

December 20, 2018

Seema Verma
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Room 445G
200 Independence Avenue, SW
Washington, DC 20201

ELECTRONIC DELIVERY

Re: CMS-5528-ANPRM (International Pricing Index Model for Medicare Part B Drugs)

Dear Administrator Verma,

The Plasma Protein Therapeutics Association (PPTA) is pleased to comment on the Advance Notice of Proposed Rulemaking regarding the International Pricing Index Model (Model) for Medicare Part B Drugs.¹ PPTA is the standard setting and global advocacy organization that represents plasma donation centers and manufacturers of plasma protein therapies. Our membership includes Bio Products Laboratory, Biotest, CSL Behring, Grifols, Kedrion SpA, and Shire.

The Model asks stakeholders for specific feedback, including which drugs should be included, how to avoid unintended consequences on the interaction of the IPI model with other federal programs, how using international reference pricing could affect innovation incentives in the biopharmaceutical market, and the best way to include new drugs and biologicals. PPTA and its members are committed to ensuring that beneficiaries of Medicare and other patients continue to have appropriate access to life-saving plasma protein therapies. Given the unique nature of this sector and its susceptibility to supply constraints, **our primary recommendation is that the Centers for Medicare & Medicaid Services (CMS) should exclude plasma protein therapies from the IPI Model.** Subjecting these therapies to the demonstration would:

- 1. Impede access to life-saving plasma protein therapies for Medicare and Medicaid beneficiaries***
- 2. Raise concerns regarding quality of care and access***
- 3. Jeopardize investment in research and development of products to address unmet clinical need***

¹ 83 FR 54546 (October 30, 2018)

BACKGROUND

Plasma protein therapies are unique, non-interchangeable biologics

Plasma protein therapies are made from human plasma² donated by healthy volunteers, or by using recombinant technology.³ These therapies treat a variety of rare, chronic, and debilitating diseases, some with a U.S. prevalence of fewer than 100 patients. Plasma protein therapies include immune globulins to treat individuals with primary immunodeficiency diseases and chronic inflammatory demyelinating polyneuropathy; C1 esterase inhibitor to treat hereditary angioedema; Alpha-1 proteinase inhibitors to treat Alpha-1 antitrypsin deficiency, and blood clotting factors to treat individuals with bleeding disorders, such as hemophilia.⁴

It is essential that plasma protein therapies have adequate reimbursement due to their unique nature. Plasma protein therapies are non-interchangeable biologicals⁵ and patients may suffer adverse health outcomes due to non-medical switching between products. For this unique class, small differences in manufacturing can result in variations in tolerability among patients. Manufacturers of plasma-derived therapies depend upon Source plasma⁶ from healthy, committed volunteers as the raw material for therapeutic production. The process to produce plasma protein therapies is highly regulated, resource-intensive, and time-consuming. Individual proteins within plasma are isolated for therapeutic use through distinct fractionation processes. The production process for these therapies can take up to 12 months. Plasma protein therapies are sole source biologicals that are critical to improving the health of rare disease patients around the world.

DISCUSSION

Plasma protein therapies should be excluded from the Model

PPTA urges CMS to exclude plasma protein therapies⁷ from the Model. We believe that the Model will have an extremely negative impact on patient access to lifesaving therapies, for beneficiaries inside and outside of the participating geographic areas. The model relies on international pricing data without considering important factors, such as patient and provider access to essential therapies and quality of care in reference countries. The Model could have a

² Plasma is the clear liquid portion of blood that remains after the red cells, leukocytes, and platelets are removed.

³ Recombinant therapies are only available for clotting factors and C1 esterase inhibitors; plasma-derived therapies are the only lifesaving treatment for most plasma protein deficiencies.

⁴ Plasma protein therapies also treat acute conditions such as rabies, tetanus, and when pregnant women's blood types are incompatible with their babies' (rhesus incompatible pregnancies).

⁵ To be interchangeable, a biologic product must be "expected to produce the same clinical result as the reference product in any given patient" and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alteration or switch." Sections 351(k)(4)(A) and 351(k)(4)(B) of the Public Health Services Act.

⁶ Source plasma is defined in 21 CFR 640.60 as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use, and may only be collected from FDA licensed collection centers. Source plasma is different than recovered plasma, defined in 21 CFR 606.122 as plasma derived from single units of whole blood as a by-product in the preparation of blood components from whole blood collection and intended for further manufacturing.

