals in manufacturing positions
- Nearly 500 research and development workers, including biochemists, chemists, quality control experts, and other highly skilled technical specialists
- More than 18,000 workers responsible for the safe and efficient collection of plasma throughout the U.S., overseen by hundreds of physicians, nurses, and other allied health care professionals

Standard economic multipliers suggest that these 25,000 jobs support approximately an additional 10,000 jobs in local economies.[23] PPT manufacturers contribute more than a billion dollars annually in wages to the U.S. economy. These earnings support local economies through taxes and spending on goods and services. Moreover, the geographic footprint of this industry is expansive, with manufacturing, sales, plasma donation centers, or headquarters located in every state.

PPT manufacturers also contribute more than a billion dollars annually to the U.S. economy through their donor compensation programs.[24] As described below, plasma donors receive a nominal amount to compensate them for the time needed for the donation process. When considered in aggregate, donor compensation is a helpful inflow of funds in local communities throughout the country and also engenders multiplier effects that would add substantially to the direct effect of such payments.

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22 Contribution based on a Bates White analysis of a survey of plasma protein therapeutic manufacturers (August 2017).

23 Multiplier effects vary by geography and job type, and a detailed assessment of the multiplier effect here would require much more information about employment locations than we have gathered in our survey. We arrive at the stated employment levels using a multiplier estimate of 1.4, which has been used in other studies of employment multiplier effects in health care settings. *See*, for example: Written Testimony of Mark Zandi Chief Economist and Cofounder of Moody's Economy.com Before the Joint Economic Committee The Impact of the Recovery Act on Economic Growth, October 29, 2009, https://www.economy.com/mark-zandi/documents/JEC-Fiscal-Stimulus-102909.pdf; and John Packham et al, "The Impact of the Local Health Care System on the Humboldt County Economy," https://www.unr.edu/Documents/business/uced/technical-reports/humboldt/health-sector-impacts-humboldt.pdf.

24 Contribution based on a Bates White analysis of a survey of plasma protein therapeutic manufacturers (August 2017).

III. PPT manufacturing requires multiple complex steps

PPT manufacturers face a more complicated and time-intensive manufacturing process than typical small molecule drug manufacturers because of the challenges of processing human plasma. Small molecule drugs are produced in large batches by combining chemical ingredients. PPTs are a unique type of biologic—a therapy derived from a living system.[25] The living systems from which some biologics are made include animal cells or microorganisms, but PPTs are unique because the starting material is donated plasma. PPT manufacturers rely on repeated donations from healthy donors, undergo a capital- and time-intensive manufacturing process that includes advanced pathogen inactivation and removal technologies, and abide by stringent quality and safety regulations. These manufacturing differences have important implications that policymakers and payers should bear in mind when considering policy challenges and solutions.

III.A. Human plasma donation

Rather than using synthetic or chemical ingredients as small molecule drugs do, plasma-derived protein therapies are manufactured from human plasma, which cannot be made in a laboratory and must be obtained from healthy human donors. The amount of source plasma available for plasma protein therapy production depends on the number of healthy individuals who repeatedly volunteer to donate plasma. The plasma supply is a natural constraint on the growth of available plasma products and the development of new products. This supply is affected by the size of the U.S. donor pool, the time-consuming means of plasma processing, and the high costs associated with collecting and testing plasma.[26]

Plasma is obtained from healthy human donors in the U.S. as either recovered or source plasma. Recovered plasma is a by-product of whole-blood donations collected from donors at blood banks. Whole blood donation can be done once every 56 days and results in the recovery of 250-300ml of plasma per whole blood donation.[27] In contrast, source plasma is typically obtained directly from donors at plasma donation centers through a process called plasmapheresis. This process uses a special medical device known as a plasmapheresis machine that removes whole blood from donors, separates the plasma from other blood components, retains the plasma, and returns cellular blood components to the donor. The entire donation process takes approximately two hours for initial donations and 90 minutes for subsequent ones.[28] Source plasma donation can be done more frequently than whole blood donation (up to twice

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[25] Biotechnology Innovation Organization, "How do Drugs and Biologics Differ?" accessed Dec. 19, 2017, https://www.bio.org/articles/how-do-drugs-and-biologics-differ.

[26] Neil Goss and John Curling, "Chapter 33: The Economics of Plasma Fractionation," in Joseph Bertolini, Neil Goss, John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013).

[27] American Red Cross, "Eligibility Requirements," accessed Dec. 19, 2017, https://www.redcrossblood.org/donating-blood/eligibility-requirements.

[28] Donating Plasma, "Donor Frequently Asked Questions," accessed July 5, 2017, http://www.donatingplasma.org/donation/donor-faq.

within a seven-day period with at least two days between donations in the U.S.) and results in more plasma per donation (approximately 600-800ml of source plasma each time).[29] The vast majority of plasma collections in the U.S. are obtained through source plasma donations rather than recovered plasma. In 2016, 94.3% of plasma collected in the U.S. was obtained from source plasma.[30] Furthermore, all PPTs that treat U.S. patients are manufactured with plasma from U.S. licensed plasma donation centers.[31]

The continued production of PPTs depends on a reliable supply of healthy repeat donors. Millions of plasma donations are necessary to treat PPT-dependent patients each year. To provide a single year of treatments for patients, roughly 130 plasma donations are needed to generate the PPTs to treat an individual with a PI, 900 donations to treat each patient with alpha-1, and 1,200 donations to treat a person with severe hemophilia.[32] Due to the high demand for plasma, identifying potential donors and a stable donor pool is vital to maintaining the supply of plasma products. To support this effort and incentivize donors to undergo the time-consuming process, plasma donation centers in the U.S. and certain other countries typically compensate donors for their time and inconvenience.[33]

In addition to the challenge of procuring sufficient donations, the process to ensure the quality and safety of donated plasma adds to the costs of producing PPTs. Donors must successfully complete health screenings for the millions of plasma donations that occur annually in the U.S. The first unit of donated plasma from a new donor is held until the donor has made a second donation, and after each donation, plasma is held in inventory for at least 60 days. Plasma collectors must document that each unit of source plasma is not released for manufacturing until after the 60-day hold period has expired. This inventory hold period is required to ensure the donor does not have disqualifying infections or other conditions. The plasma collected from qualified donors is tested for pathogens using sensitive serological tests and nucleic acid testing approved by the FDA and other regulatory bodies.

Moreover, plasma-derived therapies are one of the only medicines that require licensure for both the starting material and the final product. Multiple licensure and inspection requirements are additional considerations that differentiate the PPT industry from typical pharmaceutical manufacturing. Regulatory oversight encompasses plasma donation facility licensure/registration, plasma donor screening and testing

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29 Genna A. Jerrard, Jing Liu, Rosemary C. Case, et al., "Implications of Weight and Body Mass Index for Plasma Donation and Health," *ISRN Hematology*, 2012.

30 Marketing Research Bureau, *The Plasma Proteins Market in the United States 2016* (Orange, CT: Marketing Research Bureau, 2017).

31 U.S. Food and Drug Administration, "BER Instructions for Completing the Electronic Blood Establishment Registration and Product Listing Form," accessed January 31, 2018, https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/BloodEstablishmentRegistration/ucm055484.htm.

32 Plasma Protein Therapeutics Association, *Plasma Protein Therapies: Uniquely Saving Lives* (Annapolis: Plasma Protein Therapeutics Association, 2017).

33 *Ibid.*

procedures, quality management systems, and Current Good Manufacturing Practices, including facility inspections at least every two years.[34]

Regulations also dictate how plasma must be stored and transported as it is transferred from collection centers to manufacturing facilities. To reduce bacterial contamination and prolong its life, plasma must be separated from red blood cells and transferred to a plasma freezer within six hours of collection, or eight hours for fresh frozen plasma, where it must be stored at a temperature of -18° C or below.[35] Other industry guidelines recommend a storage temperature of below -35° C.[36] Maintaining safe temperatures from collection through transportation and storage requires the use of trained personnel and specialized equipment, such as blood refrigerators and plasma freezers, to maintain the blood cold chain.[37]

III.B. PPT manufacturing

III.B.1. Plasma manufacturing

Before donated plasma can be made into PPTs, it must undergo testing, including viral detection, at the manufacturing site to further ensure safety. FDA guidance dictates a number of steps to be taken in the manufacturing process.[38] The various processes and procedures can include: dry heat; pasteurization; solvent detergent; nanofiltration; low-pH incubation; caprylic acid treatment; sterility testing; and lot release testing to confirm the biologic activity of the final product. Additional information and definitions of these proprietary manufacturing technologies can be found in the Appendix. This process is necessary to ensure the safety of products, however it is both lengthy and expensive.[39]

To manufacture PPTs, plasma donations are pooled and undergo fractionation. Fractionation is a process through which plasma is purified and processed to isolate or "fraction off" the specific proteins that are used in producing different PPTs.

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34 U.S. Food and Drug Administration, "Blood and Blood Products," accessed August 2, 2017, https://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/default.htm.

35 See 21 CFR 640.34; Regulation pertains to source plasma.

36 World Health Organization, "The Blood Cold Chain: Guide to the selection and procurement of equipment and accessories," (Geneva: World Health Organization, 2002), 54.

37 *Ibid.*

38 Guidance documents that pertain to blood and plasma-derived product production is available at: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm, accessed November 2017.

39 Neil Goss and John Curling, "Chapter 33: The Economics of Plasma Fractionation," in Joseph Bertolini, Neil Goss, John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013).

As illustrated in Figure 1, the usable proteins exist in different concentrations within a liter of plasma, each having different uses and values in medical applications.[40] Market conditions and the strategic focus of each manufacturing company drive the production decisions of PPT manufacturers, but companies typically produce multiple products from each fractionated liter according to business strategies and medical needs.[41]

Figure 1: Production yields of specific proteins per liter of source plasma

Protein	Yield Per Liter
Immunoglobulin	3 – 5 g
Alpha-1 antitrypsin	0.15 – 0.30 g
Clotting factors	
Factor VIII	200 – 300 IU
Factor IX	250 – 350 IU
C1-esterase inhibitor	100 – 120 mg

Source: MRB (2015)

The unique economic profile of the plasma protein industry depends largely on the biological nature of the fractionation process. During fractionation, each therapeutic protein must be isolated in a specific order, adding to the complexity of overall manufacturing. A common method for fractionation is the Cohn/Kistler-Nitschmann method (Figure 2). Plasma must undergo a variety of processing steps such as thawing, precipitation/adsorption, and chromatography. As depicted at the ends of the arrows in the flowchart, the fractionation process results in several plasma proteins that can be used for production, including clotting factors (FVIII, FIX), immunoglobulins (IgG), and alpha-1 antitrypsin (alpha-1 AT). Each of these proteins has different uses; anticipating and responding to market conditions with respect to each of the various therapies adds to the complexity and cost of production.

