PLASMA PROTEIN THERAPEUTICS ASSOCIATION

May 5, 2025

Eric Longnecker
Deputy Assistant Secretary for Technology Security
Bureau of Industry and Security
U.S. Dept. of Commerce
1401 Constitution Avenue, NW
Washington, DC 20230

ELECTRONIC DELIVERY via www.regulations.gov BIS-2025-0022

Re: Notice of Request for Public Comments on Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients XRIN 0694-XC120

Dear Deputy Assistant Secretary Longnecker,

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to offer comments on the Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients. 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.

The plasma collection and PDT manufacturing industry is a uniquely American sector of the pharmaceutical industry. Unlike most pharmaceutical products, for which the starting materials are chemical active pharmaceutical ingredients (APIs), the starting material for PDTs is human plasma, collected from individual donors. Also unlike most pharmaceutical products, the starting material for PDTs used in the U.S. is sourced domestically and then manufactured into finished therapies. However, the ability for manufacturers to utilize specialized facilities and infrastructure in the U.S. and abroad is key to maintaining American patients' unparalleled access to the life-saving and life-sustaining medicines they need.

In light of this, we are writing on behalf of the PDT industry to request that the Section 232 investigation exclude PDTs, plasma and intermediate fractions from any resulting trade actions, as they do not represent a national security threat. In addition to using only U.S.-sourced starting material, this industry has a robust and consistent U.S. manufacturing base, and a complex supply chain uniquely vulnerable to disruption due to the dependence on donated human plasma.

PDTs are particularly susceptible to market fluctuations due to the unique nature of the starting material, a complex and lengthy manufacturing process, and the specialized, capital-intensive manufacturing infrastructure. PTDs are largely used to treat rare diseases and are frequently the only treatment option for those conditions. Because PDTs are not interchangeable within product categories, shortages among different formulations can have life-threatening consequences for patients. Any disruption or delay to this interconnected system puts patient access to these vital medicines at risk.

U.S. Source Plasma

Plasma-derived therapies are made from donated human plasma[1] and treat a variety of rare and often life-threatening conditions. PDTs include immune globulins to treat individuals with primary immunodeficiency diseases, neurological diseases, and rare infections like tetanus and rabies; Alpha-1 proteinase inhibitor to treat Alpha-1 antitrypsin deficiency; blood clotting factors to treat bleeding disorders, such as hemophilia and Von Willebrand Disease; and albumin, which treats liver disease and is used in the treatment of trauma, shock, and burns.

Manufacturers of PDTs depend upon plasma donated by healthy individuals as the raw material for the production of these therapies. Because plasma cannot be synthesized, it takes a significant number of donations to manufacture an annual supply of PDTs. For example, each year, it takes more than 130 plasma donations to treat one patient for primary immunodeficiency, 900 plasma donations to treat one patient with Alpha-1 Antitrypsin Deficiency, and 1,200 plasma donations to treat one patient with hemophilia.

Currently, all plasma used in PDTs to treat U.S. patients is sourced in the U.S. The process for collecting donated plasma is highly regulated, resource-intensive, and time-consuming. Notably, the uniquely pragmatic U.S. regulatory environment for plasma collection and stable business environment has allowed the industry to thrive. Last year, approximately 1,200 U.S. centers collected more than 50 million plasma donations which were manufactured into therapies for tens of thousands of Americans. On average, each center employs 50 – 100 people and provides $4-5 million in economic impact to local communities. Together with the manufacturing side of the industry, this industry supports tens of thousands of American jobs. As of 2023, around 67% of plasma for further manufacture collected worldwide was collected in the U.S.

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[1] Human plasma is the clear liquid portion of blood that remains after the red blood cells, leukocytes, and platelets are removed. Due to its human origin, complexity, and richness in therapeutically useful proteins, human plasma is a unique biological material. *See* Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, *in* 7 Pharmaceuticals Policy And Law, Blood, Plasma And Plasma Proteins: A Unique Contribution To Modern Healthcare 209 (2005, 2006).

