PLASMA PROTEIN THERAPEUTICS ASSOCIATION (PPTA) [1] POSITION ON THE REVISION OF THE GENERAL EU PHARMACEUTICAL LEGISLATION

The revision of the EU's general pharmaceutical legal framework provides a much-needed opportunity to ensure better access to pharmaceuticals for patients in the EU, including access to plasma-derived medicinal products (PDMPs). PDMPs are essential [2], lifesaving therapeutics used to treat a range of rare, chronic, and acute life-threatening diseases[3]. This position paper provides the European Commission and other stakeholders with valuable information and suggests pragmatic approaches to design and implement better policies at the EU level.

The pharmaceutical legislation should address the following issues:

Patient access: PDMPs need a tailored approach

Policymakers should focus on the core vulnerability when it comes to ensuring access to plasma-derived medicinal products (PDMPs) for EU patients: EU's current reliance on plasma from non-EU countries.

Insufficient plasma collection in the EU and the reliance on plasma imports from the US directly affects access to PDMPs for European patients. The COVID-19 pandemic further impacted plasma collections globally. Currently, the EU's supply of plasma for manufacturing of PDMPs largely depends on four countries – Austria, Czech Republic, Germany and Hungary [4, 5]. Therefore, the best way to assure Europe's PDMP supply is to increase the availability of plasma for manufacturing in the EU.

This can be achieved by:

(a) Exploring and addressing root causes of PDMPs shortages in the pharmaceutical manufacturing value chain with key stakeholders, including the European Commission.
(b) Enhanced acceptability of RWE for the authorisation of additional products for substances and indications which are already well established and in support of data needed for clinical trials for the development of new medicines from human plasma.

The measures currently considered by the European Commission to address unequal patient access to medicines do not adequately account for the specifics of the plasma industry nor the needs of patients who rely on PDMPs. National stockpiling measures, for instance, would cause PDMP supply disruptions as manufacturers conduct plasma collection, testing and manufacturing on a global level. Similarly, additional supply monitoring and oversight mechanisms would simply highlight access issues but not provide solutions. To truly benefit EU patients, existing requirements across the EU should be streamlined, considering EMA's new mandate on shortage monitoring and preparedness [6].

Improving the alignment between frameworks for plasma and PDMPs

Better alignment is needed between the legislative framework governing plasma collection and testing (Directive 2002/98/EC), those setting principles for manufacturing and regulatory management of PDMPs (Directive 2001/83/EC, Regulation (EC) No. 1234/2008) and the rules governing Good Manufacturing Practice (GMP). This includes a clear delineation of responsibility and authority for relevant bodies implementing 2001/83/EC (EMA, GMP inspectorates) and 2002/98/EC (EDQM, ECDC) without resulting in duplication of obligations and requirements for the plasma industry, which is governed by both frameworks.

Adapting administrative requirements: The EU Plasma Master File

Existing regulatory processes related to the EU Plasma Master File (PMF) result in administrative burden and create additional inefficiencies as they do not consider current knowledge and advances in the safety and quality of PDMPs.

In order to remove inefficiencies, release more plasma for manufacturing of PDMPs and ultimately ensure timely patient access to these lifesaving therapies, the revision needs to address outdated PMF requirements, which include:

(a) Revision of requirements for the addition of new plasma collection centres within the PMF;
(b) Use of plasma from centres that are compliant with EU safety and quality requirements but are not yet approved as part of an EU PMF, such as those which are nationally licensed and collect blood for transfusion;

(c) Simplification of the Second Step approval process for PMF certification: Second step approval translates into additional costs for PMF holders but has no impact on PDMP quality, safety or efficacy, as the PMF has been already assessed and approved by the EMA. Instead, less rigorous measures (such as notification) should be considered.

Ensuring regulatory efficiency to better address patient needs

A revised EU framework for pharmaceuticals needs to accelerate, refine and improve standard regulatory processes.