Particular combinations of time, temperature, pH, and alcohol concentration are used depending on which protein is being extracted. Different chromatography-based purification methods and viral inactivation/removal processes are then used based on the specific properties of the different protein classes.[42] Variations in manufacturing processes applied to different proteins and across manufacturers contribute to unique end-product characteristics. Such differences contribute to the limited interchangeability between different manufacturers' products.[43]

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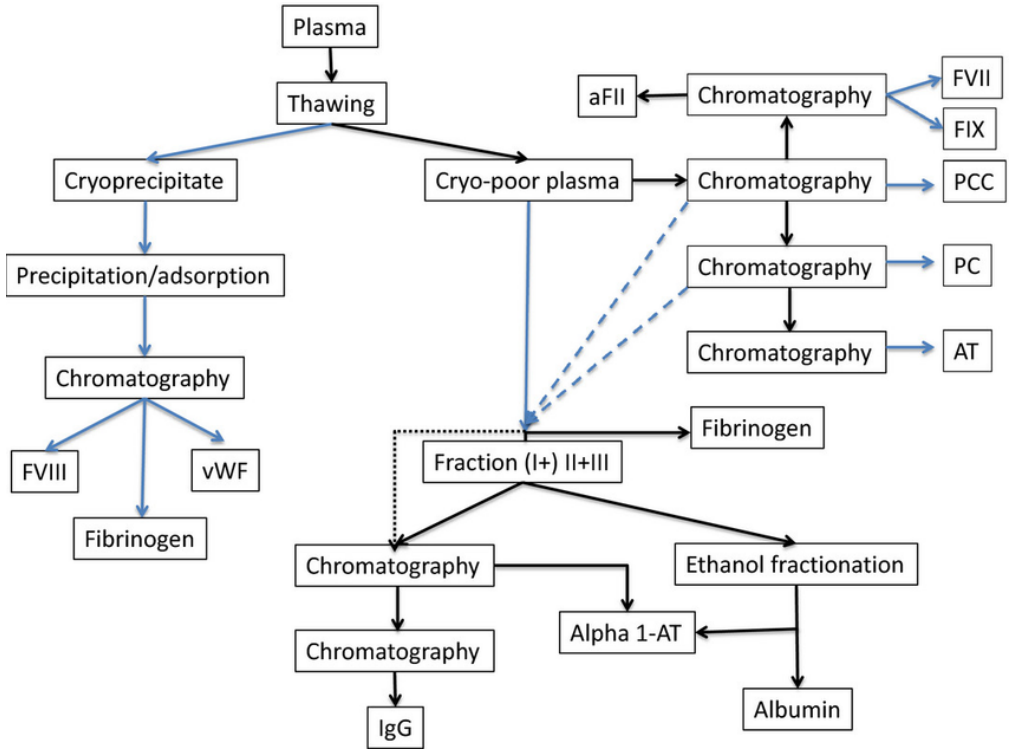
40 Ronale Tucker Rhodes, "Immune Globulin: Controlling Supply and Demand," *Biosupply Trends Quarterly* Winter 2015. http://www.bstquarterly.com/assets/downloads/BSTQ/Articles/BSTQ_2015-01_AR_Immune-Globulin-Controlling-Supply-and-Demand.pdf.

41 Victor Grifols, "Financing plasma proteins: Unique challenges," *Pharmaceuticals Policy and Law* no. 7 (2006): 189.

42 Neil Goss and John Curling, "Chapter 33: The Economics of Plasma Fractionation," in Joseph Bertolini, Neil Goss, John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013), [PAGE NO?].

43 International Patient Organisation For Primary Immunodeficiencies, *Access to Immunoglobulin Therapies for patients living with a Primary Immunodeficiency* (Downderry, UK: International Patient Organisation For Primary Immunodeficiencies, 2012),

Figure 2: The plasma fractionation process[44]



III.B.2. The unique regulatory burden faced by PPT manufacturers

The PPT manufacturing process is made more time-intensive and costly because companies comply with comprehensive regulations that govern every step of the process, implementing safeguard measures to ensure a consistent and safe supply of plasma from start to finish.[45] Plasma donation centers and manufacturers must implement precautions to prevent pathogen transmission from the human biologic starting material before manufacturing even begins. Safety regulations govern the operation of plasma donation centers and the handling of plasma, including protection of donor health, plasma storage, and refrigerated transportation.[46] Although typical pharmaceutical manufacturers must also comply with Current Good Manufacturing Practice (cGMP) standards, regulatory burdens are higher in the PPT industry due to the multiplicity of steps in the plasma collection and manufacturing process, the nature of the material, and the necessity of donation from healthy volunteers.[47]

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[44] Thierry Burnouf, "Current status and new developments in the production of plasma derivatives," *ISBT Science Series* 11, no. S2 (2016): 18-25.

[45] Joseph Bertolini, Neil Goss, John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013),

[46] See 21 CFR. 630. See also 21 CFR 606. See also 21 CFR 640.

[47] Note that the FDA publishes specific regulations reflecting the cGMP requirements for blood and blood components. See 21 CFR 606. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=606, accessed November 2017.

Examples of regulations and industry best practices specific to the PPT sector include:

- Plasma donation centers must perform donor health examinations, serological and nucleic acid testing, and deferral procedures in order to maintain the safety of plasma for fractionation.[48]
- Plasma donation centers must follow measures such as the qualified donor requirement, inventory holds, look-back and post-donation donor follow-up that may extend for years, and viral marker testing.[49]
- Manufacturers must integrate appropriate steps in the manufacturing process for complete virus inactivation and removal.[50]
- Those responsible for storing plasma and PPTs must be aware of minute details that can significantly affect product stability and, as a result, efficacy and safety. Regulations require plasma for further manufacture and PPTs to be stored at a temperature of -18° C or below at all times. Therefore donation centers, testing facilities, fractionation plants, and the means of transportation between them must invest in impeccable cold chain systems. [51]
- Manufacturers must also be aware of other variables that can affect the end shelf life of the product, making it essential that processes are well-documented and consistent throughout the manufacturing process.[52]

Plasma-derived therapies are also unique in that they require licensure for both the starting material and the final product. All plasma centers are subject to inspections to ensure they comply with:

- FDA facility licensure/registration,
- State and local authority compliance,
- Plasma donor screening and testing procedures (for example, the Clinical Laboratory Improvement Amendments),
- Quality management systems,
- Current Good Manufacturing Practices,
- Industry standards (the International Quality Plasma Program),
- For approximately 80% of centers that export to the European Union, EU licensure

The cost burden for centers can be substantial, as centers must pay a separate fee for each inspection.

Manufacturers and collectors typically not only adhere to the minimum requirements dictated by the FDA and international regulatory bodies, but also voluntarily adhere to additional industry standards such as the International Quality Plasma Program (IQPP) and Quality Standards of Excellence, Assurance, and

48 See 21 CFR 630. See also 21 CFR 610.

49 See 21 CFR 630. See also 21 CFR 610.

50 See 21 CFR 610. See also 21 CFR 606.

51 See 21 CFR 640.34.

52 Joseph Bertolini, Neil Goss, and John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013): 384-389.

Leadership (QSEAL) programs implemented by the Plasma Protein Therapeutics Association (PPTA).[53] The IQPP provides independent, third-party evaluation of plasma donation centers to ensure both donors and donation centers meet a set of rigorous standards focused on center quality, donor health, and suitability. These standards as a whole help to protect the health of both the donor and the individual treated with the end product. The QSEAL program ensures manufacturers perform an inventory hold and test for infectious agents. These voluntary standards, as well as FDA requirements and other mandated regulations, are constantly evolving to include new tests, address potential emerging pathogens, and update production technologies.

III.B.3. The nature and implications of capital-intensive manufacturing

PPT manufacturing is a lengthy and capital-intensive process. Safely collecting plasma, separating and extracting its component proteins, and manufacturing PPT treatments involve unique challenges and costs not typically found in the traditional small molecule pharmaceutical industry. As a result, it generally takes 7 to 10 months from the time plasma is collected to the time the PPT is administered to patients.[54] Even compared to other infused or injected chemically synthesized drugs or biologic products, manufacturing tends to represent a larger share of total costs per unit for PPT products. One reason for this is the relatively small size of patient populations arising from the rarity of the conditions these products treat. Without the ability to prepare product in large batches, manufacturers are limited in their ability to take advantage of manufacturing economies of scale, which might otherwise allow for cost savings in production.

The extent of the differences in cost structures between the PPT industry and the small molecule pharmaceutical industry is illustrated in Figure 3. Manufacturing and starting materials comprise a substantially larger share of total costs (57%) in the plasma protein industry than they do in the traditional pharmaceutical industry (14%).[55] The differing cost structures of the two sectors have implications for competition and pricing in the two industries.

The dynamics of innovation and competition in what might be thought of as the “traditional” small molecule pharmaceutical industry have been thoroughly studied by economists.[56] Certain key economic realities of that industry are that large investments are made in advance of a product coming to market. With relatively low probability, those investments pay off, and a new product comes to market at a price related to the value the product provides to patients and payers. However, the incremental cost of

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53 Summaries of IQPP & QSEAL standards can be found in the Appendix.

54 Marketing Research Bureau, *The Plasma Proteins Market in the United States 2016* (Orange, CT: Marketing Research Bureau, 2017),

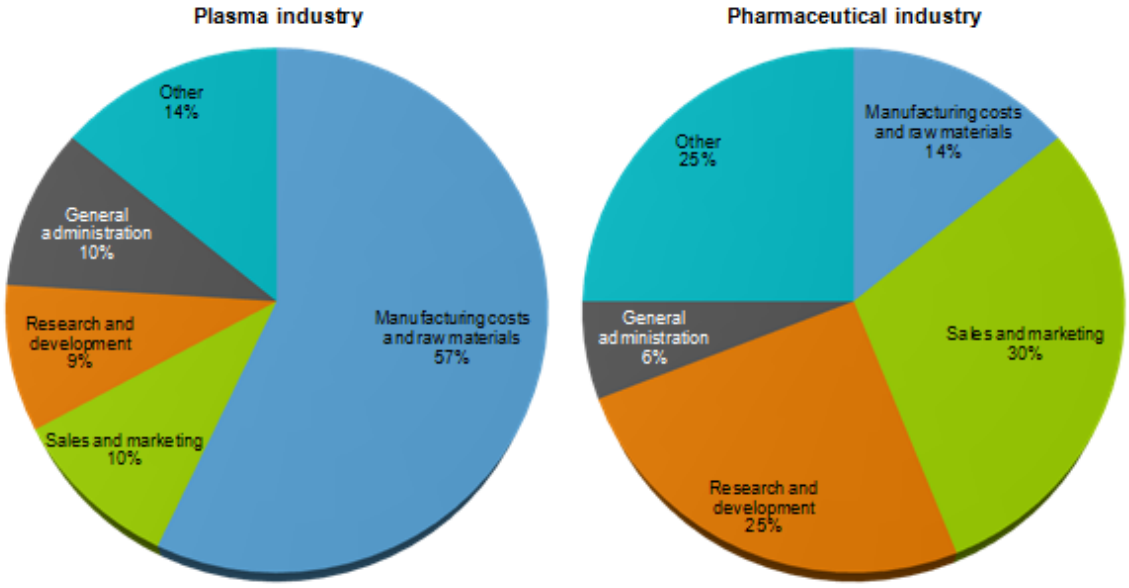
55 Marketing Research Bureau, “Plasma Procurement and Safety,” accessed 15 May 2017, http://marketingresearchbureau.com/plasma-industry/current-uses-affecting-the-plasma-industry/.

