PLASMA PROTEIN THERAPEUTICS ASSOCIATION

February 23, 2026

The Honorable Mehmet Oz, MD
Administrator, Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Attention: CMS-5545-P, Mail Stop C4-26-05

Dear Administrator Oz,

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to offer comments on the proposed Global Benchmark for Efficient Drug Pricing (GLOBE) model.[1] PPTA is the standard setting and global advocacy organization that represents plasma donation centers and manufacturers of plasma-derived therapies (PDTs). Our U.S. manufacturer members include ADMA Biologics, Grifols, Kedrion, and Takeda.

PPTA commends the Administration for its commitment to ensuring Americans can access the prescription drugs they need. While we share that commitment, we are gravely concerned that, as proposed, the GLOBE model's pricing methodology would have a disproportionately negative effect on PDTs and could impede access to these therapies.

As we will explain below, the unique nature of PDTs, their source material, and manufacturing process make them highly sensitive to payment changes like those proposed in the GLOBE model. We appreciate CMS's acknowledgement that PDTs are different from other proposed GLOBE model drugs, as well as the agency's willingness to consider arguments in favor of excluding PDTs from GLOBE model. **To assure the availability of these lifesaving therapies for Medicare beneficiaries, we urge the CMS to exempt all plasma derived therapies from inclusion in the model.**

I. BACKGROUND

Plasma -- the clear, liquid portion of blood that remains after the red blood cells, leukocytes, and platelets are removed -- is rich with proteins that serve several important functions in the human body. Key proteins found in plasma include immunoglobulins, clotting factors, fibrinogen, and albumin, among others.

[1] 90 Fed. Reg. 60244 (Dec. 23, 2025).

Plasma derived therapies (PDTs) are unique biologic medicines made from these proteins and are used to replace a person's missing, damaged, or dysregulated proteins. [2] PDTs are used to treat primary immunodeficiencies; neurological diseases like chronic inflammatory demyelinating polyneuropathy; Alpha-1 antitrypsin deficiency, a hereditary form of chronic obstructive pulmonary disease; bleeding disorders, such as hemophilia and Von Willebrand Disease; and rare infections like tetanus and rabies. They are also critical therapies in the treatment of many emergency situations such as trauma, shock, and burns.

Approximately 1.25 million Americans receive PDTs annually, but most PDTs are used to treat rare, chronic conditions, where fewer than 50,000 are Americans affected. [3] For several of these diagnoses, PDTs are the only treatment options available to manage symptoms, reduce disease burden, and improve quality of life.

Finite Source Material

PDTs are unique from other pharmaceutical products due to their finite source material, complex manufacturing, and the nature of patient demand. Plasma cannot be sourced from plants or animals, nor can it be manufactured synthetically. Manufacturers of plasma-derived therapies instead depend upon donated plasma from healthy individuals as the raw material for therapeutic production.

In 2025, more than 75 million plasma donations took place at approximately 1,250 centers across the US. [4] The process for collecting donated plasma is highly regulated by the US Food and Drug Administration (FDA), as well as state and local authorities. Plasma donors are screened to ensure they are free from infectious disease, meet eligibility requirements, and are otherwise healthy enough to donate. Plasma is collected through the plasmapheresis process, where blood is separated into its component parts, plasma is collected, and red blood cells and platelets are returned to the donor. The collected plasma is tested for pathogens, frozen, and stored for a federally-mandated inventory hold before being transported for manufacturing.

[2] *See* Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, *in* 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209 (2005, 2006).
[3] https://marketingresearchbureau.com/the-plasma-industry/#MarketDrivers
[4] https://peterjaworski.substack.com/p/americas-plasma-contribution-to-the-1d5

Complex Manufacturing Process

Once plasma is collected, it moves into a unique and complex manufacturing process called fractionation, where plasma donations are pooled, purified, and individual proteins are isolated for therapeutic use. Fractionation methods include cryo-precipitation, ethanol precipitation, chromatography, ultrafiltration, and other sophisticated processes that are performed under highly hygienic conditions in licensed facilities that are operated in compliance with good manufacturing practices and following quality assurance principles.[5] These different processes can take 7 – 12 months to complete, compared to two to three months for manufacturing traditional pharmaceuticals.[6]

The costs associated with the donation and manufacturing processes are significant. Donor compensation – which ensures an adequate supply of source plasma – accounts for approximately one-third of the overall cost of a liter of plasma. Plasma centers also employ 40 – 50 individuals each and must manage real estate costs, storage expenses, refrigerants, transportation costs and other administrative expenses. Further, a significant amount of raw material is needed to yield a year's supply of therapy. According to industry estimates, it takes more than 1,200 plasma donations to manufacture an annual supply of clotting factor, 900 donations to manufacture treatment for Alpha-1 Antitrypsin Deficiency, and 130 donations to treat immunodeficiency disease.