⁷ Plasma protein therapies include: albumin; Alpha-1 proteinase inhibitors; C1 esterase inhibitors; fibrins/fibrinogens; immune globulins/hyperimmune globulins; and coagulation products, including antihemophilic/coagulation/von Willebrand factors, anti-inhibitor coagulants, antithrombin/prothrombin/thrombin concentrates, and Protein C concentrates. All plasma protein therapies should be excluded regardless of type (plasma-derived or recombinant) or mode of administration (intravenous, intramuscular, or subcutaneous).

detrimental impact on innovation by adversely affecting investments in research and development. Further, we believe it will lower quality of care by diminishing beneficiary access to all therapies of non-interchangeable brands. Accordingly, CMS should exempt plasma protein therapies from the Model.

I. The Model introduces quality of care concerns and ignores the unique market dynamics of plasma protein therapies

PPTA is very concerned that referencing international price controls to determine Medicare payment levels for Part B drugs will adversely affect patient care. The ANPRM states that Medicare pays more for drugs than other countries.⁸ However, CMS fails to address how lower prices are achieved, omitting important questions such as whether they are achieved by restricting access to specific brands to secure lower prices.

Each of the 14 proposed countries uses competitive bidding or tenders to procure lower prices⁹. With tenders and competitive bidding, sometimes only one or a few therapies are available to treat individuals in each disease state. While these types of access restrictions to secure lower prices is suitable for generics and interchangeable biologics, they are not appropriate for sole source biologics, such as plasma protein therapies. These restrictions ignore expert clinical recommendations that require access to all available brands to ensure quality of care and positive health outcomes.¹⁰

These restrictive policies are extremely detrimental for non-interchangeable, sole source plasma protein therapies. In the non-interchangeable market, restrictive policies can also lead to the unavailability of products altogether.¹¹ In 12 of the 14 proposed countries, products or entire classes of plasma protein therapies are unavailable.¹² For example, in the United Kingdom, reduced reimbursement and lack of non-interchangeability recognition has created patient access issues for immune globulins. Only a little more than half of individuals with primary

⁸ 83 Fed. Reg. at 54547.

⁹ Countries that use tenders, competitive bidding, or other restrictive policies include: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Japan, Ireland, Italy, the Netherlands, and the United Kingdom.

¹⁰ Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis (Miami)*. 2016; 3(3): 668-682.; Goldstein, S., MD, FAAAAI, & Orange, J., MD, PhD, FAAAAI. (2011, December). Eight guiding principles for safe, effective and appropriate use of IVIG (Publication). Retrieved from American Academy of Allergy Asthma & Immunology website: <http://www.aaaai.org/practice-resources/practice-tools/ivig-toolkit>; Patwa, H. S., Chaudhry, V., Katzberg, H., Rae-Grant, A. D., & So, Y. T. (2012). 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(13), 1009-1015.; Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice* 2013; 1:458-67.; Medical and Scientific Advisory Council. (2005, March 12). MASAC Recommendation Regarding Factor Concentrate Prescriptions and Formulary Development and Restrictions (Publication No. 159). Retrieved from National Hemophilia Foundation website: <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>.; (PPT Clinical Guidelines)

¹¹ Dranitsaris, G., Jacobs, I., Kirchhoff, C., Popovian, R., & Shane, L. G. (2017). Drug tendering: Drug supply and shortage implications for the uptake of biosimilars. *ClinicoEconomics and Outcomes Research, Volume 9*, 573-584. doi:10.2147/ceor.s140063

¹² Countries that restrict access to entire classes of plasma protein therapies include: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, the Netherlands, and the United Kingdom.

immunodeficiencies receive the needed treatment, and many patients have experienced delays in treatments and suboptimal care.¹³

The unique starting material of plasma protein therapies is a finite resource that exists in somewhat fixed supply in the short term¹⁴. Due to the inelastic supply of plasma, the market for plasma protein therapies is inherently susceptible to supply constraints¹⁵. The finite starting material (donated plasma) combined with the small populations treated limits manufacturers' ability to generate cost-savings in production due to economies of scale.¹⁶ To determine reimbursement rates based on foreign prices is not only flawed, but it could negatively affect supply of plasma protein therapies, as reflected in the following finding from a recent economic analysis of the plasma protein market in the United States:

“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.”¹⁷

These unique market forces combined with a non-interchangeable product distinguish plasma protein therapies from other drugs and justify their exclusion from the Model.