The manufacturing of PDMPs from human plasma is a complex, multi-stage and multi-factorial process. It is conducted on a global scale and is dependent on the global availability of the key starting material for PDMP production: human donated plasma. Increasing regulatory efficiency through harmonisation of requirements for the plasma industry with relevant 3rd country jurisdictions which provide plasma for PDMPs for European patients would make the system more resilient in crisis situations, increase the competitiveness and sustainability of the EU's plasma industry, release more plasma for manufacturing and ultimately benefit patients through increased access to PDMPs.

Concrete steps to enhance regulatory efficiency and increase plasma availability are:

(a) Harmonization of GMP inspection conduct, best practices sharing, resources sharing, and mutual audits among EU Member States and inspection capacity building;
(b) Changes to GMP inspection rules, such as issuance of the provisional certification of new manufacturing facilities, re-certification of existing manufacturing facilities, and implementation of remote GMP inspections for plasma collection facilities.

Additional measures include:

(c) Clarification of definitions such as "inspection" and "risk-based approach" to facilitate EU Member State harmonisation and streamline GMP inspection conduct;
(d) Shortening of time between scientific advice, clinical trials, and marketing authorization applications/submissions;
(e) Inclusion of industry in the drafting of technical and regulatory provisions related to plasma quality, pathogen safety and standards;

PDMP availability would further be improved through:

(f) Addition of plasma for manufacturing and PDMPs to the EU-U.S. Mutual Recognition Agreement (MRA) on GMP inspections (5);
(g) An extensive MRA for GMP conformity with the UK.

The European Commission's revision of the EU pharmaceutical legislation presents a much-needed opportunity to address the need for equal EU patients' access to safe, state-of-the-art, and affordable medicines, including PDMPs, to treat and prevent diseases, and the need to support and foster innovation in the EU. PPTA calls upon the European Commission to recognise the specificities of the plasma industry, including the unique nature of human donated plasma, which serves as an essential biological starting material for PDMP production. A key component to meet the clinical needs of EU patients who rely on PDMPs is assuring sufficient plasma collection in Europe.

Supporting information:

1. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analogue therapies. PPTA represents private plasma donation centers and manufacturers of plasma-derived therapies, and includes Biotest, BPL, CSL Behring, Grifols, Kedrion, and Takeda, which cover more than 60% of PPTs from around the world. PPTA members are committed to assuring the safety and availability of these life-sustaining medicines
2. Due to their importance, a number of PDMPs are classified as 'essential medicines' by the World Health Organization (WHO). World Health Organization (WHO, 2021): 22nd Essential Medicines List (EML) and the 8th Essential Medicines List for Children (EMLc). Available at: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists
3. These diseases include haemophilia, deficiencies in Factors (F) VIII, IX, XIII, von Willebrand Factor, Protein C, Antithrombin III, alpha-1-antitrypsin; as well as primary immune deficiency, neurological and autoimmune disorders and albumin, which is used to treat individuals with severe liver diseases and in emergency-room settings such as shock, trauma, burns, and other conditions. Many PDMPs and their recombinant analogues fall in the Orphan Drug category, as per EMA's definition to treat rare or very rare diseases. In Europe, over 300, 000 patients rely on these essential medicines.
4. Vintura (2020): White paper: Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe. Available at: https://www.vintura.com/news/white-paper-key-economic-value-considerations-plasma-derived-medicinal-products-pdmps-europe/
5. Copenhagen Economics (2021). The impact of plasma derived therapies in Europe: The health and economic case for ensuring sustainable supply. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2022:020:TOC https://www.copenhageneconomics.com/dyn/resources/Publication/publicationPDF/0/570/1624364808/copenhagen-economics_the-impact-of-plasma-derived-therapies-in-europe_june-2021.pdf
6. Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices. Available at:
7. The U.S –EU MRA of GMP inspections for manufacturing facilities of pharmaceuticals has since its amendment in 2017 progressively been expanded to include individual EU Member States. However, at present, the scope of the agreement excludes «human blood, **human plasma**, human tissues and organs, and veterinary biologics. Available at: http://trade.ec.europa.eu/doclib/docs/2017/february/tradoc_155398.pdf, https://www.ema.europa.eu/en/documents/other/questions-answers-impact-mutual-recognition-agreement-between-european-union-united-states-11-july_en.pdf, http://trade.ec.europa.eu/doclib/docs/2019/january/tradoc_157651.pdf