These costly raw materials, lengthy manufacturing processes, and small patient populations create unique economic challenges for manufacturers of PDTs. Where raw materials and manufacturing account for only 14 percent of the overall costs of traditional pharmaceuticals**,** *they account for 68 percent of costs* for PDTs**.** As a result, PDTs are much more sensitive to resource constraints and are less able to absorb fluctuations in pricing.

Access Challenges

The unique nature of PDTs makes these products particularly susceptible to shortages. The United States has experienced national shortages of immunoglobulin (IgG) several times in recent years. In the early 2000s, shortages occurred when the FDA recommended product withdrawals because of safety concerns. While it was later determined that the safety concerns were overstated, the episode illustrates the highly regulated nature of PDTs, the

[5] Burnouf T. Modern plasma fractionation. Transfus Med Rev. 2007 Apr;21(2):101-17. doi: 10.1016/j.tmrv.2006.11.001. PMID: 17397761; PMCID: PMC7125842.

[6] Farrugia A., Scaramuccia D. (2017). The dynamics of contract plasma fractionation. Biologicals 46, 159–167. 10.1016/j.biologicals.2017.02.007 [DOI] [PubMed] [Google Scholar]

need for constant vigilance to ensure product safety, and the fragile nature of the plasma supply chain.

More recently, the US experienced a critical IgG shortage when demand exceeded manufacturing plans and available inventory. A 2020 report from the American Society of Hospital Pharmacists found that 85 percent of manufacturers could not meet demand, affecting 90 percent of market share.[7] While the IgG supply in the United States has stabilized, regional and product-specific shortages persist, with the FDA currently reporting shortages for both for immunoglobulins and albumin products.

Access challenges are even more significant in the EU, where more than three-quarters of EU countries reported a market disruption in the availability of immunoglobulin in 2022. [8] While reasons for shortages are multifactorial and varied, one analysis cited inadequate tenders (i.e., insufficient payment) as an underlying cause of IgG shortages in more than half the countries studied.[9] Moreover, these shortages are persistent - the European Medicines Agency acknowledges a current shortage of immunoglobulins that is likely to last until June 2026.[10]

These shortages are not just an economic issue - they have significant health implications for patients. A 2025 examination of neurological patients found that Ig shortages resulted in patients delaying treatment, decreasing their dosages, or switching to non-PDT products (e.g., plasma exchange or corticosteroids). The results were stark, with 52% of patients experiencing a deterioration of their disability score (e.g., their ability to ambulate, perform self-care, and manage other activities of daily living), and 28% who had **a moderate or a clinically significant** deterioration. [11]

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[7] Edington HJ, Sutton KS, Bennett C, Chandrakasan S, Sterner-Allison J, Castellino SM. Dealing with a critical national shortage-Approaches to triaging immune globulin supply in pediatric hematology and oncology. Pediatr Blood Cancer. 2020 Jul;67(7):e28260. doi: 10.1002/pbc.28260. Epub 2020 Apr 24. PMID: 32329568; PMCID: PMC7477917.

[8] https://ehaweb.org/news-updates/immunoglobulin-shortages-in-the-spotlight-ema-supply-and-the-soho-regulation#:~:text=Mar%2020%202023%20Tagged%20advocacy,use%20in%20times%20of%20crisis.

[9] Belmonte M, Albiero A, Callewaert F, Patris J, Whittal A. Understanding supply sustainability of plasma-derived medicinal products: Drivers and consequences of shortages. Vox Sang. 2025 Aug;120(8):754-764. doi: 10.1111/vox.70052. Epub 2025 May 26. PMID: 40419326; PMCID: PMC12390372.

[10] https://www.ema.europa.eu/en/medicines/human/shortages/human-normal-immunoglobulins#information

[11] E. N'kaoua, S. Attarian, E. Delmont, E. Campana-Salort, A. Verschueren, A.-M. Grapperon, E. Mestivier, M. Roche, *Immunoglobulin shortage: Practice modifications and clinical outcomes in a reference centre,*

Non-Interchangeability

PDTs are non-interchangeable, single source biologics and patients may suffer adverse health outcomes due to non-medical switching between products. Small differences in manufacturing can result in variations in tolerability among patients. Products have different characteristics and formulations (e.g., variable levels and mix of proteins, pH range, osmolality, sugars, salts, solvents/detergents, etc.) and as a result, may be contraindicated for vulnerable subsets of patients.

Expert guidance from leading professional and patient societies – including the American Academy of Neurology, the American Academy of Allergy, Asthma, and Immunology, the National Bleeding Disorders Foundation and others -- all recommend that patients and clinicians have access to all brands so that they can select the most medically appropriate therapy.

