Access to Care: Differentiating the Plasma Protein Industry

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It's widely understood that human physiology is complex, intricate, and evolving over time. Delicately balanced proteins mediate system responses, with feedback mechanisms that adjust other complicated systems, working 24 hours a day, 365 days a year.

Factory-like processes grow bone, produce blood and proteins, and replicate many different cells needed for survival—all within a self-regulating biological sphere that lasts for many decades. Medical innovations in medicine have allowed us to find a way to reach into these complex biological systems and provide patients with proteins which their own bodies may be missing. The very nature of this biological material means the resulting plasma protein therapies are difficult to produce and different from other small molecule drugs.

The starting point for plasma protein therapies is the human body itself. Complex, large proteins that are necessary for proper blood clotting and the prevention of infections by antibodies are contained in plasma—the liquid portion of blood. Plasma cannot be made in a laboratory nor can it be made by combining chemicals; plasma-derived therapies can only be made from individuals who donate their plasma. More than 600 U.S. plasma collection centers—each with 50-100 employees—collect, process, freeze, and ship plasma donations to PPTA member manufacturing centers. In order to treat some rare diseases for one year, it can take more than 1,000 plasma donations.

The collection process is highly regulated by the United States Food and Drug Administration (FDA) and plasma therapies are the only pharmaceutical for which the starting material must be licensed. The FDA then, in a second and separate regulatory process, approves the final product. Traditional pharmaceuticals only have approval of the finished product. More than 35 million plasma donations each year must be qualified, in addition to the finished product.

The limitation of a finite source of biological starting material affects every step of the collection and manufacturing process. Preparing a therapy often takes between seven to twelve months from donation to final product release. The complex manufacturing process sets plasma protein therapies apart from chemical pharmaceuticals and other biologics whose processes are

"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."

"It is unacceptable to limit availability of augmentation therapy in any way and especially to a single product."

much more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall cost: 14 percent for pharmaceuticals versus 57 percent for plasma proteins.

Integral to the story of why plasma proteins are so different are the patients they treat. Each disease group for which plasma protein therapies are indicated is considered rare, by definition having fewer than 200,000 patients afflicted. The total number of patients treated with plasma protein therapies in the U.S., across all disease groups, is slightly below 100,000. Disease groups such as hereditary angioedema patients only have about 5,000 patients on treatment. Larger, yet still rare, disease groups—such as bleeding disorders or primary immunodeficiency diseases—have between 30,000-40,000 patients taking plasma protein therapies.

While clinically different and small in number, what these patients all have in common is that they need these missing proteins to survive and thrive. In addition, these patients' diseases are genetic and chronic requiring lifelong treatment. In 1971, the 10-year survival rate for patients with common variable immune deficiency was only 37 percent, but by 2008—with the use of plasma proteins—it had increased to 90 percent. Hemophilia patients in the beginning of the 20th century only lived till 13 years of age, but in 2017 have a normal life expectancy of 77 years. Unlike some other disease treatments that have short duration improvements or modest increases in survival, patients treated with plasma proteins can live healthy lives, contribute to society, and ease the burden of their protein deficiency on their families and the health system. According to a recent study by the Jeffrey Modell Foundation, the economic impact of diagnosing and treating a primary immunodeficiency disease and treating with immunoglobulin therapy represents an average savings of more than $55,000 per year.

The uniqueness of plasma proteins is directly connected to the complexity of their processing during the manufacturing process. Manufacturing differences in fractionation, stabilization, purification, and inactivation processes are unique to each brand and can result in clinically distinct products. Plasma protein therapies can differ in terms of formulation, purity, half-life, immunogenicity, osmality, pH, and sodium or sugar content. Due to these differences, patients experience varied efficacy, tolerability, and clinical outcomes between products. Patients who are stabilized and doing well clinically often are unwilling to risk switching product; nor do expert clinical guidelines support doing so. The American Academy of Allergy, Asthma and Immunology states, "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 patient safety."

Lastly, plasma proteins are different from many of their small molecule cousins because of the heightened need and constant vigilance from evolving threats to the availability of plasma. As a biological material with a finite human supply, any degradation in the collection process from natural disasters to transportation interruptions can affect production. Strict adherence to all collection and manufacturing standards—both those from the FDA (collection and manufacturing) and stringent PPTA industry standards, such as the International Quality Plasma Program and the Quality Standards of Excellence, Assurance and Leadership program ensure plasma protein safety. Plasma protein therapies' safety protocols are constantly evolving due to new and emerging pathogens, the most recent being the Zika virus.

Today's highly regulated, complex, lengthy, and capital-intensive collection and manufacturing processes for plasma proteins produce lifesaving therapies. From the screening of donors at collection centers through the long journey of frozen plasma to manufacturing sites, each step is precise, regulated, and necessary. Rare disease patients rely on PPTA members to make these safe treatments from plasma proteins that are worlds apart from the larger pharmaceutical pill industry. •