II. The Model would impede access to life-saving plasma protein therapies for beneficiaries in the intervention group

Individuals treated with plasma protein therapies require unfettered access to all approved products in a timely manner. Each plasma protein therapy is approved by the U.S. Food & Drug Administration (FDA) for distinct clinical indications. Each patient responds to a plasma protein therapy differently. Approximately one-third of patients receiving plasma protein therapies will experience intolerance to a particular product.¹⁸ However, patients can benefit from improved tolerability and health outcomes after switching to a different plasma protein therapy. The clinical treatment guidelines created by expert medical advisory panels support the FDA's determination that plasma protein therapies are not interchangeable.¹⁹

PPTA is extremely concerned about the impact that the Model would have on Medicare beneficiary access to essential plasma protein therapies. Notably missing from the list of what would be required from Model vendors²⁰ is a mandate to furnish all Medicare Part B covered

¹³ Primary Immunodeficiency UK & Walsh, S. (2018). *Proposal to create the central framework for a PID Patient Charity* [Data: UK PIN registry report 2012 - 2017].

¹⁴ Grabowski, H., & Manning, R. (2018). *Key economic and value considerations in the U.S. market for plasma protein therapies*. Washington, DC: Bates White at 23.

¹⁵ *Id.* at 9.

¹⁶ *Id.* at 13.

¹⁷ *Id.* at 24.

¹⁸ The Immune Deficiency Foundation (IDF), *Treatment Experiences and Preferences among Patients with Primary Immunodeficiency Diseases: National Survey of Patients* (2013), available at <https://www.primaryimmune.org/2013-idf-national-immunoglobulin-ig-treatment-survey>; The National Hemophilia Foundation, *Who is at Risk for Developing an inhibitor?* (July 15, 2015), available at <https://www.hemophilia.org/Bleeding-Disorders/Inhibitors-Other-Complications/Inhibitors-for-Consumers/Who-is-at-Risk-for-Developing-an-inhibitor>.

¹⁹ PPT Clinical Guidelines, *supra* n. 10.

²⁰ 83 Fed. Reg. at 54551.

drugs. Absent such a requirement, the Model will necessarily diminish patient access to critical therapies that treat rare, chronic conditions. Failure to make all plasma protein therapies available under the Model could force beneficiaries to switch brands, away from the product determined by the treating physician to be best for that beneficiary.

Likewise, the introduction of private sector vendors may create perverse incentives for physicians and hospitals. CMS encourages model participants to enroll with more than one vendor, however the management of multiple vendor contracts may be beyond the capabilities of some providers, especially those in smaller practices or in rural areas. These participants may select one or few vendors that do not provide access to all medically necessary plasma protein therapies.

Individuals who live with rare, chronic, genetic disorders need full, efficient and timely access to all brands of plasma protein therapies so that physicians with expertise in these rare conditions can select the most medically appropriate therapy. Limited access to medically necessary therapies is contrary to expert clinical guidelines, evidence-based medicine, and best practices.²¹

“It is unacceptable to limit availability of augmentation therapy in any way and especially to a single product.” – Alpha-1 Foundation Medical and Scientific Advisory Committee Clinical Practice Guidelines

“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.” – American Academy of Allergy Asthma & Immunology Principle #8

“Given the variable nature of these diseases, individualized treatments depending on patient need and physician judgment are important.” – American Academy of Neurology Therapeutics & Technology Assessment Subcommittee Evidence-based Guidelines

“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.” – U.S. Hereditary Angioedema Association Medical Advisory Board Recommendations

“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.” – National Hemophilia Foundation Medical and Scientific Advisory Council Recommendation #159

Delayed access to necessary therapies, and unavailability of products would have detrimental effects on beneficiaries. These are some of the reasons why the initial Competitive Acquisition Program excluded plasma protein therapies by statute and subsequent regulations. PPTA urges CMS to follow this precedent and exclude plasma protein therapies from the Model.

III. The Model would impede access to life-saving plasma protein therapies for beneficiaries in the comparison group, and Medicaid beneficiaries as well

PPTA is also concerned about the negative effects the Model would have on Medicare beneficiaries in the comparison group, as well as Medicaid beneficiaries. Because sales in the Model would be factored into ASP calculations, the Model would affect Medicare providers and beneficiaries outside of the demonstration. In addition, it would affect the 27 states that base

²¹ PPT Clinical Guidelines, *supra* n. 10.

Medicaid reimbursement for physician-administered drugs on ASP. Medicare & Medicaid providers and beneficiaries may experience the same access issues from previous reimbursement reductions to plasma protein therapies. An analysis of access issues by the U.S. Department of Health and Human Services Office of the Assistant Secretary for Planning & Evaluation (ASPE)²² found that previous reductions in Medicare reimbursement resulted in access challenges, treatment delays, and shifts in site of service for individuals who use plasma protein therapies. Other studies have yielded similar findings.²³ The actual access challenges patients faced in the past underscore the need for access to all therapies through appropriate reimbursement levels.