56 For an overview of the economics of the industry and the key issues that have been studied, see Patricia Danzon and Sean Nicholson, *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*. (New York: Oxford University Press. 2012).

manufacturing those products is typically low compared to prices. In principle, once patents expire, competition from generic entrants in the small molecule segment of the industry works to drive the price down and entry, or the threat of entry, tends to keep prices in line with the incremental cost of supply.

In the PPT industry, the cost structure and the dynamics of the marketplace are not the same as those in the traditional pharmaceutical industry for several reasons. PPTs have no generic or "biosimilar" equivalents, which suggests different expectations about prices over time.[57] In this sector, manufacturing costs comprise a relatively large share of total costs, and most of the intellectual property that applies to the products is related to manufacturing processes rather than to the products themselves. However distinct manufacturing processes result in variations among products that affect patient tolerability and product behavior.[58] These variations suggest that competition among therapies will largely focus on product characteristics, most likely related to novel manufacturing processes, but competition is unlikely to result in extremely large price declines as are seen in the small molecule pharmaceutical sector when patents expire. In a sustainable market, competition cannot drive prices below the incremental cost of production. Because incremental costs are a large share of costs for PPTs, competition cannot sustain prices below those levels.

Figure 3: Cost structures of the PPT and small-molecule pharmaceutical industries



[57] A generic drug is a copy of a small-molecule brand name pharmaceutical and is typically interchangeable with the reference drug; a biosimilar is the rough parallel to a generic biologic, but since biologics tend to be highly complex molecules, exact copies are not technically feasible. Hence biosimilars are treated differently than generic drugs by regulatory authorities and are typically not considered interchangeable with the reference biologic.

[58] Jerry Siegel, "IVIG Medication Safety: A Stepwise Guide to Product Selection and Use," *Pharmacy Practice News* Sept. 2010: 1-8.

IV. Economic and policy considerations

IV.A. PPT prices have been stable over time

PPT prices are typically determined by contracts between manufacturers and purchasers in private health insurance.[59] The purchasers in this case are typically hospitals, specialty pharmacies, infusion clinics, treatment centers, physician practices, and home health care providers. Payment rates are calculated on at least a quarterly basis.[60] PPTs are primarily paid for in conjunction with a medical service and are more often covered as a medical benefit rather than a pharmacy benefit.[61] As a result, as they do in other sectors of care, large contract buyers such as group purchasing organizations (GPOs) can use their purchasing power to leverage competition among PPT manufacturers to extract discounts and other contracting concessions. In the cases where PPTs are covered under the pharmacy benefit, pharmacy benefit managers (PBMs) play generally the same role as GPOs to extract rebates. Payment rates for these types of products can also vary based on the site of care (e.g., hospital, infusion clinic, or home) in which they are used.

In the U.S., the government pays for a large share of PPT utilization through Medicare Part B. Prices paid under Part B are determined according to the average sales price (ASP), reported quarterly to the Centers for Medicare and Medicaid Services (CMS) by manufacturers. ASP is the benchmark rate that Medicare uses to reimburse hospitals, clinics, or physicians for these products and is based on the volume-weighted average price received by manufacturers after accounting for discounts offered to payers.[62] ASP rates can serve as a reliable indicator for the trend in these products' prices over time. The following figures illustrate ASPs for various PPT product categories.[63]

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59 Assistant Secretary for Planning and Evaluation, "Analysis of Supply, Distribution, Demand, and Access Issues Associated with Immune Globulin Intravenous (IGIV)," p. 4-7, https://aspe.hhs.gov/system/files/pdf/75031/report.pdf.

60 This is the case for physician-administered drugs reimbursed under Medicare. Medicare reimbursements for PPTs are done through Part B, which pays for physician services (Part A reimburses inpatient hospital care).

61 Pharmacy benefits typically cover prescriptions you can fill at a local pharmacy. Prescriptions for specialty biologics like PPTs are sometimes covered under a health insurance plan's medical benefit.

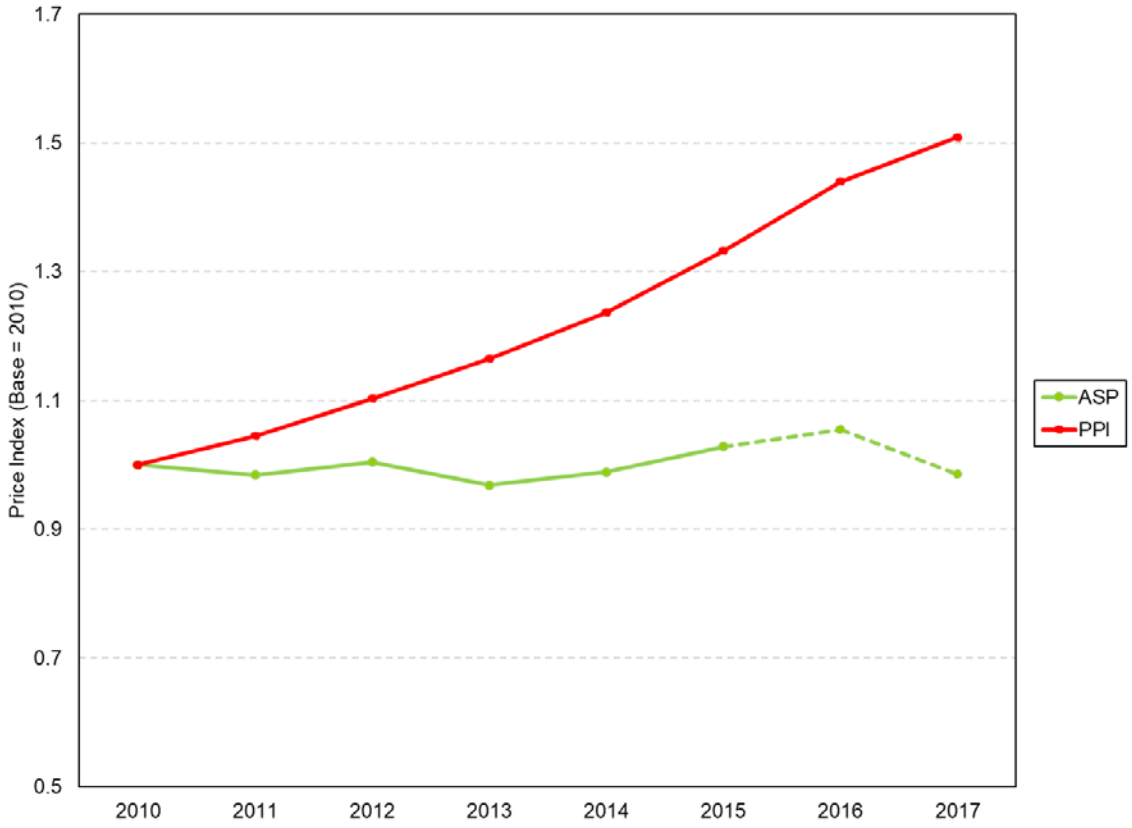
62 Medicare Part B providers are reimbursed at a rate of ASP + 6% for these products. Budget sequestration, which was put into effect in 2013, had the effect of reducing the reimbursement rate to ASP + 4.3%.

63 In most (if not all) cases, the price trend shown in these figures is a combination of individual product ASPs weighted by their respective Part B utilization as reported by CMS through 2015. At the time of this writing, utilization data were not available for 2016 and 2017. The trends reported here are projected by carrying forward the observed Part B utilization in 2015 and reflected by the dashed (versus solid) line.

These charts show indexed ASPs as well as changes in the producer price index (PPI) for pharmaceutical preparations.[64] An ASP line below the PPI line suggests PPT product prices grew less than the drug price inflation benchmark.[65]

Figure 4 shows the trend in prices for IVIG products from 2010 to 2017 (the dashed line indicates a projection based on 2015 utilization). Using 2010 as the base year, the ASP growth rate has been markedly lower than the growth in PPI. Over this eight-year period, average IVIG prices essentially remained the same, while the PPI grew just over 50 percent.

Figure 4: Indexed average sales prices for IVIG products compared with the producer price index for pharmaceutical preparations, 2010–2017



Source: Centers for Medicare and Medicaid Services; U.S. Bureau of Labor Statistics

64 The ASPs in these charts are indexed, meaning they represent the relative change in price over time in relation to the ASP for the base year. The producer price index measures the average change over time in the selling price received by domestic producers for their products. See: https://www.bls.gov/ppi/. The indexed PPI represents the change in PPI relative to the PPI of the base year and can be used as a benchmark of inflation in prescription drug production costs.

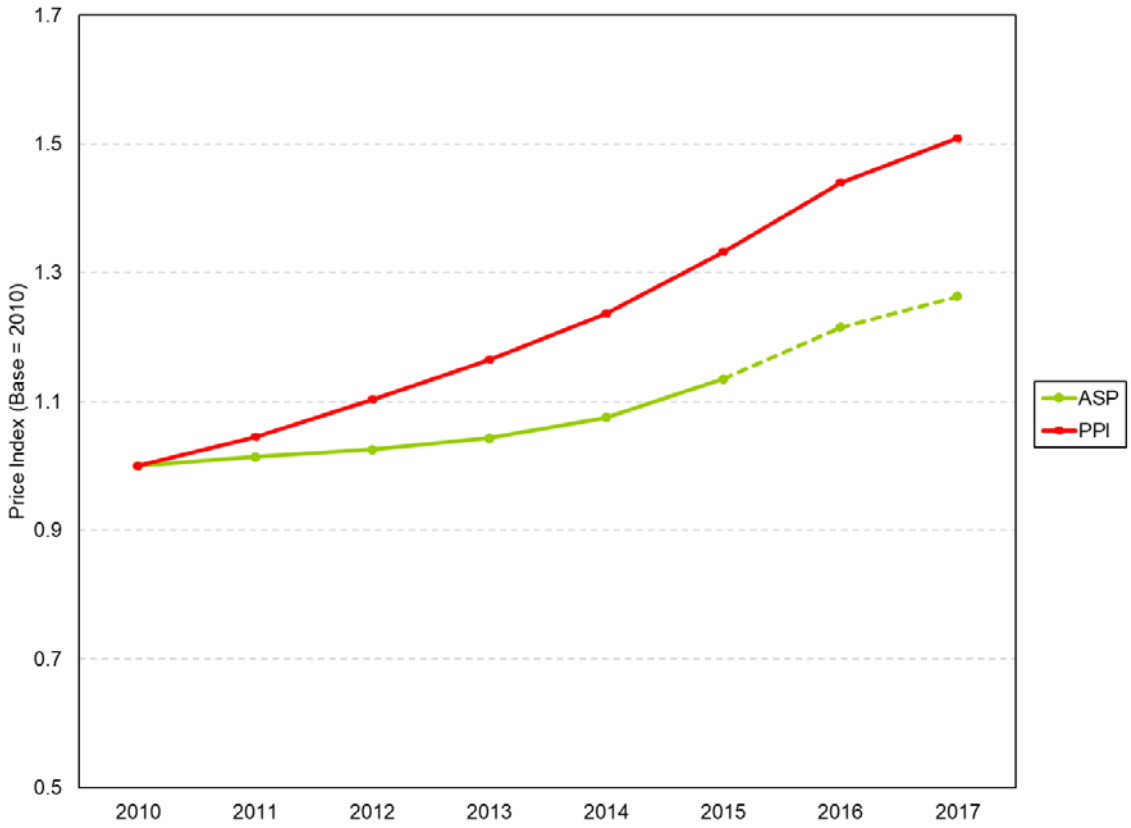
The National Summary Data File is available through the CMS website: https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/Part-B-National-Summary-Data-File/Overview.html.

