Plasma Protein Therapeutics Association

Transatlantic Trade & Investment Partnership ("TTIP")
Overview of Industry Priorities
22 May 2015

The Plasma Protein Therapeutics Association ("PPTA") welcomes the opportunity to foster an even more robust and mutually beneficial trading relationship between Europe and the United States through the TTIP negotiations. As the global representative of both manufacturers of plasma protein therapies and source plasma collectors, with members based in the E.U. and the U.S., PPTA is well aware of the challenges of navigating the transatlantic business environment.

PPTA therefore commends the TTIP negotiators for their efforts, and respectfully recommends action on a number of regulatory barriers that currently prevent E.U.-U.S. trade in this unique segment of the pharmaceutical industry form reaching its true potential. Specifically, PPTA believes that any E.U.-U.S. Free Trade Agreement emerging from the TTIP negotiations should include provisions on:

- regulatory convergence toward U.S. acceptance of European plasma
- mutual recognition of inspections, and
- "global sufficiency" for source plasma.

Plasma Protein Therapies

Plasma protein therapies are complex, biological therapies that consist of large molecules that replace missing or deficient proteins in an individual's blood. These therapies are used to treat rare, chronic, life-threatening conditions, and include: immunoglobulin, for treatment of primary immune deficiency and other immune disorders; blood clotting factors, for treatment of hemophilia and other bleeding disorders; alpha-1 antitrypsin, for treatment of genetic emphysema and other breathing disorders; and albumin, for treatment of hypovolemia, shock, and burns.

Understanding the manufacture and regulation of plasma protein therapies requires an understanding of a handful of key concepts, including:

- Plasma – The pale yellow liquid component of whole blood that holds blood cells in suspension. It constitutes 55% of blood volume and contains a number of therapeutically valuable proteins, including those that promote blood clotting and immune response.

- Source Plasma – "Plasma," without any modifier, is a product for transfusion that does not undergo significant alteration before human use. "Source plasma," in contrast, is the raw material used in a manufacturing process – the starting point for plasma protein therapies.

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- Plasmapheresis – The process by which plasma is removed from the body by drawing whole blood, separating it into plasma and cells, and returning the cells to the donor. By returning the oxygen-bearing red cells to the donor, plasmapheresis permits a larger volume donation of plasma than would be possible through whole blood donation. It also permits a donor to safely donate more frequently.

- Fractionation – The process of manufacturing plasma protein therapies. Numerous individual plasma donations are pooled and subjected to a succession of industrial processes, each of which yields a "fraction" that is rich in one or more therapeutically valuable plasma proteins.

Industry TTIP Priorities

1. Regulatory Convergence Toward U.S. Acceptance of European Plasma

Development of a regulatory pathway for U.S. regulatory acceptance of source plasma collected in Europe is a top tier priority for European source plasma collectors. Currently, plasma collected in Europe cannot be used or sold in the U.S. This is due, in part, to transatlantic regulatory differences in the areas of collection, testing, processing, storage, and distribution standards for source plasma. In Europe, these areas are covered by European Medicines Agency ("EMA") regulation, as well as individual Member State regulation in conformity with the European Blood Directive. In the U.S., they are covered by Food and Drug Administration ("FDA") regulation. Specific areas in which source plasma collection centers can potentially be subject to costly and inefficient duplicative regulation, or even conflicting and inconsistent regulatory mandates, include: (1) collection practices, (2) viral marker test kit licensing, (3) donor deferral requirements, and (4) donor risk assessments. Regulatory convergence in these areas will consequently benefit plasma collectors on both sides of the Atlantic and will provide, if not a complete solution, at least an important incremental step toward U.S. market acceptance of European plasma.

Recommendation: It is PPTA's understanding that EMA and FDA are already coordinating on the issue of regulatory convergence in the areas of source plasma and plasma protein therapies through the "Blood Cluster." PPTA commends these efforts and recommends that any agreement resulting from the TTIP negotiations be used to strengthen them by addressing two of the key shortcomings of the current Blood Cluster framework: a lack of transparency and a lack of industry participation. With that goal in mind, PPTA recommends that the TTIP negotiators explore the possibility of expediting E.U.-U.S. regulatory convergence in these areas by considering specific mechanisms for industry participation, such as mandating working groups with fully inclusive stakeholder representation. In recognition of the fact that the de facto U.S. ban on European plasma is also driven, in part, by a specific pathogen safety concern, PPTA further recommends that the TTIP negotiations be used as the impetus to spur FDA's

TSE Advisory Committee[1] to re-examine U.S. regulatory policies that, though necessary and appropriate when cases of variant Creutzfeldt-Jakob disease peaked in the United Kingdom 15 years ago, may no longer reflect a careful, science-based assessment of the safety-related risk.

2. Mutual Recognition of Inspections

The need for E.U.-U.S. regulatory convergence is particularly acute in the areas of good manufacturing practice ("GMP")-based inspections. This is the case with GMP-based inspections of fractionation facilities located in Europe and the U.S. – which, notably, manufacture the bulk of the world's plasma protein therapies – but even more so with respect to the 500+ source plasma collection centers currently operating in the same geographic footprint. Despite the fact that the regulators responsible for GMP-based inspections in Europe and the U.S. (Member State authorities in the E.U., FDA in the U.S.) are each reliable, sophisticated, and highly respected in their own right, many source plasma collection centers continue to be inspected by *both*. When these governmental inspections, each of which is on a 2-3 year rotation, are combined with inspections by source plasma purchasers (typically, manufacturers of plasma protein therapies), a month in which a collection center does *not* undergo an inspection is more the exception than the rule. This continuous stream of duplicative inspections is unlikely to improve the quality or safety of the collected plasma, but adds significantly to the cost of collection center operations.