II. CMS Should Exclude Plasma-Derived Therapies From the GLOBE Model

As explained above, patients taking plasma derived therapies typically do so because they have a life endangering condition and depend upon these medications. Economically, PDTs are unlike most drug products that would fall within the GLOBE model in light of the significantly higher manufacturing costs, susceptibility to shortages, and lack of interchangeability. Collectively, these factors warrant PDTs being excluded from the GLOBE model, which the proposed rule indicates has been considered by CMS. Acting on that consideration also would be consistent with congressional and CMS recognition in a number of different contexts of the need to treat these therapies differently. Further, as discussed, we do not believe that the proposed adjustment for shortages in the proposed rule would be sufficient to maintain patient access to PDTs.

A. Excluding PDTs Is Consistent with Congress and CMS's Treatment of PDTs

Congress and CMS have a history of recognizing the unique nature of PDTs and designing policies to safeguard beneficiary access to these therapies. Most recently, Congress exempted any "biological product that is derived from human whole blood or plasma" from the Inflation Reduction Act's Medicare Drug Price Negotiation Program.[12]

Revue Neurologique, Volume 178, Issue 6, 2022, Pages 616-623, ISSN 0035-3787, https://doi.org/10.1016/j.neurol.2021.10.004.

[12] Social Security Act (SSA) § 1192(e)(3)(C))

Over a decade ago, Congress also chose to treat certain PDTs differently under the Medicaid Drug Rebate Program, which requires manufacturers to pay rebates on drugs for which payment is made under the Medicaid program, with the level of rebate set by statute.[13] When Congress modified the statutory rebate amounts, it chose to set a rebate percentage for blood clotting factors of 17.1%, instead off the standard rebate percentage for single-source drugs of 23.1%.[14]

CMS has similarly made accommodations – where permissible by statute – to treat PDTs differently than other drug and biological products. In developing policies for Medicare payment to hospital outpatient departments and physician office, CMS has ensured that payments reflected the unique nature of these products and were sufficient to safeguard access for beneficiaries.[15]

CMS also acknowledged the difference in the PDT market in its 2020 most-favored-nation Interim Final Rule. CMS excluded plasma-derived IVIG products from that proposed model. It did so, because: "these products are at higher risk of shortage based on their complex sourcing and production."[16]

Excluding PDTs from the GLOBE Model is consistent with CMS's longstanding policy regarding these unique products. There is no reason for CMS to depart from this position; manufacturers of these products will continue to face the same challenges in sourcing and producing these products, and appropriate, stable payment remains key to safeguarding beneficiary access.

B. **The Adjustment to the GLOBE Rebate Amount for Drug Shortages Is Insufficient to Safeguard Access to PDTs**

As CMS acknowledges, PDTs are *more likely* to experience shortages than other drugs or biological products.[17] Given the inherent challenges to the manufacturing these therapies, this risk will continue. As proposed, the GLOBE Model would adjust the rebate amount for products facing shortages, building upon such an adjustment under the Part B Inflation Rebate Program. While this adjustment may be sufficient to account for less common

[13] *Id.* §1927(c)
[14] *Id.*
[15] *See* 70 Fed. Reg. 68516, 68648 (Nov. 10, 2005). Similar statement in the PFS 2006 rule 70 Fed. Reg. 70116, 70219 (Nov. 21, 2005).

[16] 85 Fed. Reg. 76180,76191 (Nov. 27, 2020).
[17] 90 Fed. Reg. at 60246 and 60259; 85 Fed. Reg. at 76191.

shortages of other products, imposing any additional rebate beyond that established by Congress in the Part B Inflation Rebate Program poses a greater risk for PDTs and could result in access challenges.

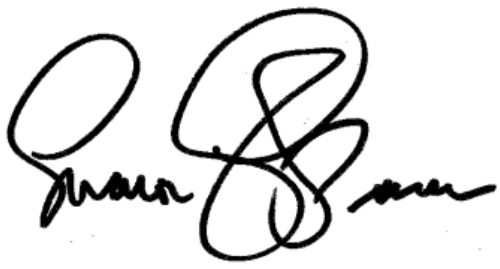
Even if these access challenges could be addressed, this proposal also presents operational and evaluation challenges as applied to PDTs. Over the course of the five-year GLOBE model, shortages of PDTs are more likely to lead to varying incremental GLOBE rebates over time as compared to other Part B drugs and biological products. Such variations will complicate CMS's proposed evaluation of comparing the products' payments under Medicare part B to an international benchmark, undermining the usefulness of these comparisons.

III. Conclusion

For these reasons, PPTA urges CMS to exempt PDTs from the GLOBE Model. This policy is also consistent with the CMMI statute, which requires that Models to be tested "preserv[e] or enhance[e] the quality of care furnished to individuals [with Medicare]."[18] Excluding PDTs from the GLOBE Model is fully consistent with this statutory requirement.

We are grateful for the opportunity to comment on this important initiative and appreciate your consideration of our recommendations. If you have questions or require further information about PDTs, please contact me at (703) 593-7143 or spearce@pptaglobal.org.

Sincerely,



Sharon Pearce
Vice President, Government Affairs

[18] Social Security Act (SSA) §1115A(a)