Volume data are only available through 2015.

65 It should be noted that the changes in the PPI over time may not consistently capture discounts and rebates paid by manufacturers.

Alpha-1 proteinase inhibitor prices demonstrate a similar trend to IVIG products in that price growth for these products has remained lower than the inflationary trend for prescription drug production costs (Figure 5). On average, the alpha-1 ASP-based rates have risen less than 20 percent when compared to their base years, showing substantially less growth than PPI.

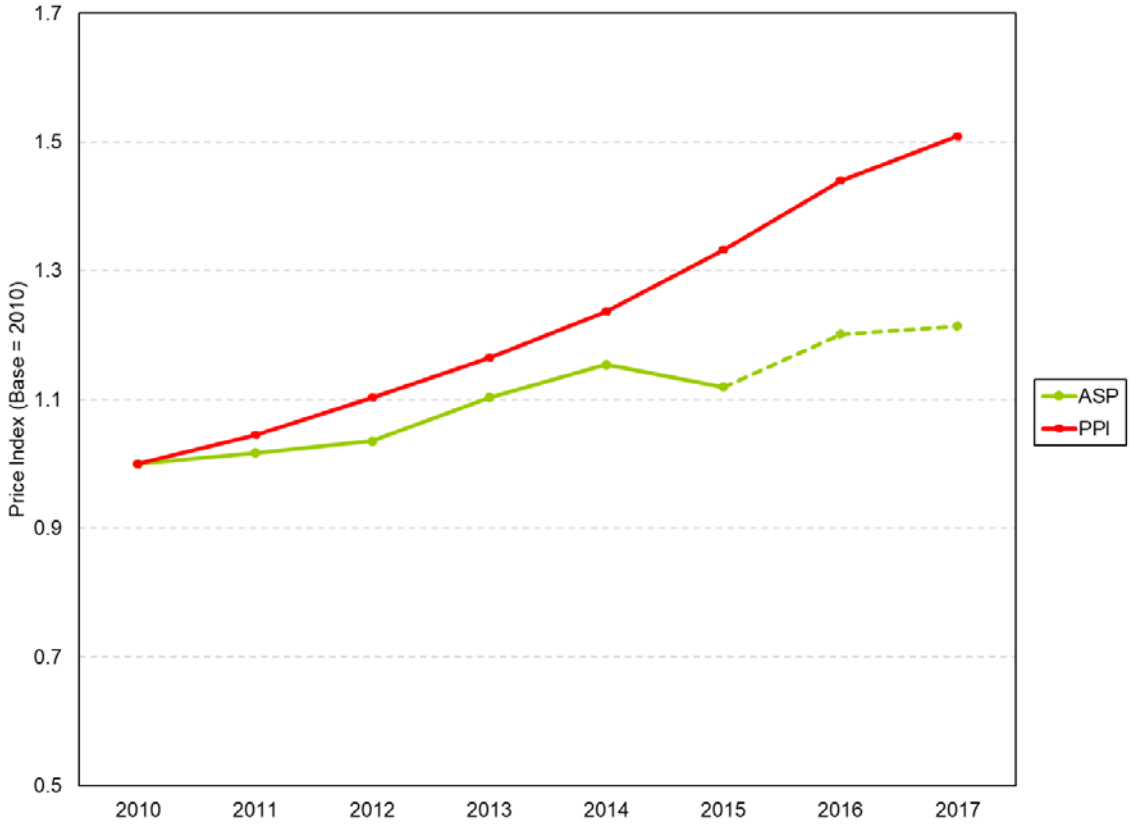
Figure 5: Indexed average sales prices for alpha-1 proteinase inhibitor products compared with the producer price index for pharmaceutical preparations, 2010–2017



Source: Centers for Medicare and Medicaid Services; U.S. Bureau of Labor Statistics

Price trends for C1 esterase inhibitor roughly follow the PPI trend, growing steadily over time up until 2015 (Figure 6). However assuming C1 esterase utilization remained the same from 2015 forward, the price trend essentially flattens out.

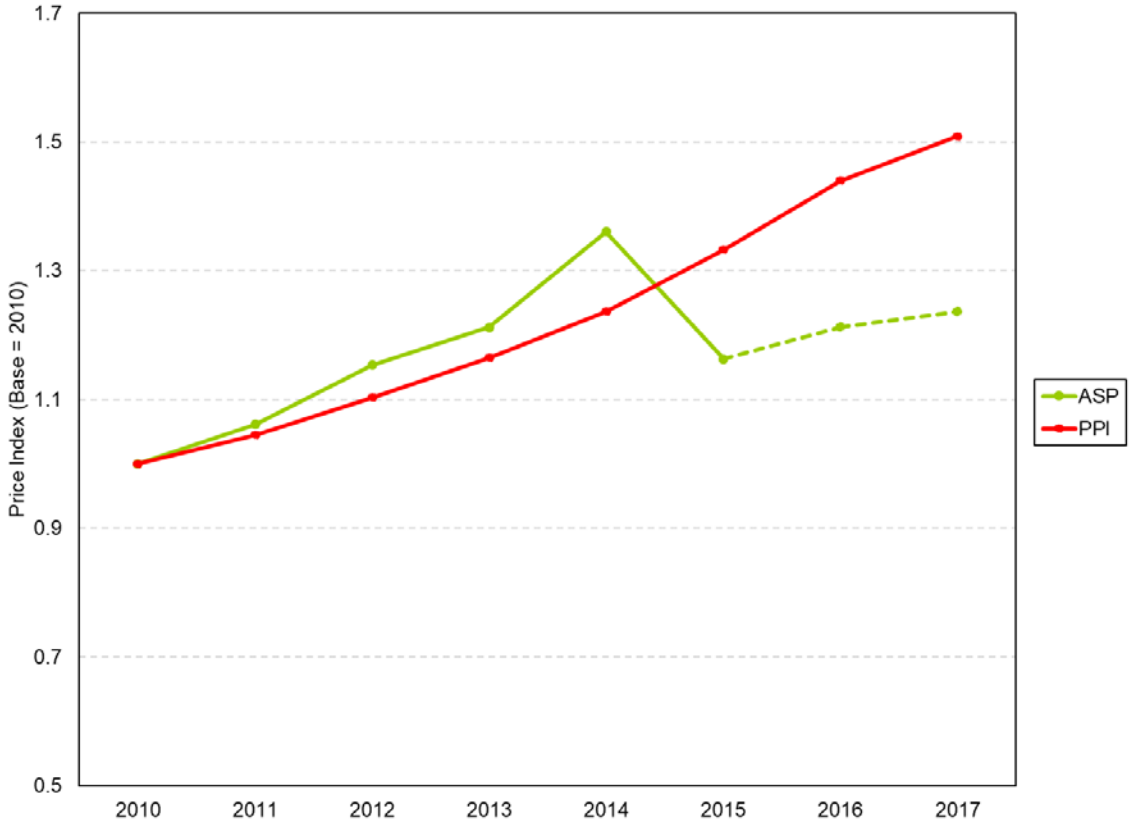
Figure 6: Indexed average sales prices for C1 esterase inhibitor products compared with the producer price index for pharmaceutical preparations, 2010–2017



Source: Centers for Medicare and Medicaid Services; U.S. Bureau of Labor Statistics

The price trend for factor IX products, in contrast to the other product classes previously cited, exceeded that of the PPI through 2014 (Figure 7). However beginning in 2015, the entry of competing factor IX products resulted in a sharp reduction of average prices.

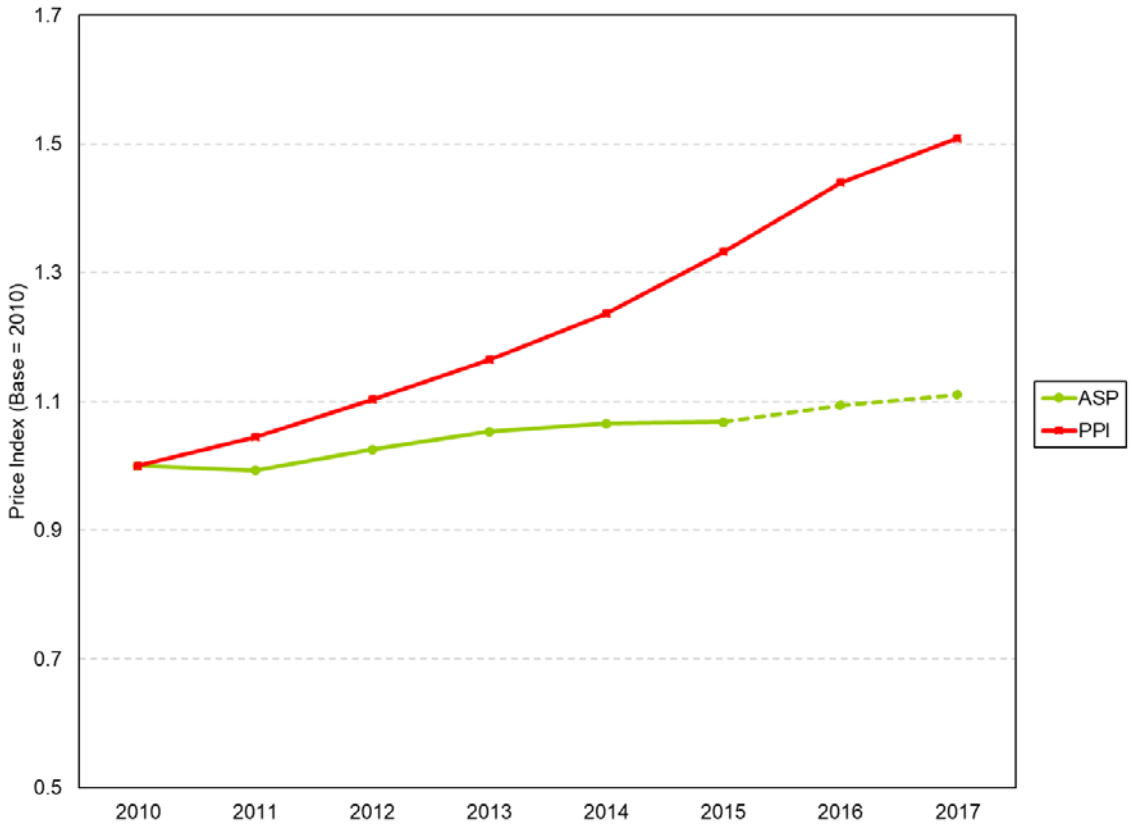
Figure 7: Indexed average sales prices for factor IX products compared with the producer price index for pharmaceutical preparations, 2010–2017



Source: Centers for Medicare and Medicaid Services; U.S. Bureau of Labor Statistics

Factor VIII prices grew marginally from 2010–2017 and essentially remained flat (Figure 8).