Recommendation: It is PPTA's understanding that other trade associations representing various segments of the pharmaceutical industry in Europe and the U.S. – including EFPIA, PhRMA, and BIO – have recommended that any agreement emerging from the TTIP negotiations call for mutual recognition of GMP-based inspections. PPTA now adds its voice to this chorus and reiterates that mutual recognition, rather than mere mutual reliance, should be the goal. With ministries of health around the world placing increasing pressure on pharmaceutical reimbursement, eliminating the significant costs imposed by unnecessary, duplicative inspections is a sensible step that would benefit not only source plasma collectors and manufacturers of plasma protein therapies, but payers and patients. The move would also yield substantial benefits for regulators, who are stretched to carry out their current responsibilities with limited inspections budgets and personnel. Finally, to the extent that an assessment and/or phase-in period is needed prior to full mutual recognition, PPTA again recommends that the TTIP negotiations be used to strengthen the current EMA-FDA Blood Cluster framework by providing a mechanism for meaningful industry participation.

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[1] "TSE" stands for "transmissible spongiform encephalopathies" – a category of progressive diseases that affect the brain and nervous system, including variant Creutzfeldt-Jakob disease (the human version of mad cow disease).

3. "Global Sufficiency" for Source Plasma

A number of E.U. Member States continue to support self-sufficiency policies for plasma collection and link these policies to national use of plasma protein therapies. The concept also finds support in certain provisions of the European Blood Directive. Supporters of self-sufficiency policies assert that, as in the case of whole blood, individual nations, including individual E.U. Member States, should strive to create national plasma collection networks that serve 100% of domestic need without outside support.

PPTA believes that national self-sufficiency policies constitute both bad public health policy and bad trade policy. Here the distinction between whole blood for transfusion and source plasma for fractionation (*i.e.*, for the manufacture of plasma protein therapies) is critical. Self-sufficiency works for whole blood due to it being a localized resource, but self-sufficiency for source plasma and plasma protein therapeutics does not reflect current manufacturing practices and economies of scale, cannot satisfy clinical need for plasma protein therapies and, most importantly, is not supported by patients.

Support for national self-sufficiency policies is rooted, in large part, in opposition to compensated plasma donation. Here too the distinction between whole blood for transfusion and source plasma for fractionation is critical. Relying on uncompensated donors has worked for whole blood, but this is because as few as 1-6 whole blood donations might satisfy an individual patient's transfusion needs. In contrast, the number of source plasma donations needed to treat a single patient with primary immune deficiency, genetic emphysema, or hemophilia for one year is 130, 900, and 1200, respectively. Securing plasma in these volumes requires an extremely committed base of donors that are willing to donate frequently – as often as several times per month, with each individual plasmapheresis session lasting more than an hour – and deserve to be compensated for their time.

Opponents of compensated donation raise purported safety concerns, but the reality is that source plasma donation is highly regulated. It is governed by both EMA and FDA rules, as well as voluntary industry standards – the International Quality Plasma Program ("IQPP") – that PPTA develops and audits against through the use of a cadre of trained, third-party auditors. The EMA, FDA, and IQPP rules all incorporate rigorous standards for donor selection and screening. Furthermore, as part of the manufacturing process, source plasma donations are subject to robust viral clearance steps that are simply not feasible in the whole blood context, as they would result in the destruction of red cells, platelets, and other non-plasma elements. Indeed, the European Court of Justice has held that "the obligation that the blood donation must have been made without any of the costs incurred by the donor being reimbursed is . . . not necessary in order to ensure the quality and safety of the blood and blood components." *Humanplasma GmbH v. Republik Österreich*. In addition, in 2002, EMA (then EMEA)

noted that there is no difference in safety in products made from plasma donated by people who had been remunerated or non-remunerated.[2]

Recommendation: National self-sufficiency policies for source plasma cannot satisfy global patient need for life-sustaining plasma protein therapies and are not justified by valid safety concerns. PPTA is also concerned that these policies can be used in a protectionist manner to shield state-owned manufacturers of plasma protein therapies from private sector competition, thereby depriving patients of needed product and resulting in artificially low levels of diagnosis of rare conditions. PPTA therefore recommends that any agreement emerging from the TTIP negotiations reflect support for "global sufficiency" in source plasma. This can be achieved by amending specific provisions of the European Blood Directive that can be interpreted as supportive of national self-sufficiency policies – a step that is particularly timely in light of the European Commission's ongoing effort to revise and update the Directive.

Conclusion

These three major areas of focus stand as areas of importance not only for the industry, but for patients suffering from chronic, rare, and serious diseases. Certainly the European Union and the United States both lead the world in terms of appropriate diagnosis and treatment for these conditions, but there are many areas which can be improved through targeted, value-added regulatory convergence. Ultimately, patients will benefit from these suggestions for improvement.

PPTA member companies, which employ tens of thousands of workers in the E.U. and U.S., are especially well-suited to contribute to the ongoing TTIP discussions. Plasma protein therapies are used to treat serious conditions around the world in many different countries. Improved efficiencies and optimized requirements could assist this international industry in further economic development. We look forward to continuing engagement as the TTIP negotiations move forward, and are willing to answer any questions to further the dialogue.

[2] European Agency for the Evaluation of Medicinal Products, CPMP Position Statement, *Non-Remunerated and Remunerated Donors: Safety and Supply of Plasma-Derived Medicinal Products* (30 May 2002), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/10/WC500004488.pdf.