In recognition of previous access issues and the unique attributes of plasma protein therapies, CMS has historically made a number of modifications to its payment policies to protect access to plasma protein therapies. For example:

- CMS gave plasma protein therapies pass-through status in the initial, and subsequent, hospital outpatient prospective payment system rules
- In 2005, CMS adopted site neutral payments with respect to furnishing fees for blood clotting factor across the physician office and hospital settings.²⁴
- CMS created a temporary add-on payment for IVIG pre-administration services following concerns that there was inadequate access to IVIG products.²⁵
- CMS excluded all available plasma protein therapies at that time from the previous version of the CAP.²⁶
- In 2007, CMS established unique Healthcare Common Procedure Coding System (HCPCS) codes for IVIG products.

These past actions set a precedent of recognizing the non-interchangeability of sole source plasma protein therapies. Consistent with these policies, CMS should exclude all plasma protein therapies from the Model.

IV. The Model will negatively affect innovation

In addition to preserving patient access, appropriate reimbursement for Part B drugs fosters innovation by encouraging manufacturers to invest in research and development. An unfavorable reimbursement environment will discourage companies from investing in research and development and may discourage the investor community from making funds available for drug research. The Under Secretary for International Trade for the Department of Commerce

²² HHS, Office of the Assistant Secretary for Planning and Evaluation, Analysis of Supply, Distribution, Demand, and Access Issues Associated with Immune Globulin Intravenous (IGIV), pp. 4-31 (February 2007). (2007 ASPE Report).

²³ One study found that after a reduction in Medicare reimbursement rate for intravenous immune globulin (IVIG) at the start of 2005, the average number of IVIG claims among Medicare eligible individuals grew more slowly than in the non-Medicare eligible population, despite growing at the same rate in the previous three years. There was a significant reduction in the share of IVIG claims for Medicare beneficiaries originating in the physician office with no accompanying change in the non-Medicare population. Changes in the Medicare reimbursement of IVIG negatively impacted access to IVIG. Philipson T, Jena AB, *The Impact of Medicare Modernization Act Reimbursement Changes on the Utilization of Intravenous Immune Globulin*, The University of Chicago; The Irving B. Harris Graduate School of Public Policy Studies. A different study noted a significant shift in the site of service of IVIG utilization after implementation of reimbursement cuts as a result of the Medicare Modernization Act. The Moran Group, 2003-2010 IVIG [Intravenous Immune Globulin/SCIG [Subcutaneous Immune Globulin] Utilization by PID [Primary Immune Deficient] Patients by Site of Service (Dec. 21, 2012).

²⁴ 70 Fed. Reg. 68,516, 68,661 (Nov. 10, 2005).

²⁵ 70 Fed. Reg. at 68,649.

²⁶ 70 Fed. Reg. 39,002, 39028-29 (Jul. 6, 2005) (excluding blood clotting factors, IVIG, and alpha-1 proteinase inhibitors).

testified in Congress that foreign price controls led to a reduction in research and development spending in the range of 11% -16%, based on a study they conducted.²⁷ The de facto incorporation of price controls from foreign countries that would accompany the Model would thus adversely impact research and development across all Part B drugs. That negative impact would be particularly detrimental for plasma protein therapy research and development, which already faces research and development challenges. For example, while many other drug manufacturers benefit from broader protection of intellectual property, there is less exclusivity based on patents related to manufacturing technology, an important component of plasma protein production.²⁸ Thus, the potential negative impact on innovation accompanying the Model would be exacerbated with respect to plasma protein therapies. Therefore, CMS should not proceed further with the Model without exempting plasma protein therapies.

CONCLUSION

While we are grateful for this opportunity to offer comments on the ANPRM concerning the Model, we urge CMS to exclude plasma protein therapies as we do not believe this Model is in the best interests of Medicare beneficiaries. As proposed, we believe the Model will impede patient access to plasma protein therapies for Medicare beneficiaries struggling with life-compromising rare diseases.

Thank you for considering our comments, and please feel free to contact Thomas Lilburn, Senior Director of Government Relations at 443-458-4682 or tlilburn@pptaglobal.org if you have any questions.

Sincerely,

Thomas B. Lilburn

Senior Director of Government Relations

Attachment: *Key economic and value considerations in the US market for plasma protein therapies*

²⁷ Testimony of Grant D. Aldonas to the Senate Committee on Health, Education, Labor and Pensions (February 17, 2005), available at <https://www.help.senate.gov/imo/media/doc/Aldonas-SenHELP-Rx-2-17-05.pdf>.

²⁸ Grabowski & Manning, *supra* n. 14, at 29.