Figure 8: Indexed average sales prices for factor VIII products compared with the producer price index for pharmaceutical preparations, 2010–2017



Source: Centers for Medicare and Medicaid Services; U.S. Bureau of Labor Statistics

For the most part, growth in prices for PPTs has remained stable over time. This trend is important to note in an environment where there is greater attention to pharmaceutical prices and costs. The data demonstrate that despite economic constraints such as a finite supply of starting material, PPT prices have generally risen at lower rates than have prescription medicines since 2010.

IV.B. Pricing and reimbursement policy concerns

The perception of high and rising prices for prescription drugs has received intense scrutiny from both federal and state policymakers. Responding to perceived problems in the pricing of drugs, both Congress and state legislatures have either enacted or are considering rules calling for increased pricing transparency and in some cases requiring that drug prices be benchmarked to the overall measures of inflation.[66]

It might be tempting to conclude, particularly having seen the recent price trends illustrated in the previous two charts, that mandated price limits would pose no problems for the PPT sector. That conclusion would be incorrect. A fundamentally important economic principle is that the balance of supply and demand is reflected in the prices of goods. The same is true of PPTs. Policies that artificially mandate prices interfere with such signals and can lead to imbalances between supply and demand and could seriously exacerbate what otherwise might simply be short term departures from an otherwise balanced equilibrium. This would be particularly true for the PPT market for the following reasons:

- **Attempts to mandate prices can create access problems for patients:** Government attempts to regulate prices can and do result in access issues. An introduction of a price mandate or cap on PPTs will raise the likelihood that providers will lose money if they continue to care for patients who require these treatments. As a result, providers are faced with the difficult choice between financial viability and serving their patients. This is not just a theoretical concern. In 2005 and 2006, a new approach to setting Medicare reimbursements for IVIG put more than half of providers "under water," or in a situation where the amount Medicare paid for IVIG was below the actual cost of the drug. As a result, providers were losing hundreds of dollars per treatment and were eventually forced to tell patients to seek treatment elsewhere.[67]
- **Inelastic short-run supply of human plasma:** Plasma donations are a resource that exists in somewhat fixed supply in the short term. In order to respond to any increased demand, PPT manufacturers would need to develop strategies to increase the protein yield from each liter of plasma or shorten the time to manufacture. Both mechanisms would be challenging as much of the manufacturing process is regulated.
- **High capital costs and regulatory burden:** In contrast to producing a small molecule drug, both the capital investment and regulatory burden associated with producing PPTs would delay entry by other

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66 Congress recently enacted legislation mandating that generic drug providers rebate back the difference between drug price increases and the benchmark Consumer Price Index for drugs purchased by Medicaid.

67 U.S. Department of Health and Human Services Office of Inspector General, "Intravenous Immune Globulin: Medicare Payment and Availability," https://oig.hhs.gov/oei/reports/oei-03-05-00404.pdf.

One competing explanation for the reduction in IVIG access is that off-label use had dramatically increased during this time. A University of Chicago analysis of this issue suggests that the access issues are more likely attributable to the change in Medicare reimbursement. See: Tomas Philipson and Anupam Jena, "The Impact of Medicare Modernization Act Reimbursement Changes on the Utilization of Intravenous Immune Globulin," University of Chicago Harris Graduate School Working Paper.

> potential competitors. Moreover, PPT manufacturing requires specific knowledge and skill sets that would raise human capital costs as potential competitors look to enter the market. For these reasons, potential competitors would be unlikely to enter the market unless they could anticipate tangible growth opportunities. It is estimated that the costs to bring a new fractionation plant online ranges from $74 million to $100 million.[68]

Under a price control regime in which PPTs were required to adhere to an inflation benchmark, investment in discovering new proteins to meet unmet clinical need or improving fractionation processes to increase yield would be severely dampened. Manufacturers would be willing to pay the higher costs associated with these goals only if they could expect to receive a reasonable return on their investment in the future. Artificial price controls and other related mandates would negatively impact incentives to expand capacity since companies could be prevented from taking steps, such as increasing prices, that would allow them to improve processes and develop new therapies. Further, standard economic theory predicts that price controls would result in shortages for these lifesaving products. In view of the high-value that patients and the health care system receive from these therapies, and noting the relative price stability observed in these markets in recent years, there appears to be substantial risk of adverse unintended consequences to this market from imposing artificial price mandates.

IV.C. Access to plasma protein therapies

When considering access to care, it is important to bear in mind that patients with rare, genetic conditions who are treated with PPTs typically exhibit different responses to therapy. Due to differences in patients and because of the complex nature of the products, different PPTs are not interchangeable from a medical perspective. They should not be treated as such by regulatory and payer policies.

Medical guidelines for the effective use of immunoglobulin replacement therapy note that “IVIG/SCIG are not a [sic] generic drugs and products are not interchangeable; a specific product needs to be matched to patient characteristics to ensure patient safety; a change of product should occur only with the active participation of the prescribing physician.”[69] Another study asserted that “one size does not fit all” in treating patients with clotting factor concentrate; “the behaviour of the same [clotting factor products] may be different in each patient.”[70]

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[68] Neil Goss and John Curling, “Chapter 33: The Economics of Plasma Fractionation,” in Joseph Bertolini, Neil Goss, and John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013): 456.

[69] Elena E. Perez, et al. “Update on the use of immunoglobulin in human disease: A review of evidence.” *J Allergy Clin Immunol*, March 2017, p. S27 http://www.jacionline.org/article/S0091-6749(16)31141-1/fulltext.

[70] Massimo Morfini, “The History of Clotting Factor Concentrates Pharmacokinetics,” *Journal of Clinical Medicine* 35, no. 6 (2017): http://www.mdpi.com/2077-0383/6/3/35/html. Note that this study evaluated both plasma-derived and recombinant clotting factors.

Although differences across patients and products can be difficult to characterize, Figure 9 illustrates, as an example, certain observable differences across IG products from different manufacturers that arise from distinct manufacturing methods.[71] Similar differences exist in other product classes as well.[72]

[71] Jerry Siegel, "The Product: All Intravenous Immunoglobulins Are Not Equivalent," *Pharmacotherapy* 25, no. 11P2 (2005): 78S-84S.

[72] Immune Deficiency Foundation, "USIDNET & PI CONNECT Patient Powered Research" (presentation, January 9, 2017), 17

Figure 9: Examples of manufacturers, preparation methods, and properties of Immunoglobulins (IG)

Product	Manufacturer	FDA-approved indications	Half-life[73]	pH range	IgA content
Bivigam	Biotest	PI	19.6 days (3 wk cycle); 33.5 days (4 wk cycle)	4.0–4.6	≤ 200 µg/mL
Carimune NF	CSL Behring	PI, ITP	Unknown	6.4–6.8	720 µg/mL
Cuvitru	Shire	PI	33.1 days	4.6–5.1	Ave 80 µg/mL
Flebogamma DIF – 5% Flebogamma DIF – 10%	Grifols	PI	37 days 34 ± 10 days (3 wk cycle); 37 ± 13 days (4wk cycle)	5.0–6.0	< 50 µg/mL < 100 µg/mL
Gammagard Liquid	Shire	PI, MMN	35 days	4.6–5.1	37 µg/mL
Gammagard S/D – 5% Gammagard S/D – 10%	Shire	PI, ITP, B-cell CLL, KD	37.7 ± 15 days	6.8 ± 0.4	< 1 µg/mL
Gammaked	Kedrion	PI, ITP, CIDP	35 days	4.0–4.5	Ave 46 µg/mL
Gammaplex – 5% Gammaplex – 10%	Bio Products Laboratory	PI, ITP	42 ± 26 days (3 wk cycle); 41 ± 14 days (4 wk cycle)	4.6–5.1 4.9–5.2	< 10 µg/mL < 20 µg/mL
Gamunex-C	Grifols	PI, ITP, CIDP	35 days	4.0–4.5	Ave 46 µg/mL
Hizentra	CSL Behring	PI	40.6 days	4.6–5.2	≤ 50 µg/mL
HYQVIA	Shire	PI	59.3 days	4.6–5.1	Ave 37 µg/mL
Octagam – 5% Octagam – 10%	Octapharma	PI ITP	35.9 ± 1.4 days (3 wk cycle); 40.7 ± 17 days (4 wk cycle)	5.1–6.0 4.5–5.0	< 200 µg/mL Ave 106 µg/mL
Privigen	CSL Behring	PI, ITP	36.6 days	4.8	≤ 25 µg/mL

Source: Immune Deficiency Foundation (2017)

PI: Primary immunodeficiency diseases; ITP: Idiopathic thrombocytopenic purpura; MMN: Multifocal motor neuropathy; B-cell CLL: Chronic lymphocytic leukemia; KD: Kawasaki disease; CIDP: Chronic inflammatory demyelinating polyneuropathy

[73] BDI Pharma, Intravenous Immune Globulin (10%) (Columbia, SC: BDI Pharma, 2015) (for Flebogamma DIF 10%, Gammagard Liquid, Gammaked, Gamunex-C, Privigen); U.S. Food and Drug Administration, "Highlights of Prescribing Information: Bivigam," accessed Dec. 21, 2017, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm334609.pdf (for Bivigam); U.S. Food and Drug Administration, "Cuvitru Original Application," accessed Dec. 21, 2017, https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM524404.pdf (for Cuvitru); Melvin Berger and Paul Pinciaro, "Safety, Efficacy, and Pharmacokinetics of Flebogamma® 5% [Immune Globulin Intravenous (Human)] for Replacement Therapy in Primary Immunodeficiency Diseases," *Journal of Clinical Immunology* 24: no. 4 (2004): 389-396 (for Flebogamma 5%); U.S. Food and Drug Administration, "Highlights of Prescribing Information: Gammagard S/D," accessed Dec. 21, 2017, https://www.fda.gov/downloads/BloodBloodProducts/UCM197905.pdf (for Gammagard S/D); Carole Chrvala and Alan Caspi, "Immune Globulin Intravenous (Human), 5% Liquid Gammaplex," *Pharmacy and Therapeutics* 36: no. 6 (2011): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138361/ (for Gammaplex 5%); Epocrates, "Hizentra," accessed Dec. 21, 2017, https://online.epocrates.com/u/10a5690/Hizentra (for Hizentra); U.S. Food and Drug Administration, "Highlights of Prescribing Information: HYQVIA," accessed Dec. 21, 2017, https://www.fda.gov/downloads/ApprovedProducts/UCM414440.pdf (for HYQVIA); Octapharma Australia Pty. Ltd., Product Information: Octagam (Pyrmont, NSW: Octapharma Australia Pty. Ltd., 2011) (for Octagam).