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A Unique, Complex, and Lengthy Manufacturing Process

Once plasma is collected, it moves into unique and complex manufacturing operations called fractionation and purification. The plasma donations are pooled and individual proteins are isolated for therapeutic use through distinct fractionation processes. These processes, which differ from protein to protein, company to company, and even facility to facility, result in PDTs that are sole source biologics that produce different therapeutic outcomes depending on the patient.

Specialized Manufacturing Infrastructure

Because of the highly specialized and capital-intensive nature of production, wide variety of therapies, and small patient populations, it is often not feasible for companies to make every type of therapy in the U.S. Certain facilities are licensed and equipped for specific products, allowing companies to dedicate resources and expertise to the facility that specializes in manufacturing the best possible product for patients.

As a result, the collected plasma moves to the facility best suited to manufacture the required end-product. In some cases, this means plasma or plasma that has gone through initial fractionation steps in the United States will be sent to a foreign (generally European) facility, usually within the same company. Plasma exported from the U.S. returns to the country in the form of a finished therapy or for final manufacturing steps, for domestic use. Industry experts estimate that for therapies partially manufactured outside of the US, the value added abroad only accounts for 15-25% of the total value of the therapy.

Along these same lines, when the appropriate manufacturing facility for plasma collected abroad is located in the U.S., plasma is imported into the U.S. for manufacturing and the resulting PDTs are reexported to the originating country for use. Applying trade remedies to plasma in this scenario would disincentivize U.S. manufacturing.

The cross-border flow of plasma, partially-manufactured intermediates and returning PDTs may appear as increased imports in trade data, but in reality, represents the ability of companies to utilize a carefully constructed global supply chain to meet patient need.

U.S. Manufacturing Base

Our members have made significant investments in U.S. manufacturing facilities. These are complex, highly regulated and technologically advanced facilities that employ thousands of Americans in jobs that demand unique skills and expertise. Though the development of a new facility can cost more than $1 billion over a 7 to 10-year period from conception to operation, manufacturing capacity is continually growing. The economics of the industry require appropriate product rationalization within a company's facilities. Tariffs or other trade remedies that restrict the ability of companies to rationalize their capacity would likely

hamper additional manufacturing capacity in the United States and result in decreased availability of medicine.

Additionally, unlike with other manufacturing industries, plasma fractionation has not undergone significant offshoring. In 1996, 35% of worldwide fractionation capacity was located in the U.S. Nearly 30 years later, and despite a threefold increase in global capacity, that percentage remains roughly the same, at 32%. The flow of plasma and PDTs, mainly between the U.S. and Europe, may have increased, but not at the expense of American capacity or jobs.

Conclusion

Imports of PDTs, plasma and intermediates do not represent a national security threat because the source material for these products comes entirely from the U.S. The U.S. manufacturing base has remained robust and consistent for decades. A realignment of existing U.S. manufacturing capacity to increase the percentage of therapies produced domestically would in reality decrease the total volume manufactured, seriously impacting the ability of patients to access the medicines they need

Introducing additional trade friction in the form of tariffs or other trade actions with the intended goal of increasing domestic production would only serve to eliminate the significant efficiencies gained – likely increasing manufacturing costs and decreasing yields (product available) – without the intended macroeconomic benefits.

The unique nature and delicate supply chain of plasma-derived therapies has been recognized in many policies over the years, such as the first Trump Administration's exemption of immune globulin, the industry's driving product, from the Most Favored Nation Model in 2018 and recognition[2,3] by U.S. Customs in the 1990s that plasma exported for further processing and returned to the United States retains its fundamentally American character.

We urge that this Section 232 investigation refrain from including plasma, intermediate fractions and finished therapies in any trade remedy taken. While PPTA commends this Administration's commitment to a secure pharmaceutical supply chain, we believe that applying trade remedies to these products or their U.S.-sourced starting materials would not serve to increase national security, could undermine U.S. export competitiveness, and adversely affect the ability of the American public to access the medicines they need.

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[2] CROSS Ruling - 856113: The tariff classification of three blood fraction products
[3] CROSS Ruling - 733248: Country of origin marking of imported Immune Serum Globulin