There is evidence that even small differences in product characteristics such as sodium content, type and concentration of sugar, osmolarity/osmolality, pH, IgA content, and infusion rate can affect patient tolerability, risk of adverse events, and potential efficacy.[74] One study found 35% of participants experienced adverse reactions during or within 48 hours of administration of a standard immune globulin preparation that did not recur after switching to an alternative preparation, demonstrating that patients often respond significantly better to one product than to another.[75] An Immune Deficiency Foundation patient survey found that less than a third of patients responded similarly to all immunoglobulin products.[76]

Informed by these medical realities, the Medicare system treats PPTs differently than more commonly prescribed drugs. In contrast to generic drugs, where all interchangeable generic drugs and the innovators they copy are assigned the same payment code, PPTs are often assigned individual payment codes (HCPCS/J-codes) by CMS, and these products do not meet the standards for interchangeability of biologic and biosimilar products established by the Food and Drug Administration.[77]

Changing reimbursement to eliminate individual J-codes for similar but not interchangeable therapies is a policy risk that could have negative impacts on patients who rely on PPTs. Correspondingly, the structure of price negotiations and existence of formulary restrictions in this industry can limit physician and patient drug access, thereby resulting in potentially severe medical consequences when patients lack access to appropriate therapy. Providers and insurers use competition between suppliers to negotiate discounts to control costs. As noted above, hospitals and other providers use GPOs to exercise buying power and discipline prices. This buying power is significant, accounting for over 70% of total hospital purchases with only six GPOs accounting for 90% of all hospital purchases made through this channel.[78] One mechanism through which GPOs can extract discounts is by establishing exclusive arrangements with one or two manufacturers, thereby limiting access to competing products. Outside of the hospital, insurers can also extract discounts by favoring one manufacturer over others in the form of favorable formulary placement. By using their buying power, insurers can impose coverage/formulary restrictions, including requiring prior authorization or applying a high copayment or coinsurance.

These restrictions can have unintended consequences for patients. In general, buying power and formulary restrictions enable payers (GPOs and insurers) to get lower prices and, in principle, this should lead to lower premiums for patients. This is generally an efficient outcome if the differences between the

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74 National Hemophilia Foundation, *MASAC Recommendation Regarding Factor Concentrate Prescriptions and Formulary Development and Restrictions* (New York: National Hemophilia Foundation, 2005),

75 Laurence Feldmeyer, Christian Benden, Sarah Haile, Annette Boehler, Rudolf Speich, Lars French, and Gunther Hofbauer, "Not all intravenous immunoglobulin preparations are equally well tolerated," *Acta Dermato-Venereologica* no. 90 (2010): 494-497.

76 Immune Deficiency Foundation, "USIDNET & PI CONNECT Patient Powered Research" (presentation, January 9, 2017), 17

77 Fractionated plasma products are regulated as biologics and are approved through biologics license applications (BLAs).

78 Mike Cowie, *Group Purchasing Organizations and Antitrust Law: Recent Developments* (Washington, DC: Dechert LLP, 2011).

competing products are not significant. However, as described above, the lack of interchangeability and the potential clinical consequences are an important distinction here. Indeed, there is evidence that patient tolerance or responsiveness can vary across different PPT products.[79] As a result, applying a "one size fits all" approach to extract discounts can result in higher costs and adversely affect patient health.[80]

In addition to these exclusive arrangements, insurers also try to control costs by either (1) requiring prior authorization before an individual can start a PPT therapy or (2) requiring the insured to use one or more products that are preferred by the insurer's formulary before allowing access to another product.[81] Delays or unwarranted refusals of appropriate PPT therapy can result in significant disability or potentially death.[82]

The importance of providing individuals with their medically appropriate therapy is critical to all PPT patient populations. As the Medical and Scientific Advisory Council of the National Hemophilia Foundation emphasizes, "It is critical that the bleeding disorder community has access to a diverse range of therapies and that prescriptions for specific clotting factor concentrates are respected and reimbursed."[83]

The impact of treating patients with poorly tolerated therapies will not only adversely affect patient health, but it will also likely have adverse budget consequences due to the likelihood of additional

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79 Jerry Siegel, "The Product: All Intravenous Immunoglobulins Are Not Equivalent," *Pharmacotherapy* 25, no. 11P2 (2005): 78S-84S.

80 "IVIG is not a generic drug, and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure [*sic*] patient safety." See American Academy of Allergy Asthma & Immunology, *Guiding Principles* (Milwaukee, WI: American Academy of Allergy Asthma & Immunology, 2011), 1.

"It is unacceptable to limit availability of augmentation therapy in any way and especially to a single product." See Alpha-1 Foundation, "Clinical Practice Guidelines," accessed Dec. 21, 2017, https://www.alpha1.org/Healthcare-Providers/Testing-and-Treatment/Clinical-Practice-Guidelines.

"Given the variable nature of these diseases, individualized treatments depending on patient need and physician judgment are important." See Huned Patwa, Vinay Chaudhry, Hans Katzberg, Alexander Rae-Grant, and Yuen So, "Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology," *Neurology* 78: no. 13 (2012): 1009-1015.

"Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient." See Bruce Zuraw, Aleena Banerji, Jonathan Bernstein, Paula Busse, Sandra Christiansen, Mark Davis-Lorton, Michael Frank, Henry Li, William Lumry, and Marc Riedl, "U.S. Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency," *Journal of Allergy and Clinical Immunology: In Practice* 1: no. 5 (2013): 458-467.

"It is critical that the bleeding disorder community has access to a diverse range of therapies and that prescriptions for specific clotting factor concentrates are respected and reimbursed." See National Hemophilia Foundation, "MASAC Recommendation Regarding Factor Concentrate Prescriptions and formulary Development and Restrictions," accessed Dec. 21, 2017, https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendation-Regarding-Factor-Concentrate-Prescriptions-and-Formulary-Development-and-Restrictions.

81 These are known as fail-first or step-therapy protocols.

82 Anna Gorman, "When An Insurer Balks and Treatment Stops," *Kaiser Health News*, June 7, 2017. http://khn.org/news/when-an-insurer-balks-and-treatment-stops/.

83 National Hemophilia Foundation, *MASAC Recommendation Regarding Factor Concentrate Prescriptions and Formulary Development and Restrictions*. (New York: National Hemophilia Foundation, 2005.

required treatments.[84] From a cost-effectiveness perspective, the evidence suggests that prescribing physicians should have the flexibility to choose the most appropriate therapy for their patients based on each individual's unique conditions and tolerability profile. An essential element of the importance of access to well-tolerated therapies is patient compliance. Patients who do not tolerate therapies are less likely to remain on them or to use them in accordance with physician directions. This can result not only in reduced patient health but also higher treatment costs.

IV.D. Incentives for innovation

Small molecule pharmaceutical manufacturers benefit from the traditional forms of intellectual property protection, including patent claims involving the molecule's chemical structure and its method of use. These protections are not available to most current PPTs. Rather, PPT manufacturers encounter more limited exclusivity based on patents (and perhaps trade secrets) that are related to manufacturing technology. The relatively limited ability of manufacturers to protect their intellectual property suggests that the incentives for innovation in the PPT market are lower than they would be if protections were comparable to what exists in other life science product areas. Instead, competition in this sector rests on product characteristics, administration, and differences in price related to manufacturing technology and short-term capacity constraints. Unique product profiles result from characteristics including concentration of proteins, length of effective half-lives in patients, pharmacokinetic profiles, side effects, tolerability, packaging, and shelf life. Differences in how a drug is administered are also taken into consideration when physicians select the medically appropriate therapy for patients. Important factors include whether the drug is self-administered at home or administered by a medical professional in a clinic, how frequently infusions are required, and whether the drug is infused intravenously or subcutaneously.

Purchasers will have a financial incentive to choose a product with a higher price if they believe that the non-price attributes, such as product quality and ease of administration, are worth more than the price difference. This behavior provides incentives to PPT manufacturers to innovate new and improved therapies that result in better patient health. In contrast, policy changes in reimbursement procedures that treat PPTs from different manufacturers as equivalent therapies would have adverse consequences for innovation incentives and market competition.

Other policies, such as the Orphan Drug Act, positively affect innovation incentives. The 1983 Orphan Drug Act gives firms special incentives to develop drugs for diseases affecting fewer than 200,000

[84] National Hemophilia Foundation, *MASAC Recommendation Regarding Factor Concentrate Prescriptions and Formulary Development and Restrictions*. (New York: National Hemophilia Foundation, 2005.

Americans.[85] The act has induced increased development of drugs targeted at small populations.[86] However this tax credit was recently reduced by half in the tax bill passed by Congress at the end of 2017.[87] While the reduction in the credit reduces the direct incentives for innovation specifically targeted at small population illnesses, the overall reduction in the corporate tax rate increases the amount of cash available to companies. If companies allocate additional resources to research and development, this could potentially offset the impact of the reduced orphan drug tax credit. The impact of the reduced credit on the development of new therapies, and on patient wellbeing, will need to be evaluated over time.

85 U.S. Food and Drug Administration, "Developing Products for Rare Diseases and Conditions," accessed Dec 21, 2017, https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.

86 Frank Lichtenberg and Joel Waldfogel, "Does Misery Love Company? Evidence from Pharmaceutical Markets before and after the Orphan Drug Act," *Michigan Telecommunications and Technology Law Review* 15: no. 2 (2009): 335-357.

87 Zachary Brennan, "Senate, House Agree to Cut Orphan Drug Research Credit in Half in Tax Bill," December 18, 2017, *Regulatory Focus*, accessed February 1, 2018, https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/senate,-house-agree-to-cut-orphan-drug-research-credit-in-half-in-tax-bill.

V. Conclusion

The aim of this paper is to analyze the unique economic characteristics of PPTs and highlight their value in saving and improving patient lives. The unique nature of these products, such as the acquisition of source plasma and complex manufacturing techniques, results in higher costs relative to the typical small molecule drug industry and even the biologics sector. In addition to meeting a high regulatory bar for product safety, the industry has adopted steps to decrease the possibility of infection. These steps further raise the cost of producing therapies but ultimately lead to an exceptional degree of product safety.

The pricing environment for these products has been relatively stable in light of the extraordinary benefits they provide to the patients who need them. The use of PPTs to treat plasma protein deficiencies is an incredible value compared to the costs of treating the symptoms that would arise absent high-quality treatment in many conditions and compared to the shortened lives that would accompany no treatment at all.

The clinically indicated use of PPTs stands to grow in the future as new proteins for manufacture are identified and as treatment becomes available to currently undertreated patient populations. This growth suggests a need to plan for and address potential manufacturing capacity constraints, or insufficient donations. It also highlights the need to assure that new legislation or regulation pay attention to the particular issues that affect this industry so that patients today and into the future continue to have access to these vital medicines.

As policymakers suggest proposals to address high drug expenditures, they should take into consideration how these policies would affect the individuals who rely on these lifesaving therapies, given the unique nature of plasma protein therapies. These lifesaving therapies cannot simply be substituted one for another. Therefore patient access to medically appropriate therapy should remain a priority in the changing U.S. health care environment.

VI. Appendix: Background on PPTs

Human blood is made up of four components: red blood cells, white blood cells, platelets, and plasma. Each of these has been used to treat serious medical conditions for many years, dating back to the first widespread use of blood products, like albumin, to treat injuries during World War II (WHO, 2013b). Plasma is the liquid portion of blood that contains albumin, immunoglobulins, clotting factors, hormones, nutrients, electrolytes, and other components.

Healthy volunteers can donate plasma to be made into medicines known as plasma protein therapies (PPTs). These therapies have been a mainstay for more than six decades in treating individuals who lack these proteins.[88] Despite advances in technology that allow for the production of certain plasma proteins from animal cells, human plasma remains an important, and sometimes the only, reliable source of lifesaving complex therapeutic products for the individuals with plasma protein deficiencies.[89]

VI.A. PPTs address vital medical needs

More than 200 different therapeutic uses have been identified for PPTs, including replacing blood lost during surgery or trauma, treating immunodeficiencies and autoimmunity, preventing and treating infections, and controlling bleeding in congenital and acquired coagulation factor deficiencies (MRB, 2015). Table 1 provides a partial list of common uses of the most widely used PPTs. Many of the conditions treated with these products are rare and chronic. Patients often require lifelong treatment, and often there are no clinically equivalent therapies (NHS, 2015; Scheinfeld, 2015).

PPTs treat many chronic disorders including primary immunodeficiency diseases (PIs), chronic inflammatory demyelinating polyneuropathy (CIDP), alpha-1 antitrypsin deficiency, hereditary angioedema (HAE), and bleeding disorders such as hemophilia.[90] A common thread across these disorders is that each is rare, defined as affecting fewer than 200,000 individuals.[91] PIs are a group of more than 300 rare, chronic, hereditary disorders in which individuals are more susceptible to infections

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88 Joseph Bertolini, Neil Goss, and John Curling, *Production of Plasma Proteins for Therapeutic Use* (Hoboken: John Wiley & Sons, Inc., 2013).

89 These therapies are known as recombinant plasma proteins and are made by "recombining" animal cells and human DNA and cloning them to produce large proteins. Although these are a type of plasma protein therapy, the focus of this paper is on therapies derived from donated human plasma.

90 Plasma Protein Therapeutics Association, "Who Needs Plasma Therapies?" accessed June 9, 2017, http://www.pptaglobal.org/plasma-protein-therapies/who-needs-plasma.

91 In the US, the Food and Drug Administration grants a special "orphan drug designation" for products that treat diseases or disorders that affect less than 200,000. This designation, which provides temporary regulatory exclusivity for these products, is aimed at spurring the development of products that treat rare diseases.
See: https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/ucm2005525.htm.

and other health issues.[92] For many types of PIs, PPTs are used to supplement low antibody levels and boost immunity, allowing patients to live normal lives.[93] In addition to primary immunodeficiency diseases, PPTs have both prolonged and enhanced the lives of individuals with a variety of blood, liver/lung, autoimmune, and neurological disorders. Prior to the development of infusible clotting factors, those affected by severe hemophilia faced the certainty of a shortened life expectancy characterized by periodic and life-threatening bleeding events.[94]

PPTs are also being used for acute conditions such as idiopathic thrombocytopenic purpura, Rh-incompatible pregnancies, and infectious diseases like varicella zoster, cytomegalovirus, hepatitis B, and rabies.[95] They are also part of the U.S. Strategic National Stockpile for use in a public health emergency, including a PPT treatment for complications due to vaccinia vaccination and for treatment of inhalational anthrax.

Figure 10: Prevalence of PPT-treated conditions

PPT	Condition	Estimated Prevalence
Albumin	Burns	
	Cardiopulmonary bypass	
	Cirrhosis complications	
	Major surgery	
	Shock	
	Trauma	
	Plasma exchange treatments	
	Acute respiratory distress syndrome	
Coagulation Factors	Bleeding/trauma	
	Hemophilia A (factor VIII deficiency)	1 in 10,000
	Hemophilia B (factor IX deficiency)	1 in 25,000
	Liver disease	
	Other factor deficiencies (factor II, V, VII, X, XI, XIII, and fibrinogen)	Between 0.33 in 1,000,000 to 1 in 10,000,000
	Anticoagulant overdose	
	von Willebrand disease	1.25 million (US), 6.9 million (worldwide)
Immune globulins	Chronic inflammatory demyelinating polyneuropathy	1.5–3.6 per million people
	Acute inflammatory demyelinating polyneuropathy (Guillain-Barré)	1-2 per 100,000
	B-cell chronic lymphocytic leukemia	1 in 200 (U.S., 2014)

92 Immune Deficiency Foundation, "About Primary Immunodeficiencies," accessed June 9, 2017, http://primaryimmune.org/about-primary-immunodeficiencies/.

93 BriovaRx, "Primary Immunodeficiency Disease (PIDD)," accessed June 9, 2017, http://www.axelacare.com/node/77.

94 Sarah Darby et al., "Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV," *Blood* (2007): 110:3.

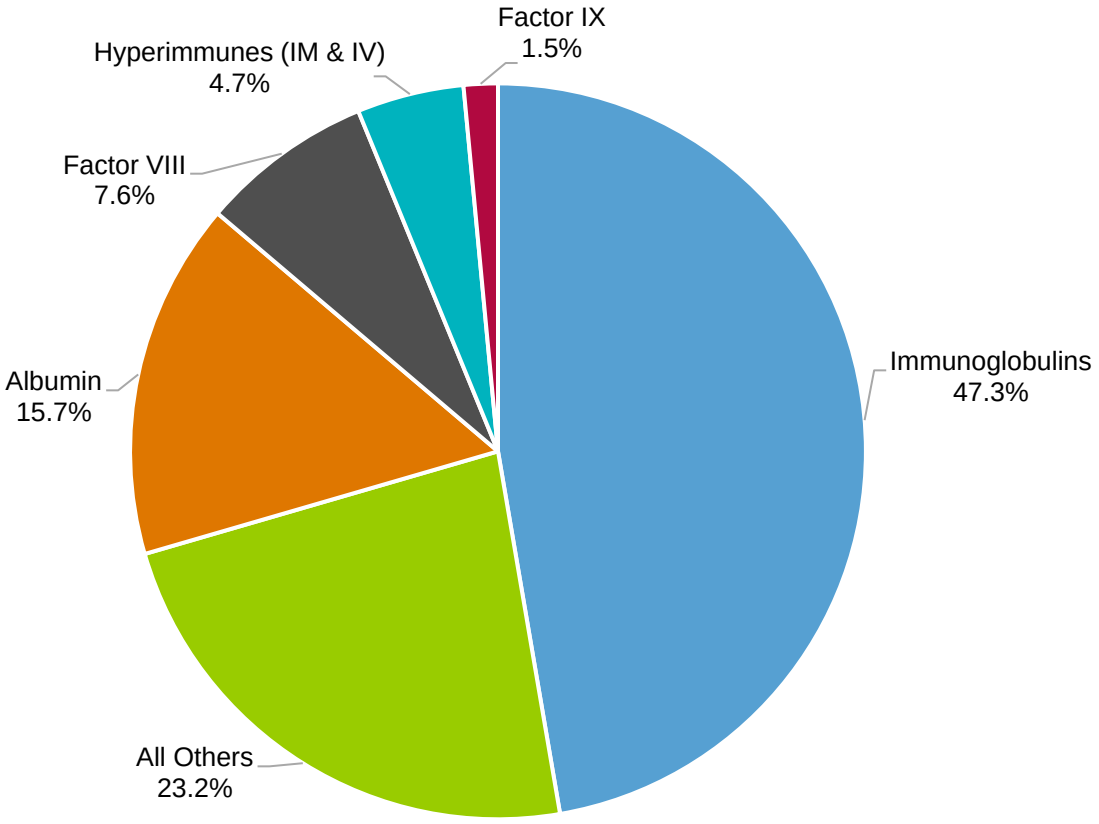
95 FFF Enterprises, "The Role of Hyperimmune Globulins," June 7, 2011, accessed August 11, 2017, http://www.fffenterprises.com/news/articles/article-2011-06-07.html.

	Multiple myeloma	1 in 143 (U.S.)
	Cytomegalovirus	1 in 1,000 births (U.S., 2011)
	Hepatitis A	
	Hepatitis B	850,000–2.2 million people (U.S.)
	Idiopathic thrombocytopenic purpura	9.5 per 100,000
	Inhalational anthrax	
	Kawasaki disease	67.3 per 100,000 children under 5 (incidence)
	Multifocal motor neuropathy	0.3 per 100,000 (Japan, 2012)
	Organ and bone marrow transplants	
	Pediatric HIV	
	Primary immunodeficiency	250,000 (U.S.)
	Rabies	
	Rh disease	6 in 1,000 (U.S.)
	Tetanus	
	Vaccinia vaccine complications	3.0–38.5 per million (eczema vaccinatum) 1.5–3.0 per million (progressive vaccinia) 9.0–241.5 per million (generalized vaccinia)
	Varicella	
Protease Inhibitors	AAT deficiency	100,000 (U.S.)
	AT-III deficiency congenital and acquired	1 in 2,000 to 1 in 20,000 (congenital)
	Hereditary angioedema	1 per 50,000–150,000

Sources: (Skinner, 2012; GBS-CIDP Foundation, n.d.; CDC, 2001, 2009, 2013; ACS, 2015, ACS 2016; Matsui, 2012; IDF, n.d.; WHO 2013; Moise, 2008; Frank, 2015; Hirsh, Piovella, and Pini, 1989). Henry G. Grabowski and Richard L. Manning, "An Economic Analysis of Global Policy Proposals to Prohibit Compensation of Blood Plasma Donors, *Int. J. of the Economics of Business,* 2016 Vol. 23, No. 2, 149-166, http://dx.doi.org/10.1080/13571516.2016.1182690.

Although 20 of the 1,000 or more proteins in human plasma are currently used for therapy, four products drive overall demand: immunoglobulin, albumin, factor VIII, and alpha-1 protease inhibitor (MRB, 2017). Figure 11 illustrates the composition of global plasma demand, showing that (in 2016) the three largest selling proteins accounted for 47% (or 52%, including hyperimmune globulins), 16%, and 8% of sales, respectively.

Figure 11 Worldwide PPT sales, 2016 [96]

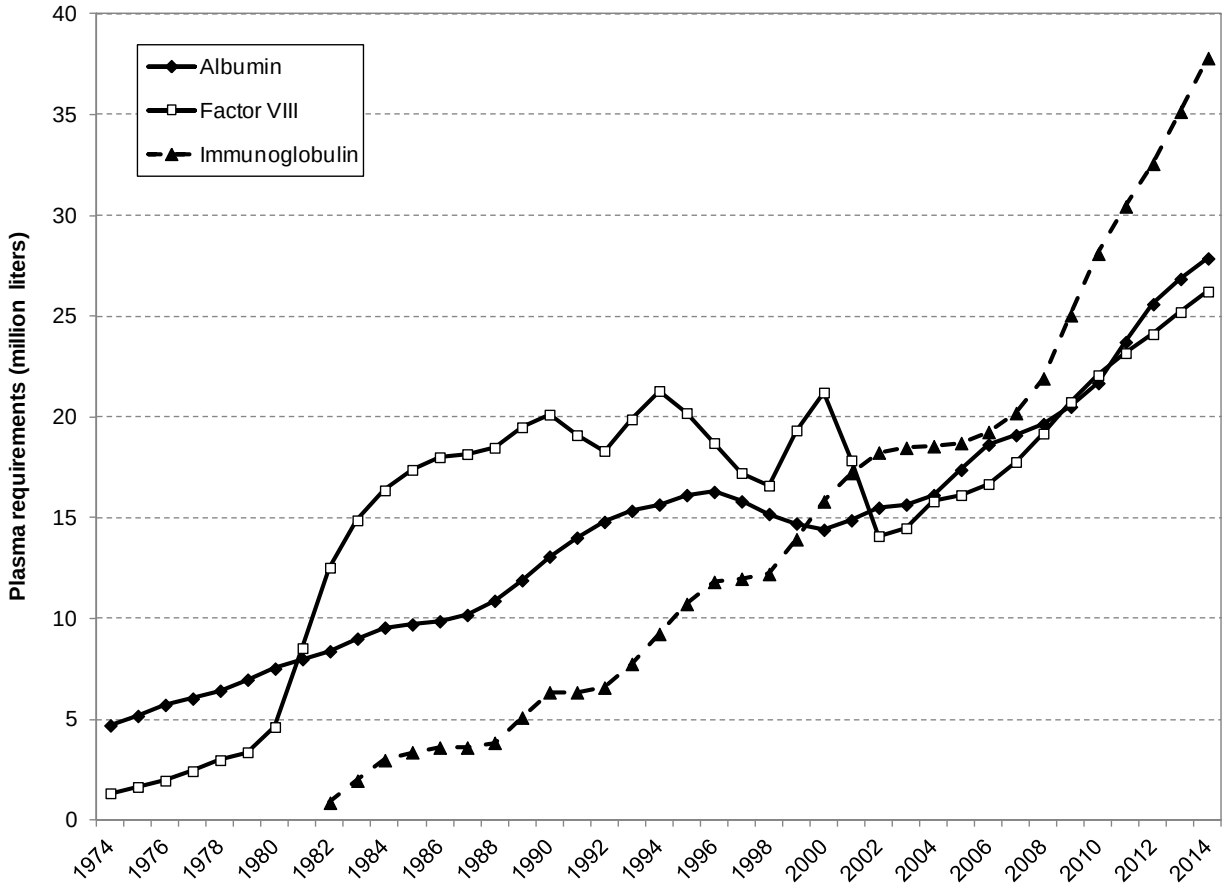


Source: (MRB, 2017).

The composition and level of demand for PPTs has changed over time. Accordingly, as new PPTs have been developed and new indications have been identified, the demand for plasma has grown. Changes in the market for plasma-derived products is illustrated in Figure 12**.** Albumin drove early plasma utilization as a replacement for blood and proteins lost through burns and trauma. Plasma-derived factor VIII, which is a clotting factor replacement therapy for the treatment of hemophilia A, became the dominant product in the 1980s and 1990s. More recently, as recombinant factor VIII became available and as numerous treatments involving immunoglobulin have been found, immunoglobulin has become the predominant driver of the demand for plasma. Furthermore, the introduction of immunoglobulin therapy in areas such as neurology, oncology, rheumatology, and dermatology suggests that the utilization of immunoglobulin will continue to grow (Robert, 2009, 359-360).

[96] This chart does not include recombinant factor products.

Figure 12 Worldwide plasma utilization: Albumin, factor VIII, and immunoglobulin (1975–2014)



Source: (MRB, 2014). Grabowski and Manning (2016)

VI.B. Glossary

- **Caprylic acid treatment:** A process of viral inactivation that has been shown to robustly inactivate or remove infectivity of lipid-enveloped viruses.[97]
- **Dry Heat:** A method of viral inactivation that involves the heating of protein following lyophilization, typically at 80° C or higher.[98]
- **Lot release:** A form of testing that relies on previously established specifications to demonstrate product identity, purity, and potency. It is conducted at all stages of drug development.[99]
- **Low-pH incubation:** A process of viral inactivation used to inactivate large enveloped viruses.[100]
- **Lyophilization:** Also known as freeze-drying, lyophilization is a process used to preserve biological material by freezing and drying the sample under a vacuum at very low temperatures, resulting in the removal of water from the sample.[101]
- **Nanofiltration:** A process that removes viruses according to their size while permitting flow-through of the desired protein.[102]
- **Pasteurization:** A process through which pooled human plasma is subjected to a viral inactivation treatment by heating in the liquid state for 10 hours at 60° C.[103]
- **Solvent detergent:** A process that inactivates enveloped viruses in pooled plasma and virtually eliminates the risk of transmission of enveloped viruses.[104]
- **Sterility testing:** A test that detects the presence of viable contaminating microorganisms.[105]

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97 Magdy El-Ekiaby, Mariángela Vargas, Makram Sayed, George Gorgy, Hadi Goubran, Mirjana Radosevic, and Thierry Burnouf, "Minipool Caprylic Acid Fractionation of Plasma Using Disposable Equipment: A Practical Method to Enhance Immunoglobulin Supply in Developing Countries," *PLoS Negl Trop Dis* 9, no. 2 (2015), [PAGE NO?], https://doi.org/10.1371/journal.pntd.0003501.

98 World Health Organization, WHO Technical Report (Geneva: World Health Organization, 2004), http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf.

99 BioReliance, "Comparability and Lot Release Testing," accessed Dec. 19, 2017, https://www.bioreliance.com/eg/services/biopharmaceutical-services/final-product-release-testing/comparability--lot-release-testing.

100 Joe Makowiecki and Heather Mallory, "Adjusting pH During Viral Inactivation," *Genetic Engineering and Biotechnology News* 33, no. 8 (2013), https://www.genengnews.com/gen-articles/adjusting-ph-during-viral-inactivation/4838.

101 Theresa Phillips, "How Lyophilization Preserves Biological Material," *The Balance*, June 26, 2017, https://www.thebalance.com/lyophilization-preserving-biological-material-375590.

102 World Health Organization, WHO Technical Report (Geneva: World Health Organization, 2004), http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf.

103 Mirjana Burnouf-Radosevich, Thierry Bumouf, and J.J. Huart, "A Pasteurized Therapeutic Plasma," *Infusionstherapie* 19, no. 2 (1992): 91-94.

104 Marco Marietta, Massimo Franchini, Lucia Bindi, Francesco Picardi, Matteo Ruggeri, and Giustina De Silvestro, "Is solvent/detergent plasma better than standard fresh-frozen plasma? A systematic review and an expert consensus document," *Blood Transfusion* 14, no. 4 (2016): 277-286.

105 See 21 CFR 610.

VI.C. PPTA voluntary standards program

VI.C.1. Mark of quality

The industry's commitment to continual improvement and enhancement through the PPTA voluntary standards program is recognized by regulators, patients, and the public at large. Conformance to standards is the benchmark for quality. PPTA's IQPP and QSEAL certifications provide confidence in an established process that includes openness, public notification, coordination, consideration of views, agreement, and appeals.

VI.C.2. Source plasma collection standards: IQPP

To further improve the quality and safety of source plasma, in 1991, PPTA implemented the International Quality Plasma Program (IQPP). IQPP provides independent, third-party evaluation and recognition of a collection center's adherence to global industry standards for source plasma.

More than 600 licensed plasma collection centers in North America and approximately 50 in Europe are members of the program. IQPP-certified manufacturing facilities adhere to the following standards:

- **Community-based donor standard:** Donors must provide proof that they reside within the center's defined donor recruitment area.
- **Cross donation management standard (certain requirements U.S. only):** Centers check to make sure individuals only donate plasma within pre-defined time frames to protect donor health.
- **Donor adverse events recording standard:** Centers must classify and record occurrences in accordance with defined parameters.
- **Donor education standard:** Centers offer educational programs that promote healthy donor lifestyles.
- **Donor fluid administration standard:** Centers must administer fluids to donors as part of the donation process.
- **National Donor Deferral Registry Standard (U.S. only):** Donors who test reactive for the human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C (HCV) will be entered into a national database and prohibited from donating.
- **Personnel education and training standard:** Center staff must undergo initial and ongoing training on safety, regulatory requirements, and procedures.
- **Professional plasma collection facility standard:** Requires centers to maintain a high level of professionalism and quality with regard to cleanliness, safety, and appearance.
- **Qualified donor standard:** Potential donors must pass two separate medical screenings within a six-month period, including testing for HIV, HBV, and HCV.
- **Quality assurance standard:** Defines requirements for the center's quality assurance program.

- **Viral marker standard:** Focuses on the importance of collecting source plasma from a low-risk population.

VI.C.3. Manufacturing standards for plasma protein therapies: QSEAL

The PPTA's Quality Standards of Excellence, Assurance, and Leadership (QSEAL) program was established in 2000 to address the manufacture and fractionation of plasma protein therapies, regardless of the source of plasma. QSEAL certification provides third-party evaluation and recognition of a company's adherence to global industry standards that address product safety during the manufacture of lifesaving plasma protein therapies. QSEAL-certified manufacturing facilities adhere to the following standards:

- **Controls on incoming plasma standard:** Delineates the QSEAL responsibilities of the manufacturer with respect to the quality and safety of incoming plasma used for manufacturing plasma protein therapies. Places controls on a manufacturer's incoming plasma, regardless of its source.
- **Intermediates purchased from an external supplier standard:** Mandates a contract chain between the supplier and purchaser of intermediates, for traceability from each donation to the final product.
- **Inventory hold standard:** Collected plasma is held in inventory for at least 60 days after donation to allow for retrieval and destruction of plasma based on post-donation disqualifiers such as high-risk behavior or testing reactive for HIV, HBV, or HCV.
- **Nucleic acid amplification technology (NAT) testing standard:** Requires NAT testing for HIV, HBV, and HCV at the donation (minipool) level and again at the first homogeneous plasma pool level. Also requires in-process testing for hepatitis A (HAV) and parvovirus B19.
- **Recovered plasma specification:** Specifies acceptance criteria for manufacturing facilities that use recovered plasma, including infrequent source plasma collected by blood establishments. The goal is to assure the residual risk of the manufacturing pool is comparable to that for source plasma.
- **IQPP:** QSEAL-certified manufacturing facilities must only accept plasma from collection centers that comply with requirements of the PPTA's IQPP Standards Program