Position Paper

PLASMA PROTEIN THERAPEUTICS ASSOCIATION

November 2023

Revision of the EU general pharmaceutical legislation: Strengthening the regulatory framework and improving access for plasma-derived medicinal products (PDMPs)

The revision of the EU general pharmaceutical legislation is an opportunity to strengthen the current legislative and regulatory frameworks and to address the need for equal access to safe, state-of-the-art medicines, including plasma-derived medicinal products (PDMPs) across the EU, which are essential medicines for 300,000 European patients with rare diseases. This will require:

- **Improving security of PDMP supply by addressing the root causes of shortages.**
- **Ensuring harmonisation of rules for inspection conduct in the EU and globally.**
- **Reducing redundant administrative procedures for PDMPs that do not have impact on the quality, safety, and efficacy of the final product.**
- **Safeguarding strong presence of the European plasma industry in the global market.**

PLASMA-DERIVED MEDICINAL PRODUCTS (PDMPS)

PDMPs are unique biologic medicines that are used to treat patients with rare, often genetic conditions with a high disease burden, including primary immunodeficiencies (PID), certain secondary immunodeficiencies (SID), bleeding disorders, alpha-1 antitrypsin deficiency, neurological diseases other than orphan diseases associated with absence or malfunction of specific proteins. The starting material for PDMPs is human plasma, which is donated by healthy volunteer donors. The production of PDMPs is a highly complex and regulated process that depends on a constant supply of donated plasma for fractionation and takes approximately six to twelve months from donation until a final product is available. In this context, PPTA calls upon EU policymakers to recognise the specificities of these products and ensure that EU pharmaceutical frameworks can meet the needs of patients who rely on PDMPs.

1. SECURITY OF SUPPLY: A NEED FOR A TAILORED APPROACH FOR PDMPS

Over the past decade, the use of PDMPs has almost doubled and the need for these therapies is projected to rise, mostly due to ageing population and advancements in diagnosis. Since the manufacture of PMDPs depends on a continuous supply of plasma for fractionation, the production of PDMPs cannot be rapidly scaled up. Therefore, improving the visibility of patient needs and regular dialogue with the industry and other stakeholders could facilitate the development of more comprehensive, systemic, and fit-for-purpose measures to support a shared objective of increasing PDMP supply.

PPTA recognises that early notification of potential medicine shortages in the Commission's draft of EU Pharmaceutical Regulation (Article 116) could help to highlight the issue and serve as a monitoring tool for the information on availability of therapies. However, early notification does not sufficiently address the root causes of PDMP supply chain disruptions and is not effective in mitigating shortages caused by factors beyond the control of marketing authorisation holders, such as availability of plasma for fractionation. Additionally, sole reliance on early notifications may have unintended consequences, as some challenges can be resolved before the shortage occurs, while contingency plans and prevention systems developed in response to these notifications (Regulation article 134), including stockpiling, could cause PDMP supply disruptions instead of addressing the systemic issues that contribute to shortages. Building a stockpile in one Member State would require a diversion of products from another EU Member State and patients who need them immediately. Furthermore, PPTA is concerned about the possible administrative burden caused by unclear and duplicative reporting requirements in the proposed monitoring and notification provisions.

To meet the growing need for PDMPs, policymakers should focus on the core vulnerability of PDMP supply – insufficient collection of plasma for fractionation. Given the EU's reliance on sourcing of the starting material, a closer alignment of provisions in the pharmaceutical legislation with those of the Regulation governing the collection and testing of Substances of Human Origin (SoHO) will be necessary. Regulatory provisions such as harmonisation of GMP inspections of plasma centres and manufacturing sites could play an important role in facilitating the flow of plasma necessary for the manufacture of medicines. Additionally, a clear delineation of roles, responsibilities and remits of different EU bodies and agencies will be necessary to avoid duplication and discord in decision-making on medicinal products.

RECOMMENDATIONS

- Consider the whole PDMP value chain when addressing the root causes of shortages, in consultation with stakeholders including industry via structured dialogues and other channels.
- Harmonisation of inspections under the legislative frameworks governing collection of plasma for fractionation (SoHO Regulation) and the pharmaceutical framework setting principles for manufacturing and regulatory management of PDMPs and the rules governing Good Manufacturing Practice (GMP).
- A clear delineation of responsibility and authority for relevant bodies and agencies implementing the provisions of the pharmaceutical legislation, SoHO Regulations and relevant technical guidelines or supplementing regulations, including the EMA, ECDC, EDQM and GMP inspectorates.

2. ENSURING AN EFFECTIVE INSPECTION CONDUCT

PPTA welcomes a risk-based approach to GMP inspections of manufacturing sites and sites producing active pharmaceutical ingredients (APIs), which would allow for a more efficient allocation of inspection and operational resources by regulators and industry. To facilitate availability of plasma for fractionation and enable timely patient access to lifesaving PDMPs, inspections of plasma collection facilities that collect plasma exclusively for fractionation into medicines should also fall under comparable provisions as proposed for APIs. The assessment of the necessary frequency of inspections and control measures for both plasma collection and manufacturing sites should be based on the activities which these establishments undertake and on the compliance records.

PPTA further commends the European Commission's attempts to ensure more harmonised inspection conduct in the EU by establishing the Joint Audit Programme as well as strengthening EMA's role for GMP inspections in third countries and providing support to inspections conducted by EU Member States. Harmonisation of EU GMP inspections is key to improving regulatory efficiency and streamlining inspection processes, so resources can be allocated more effectively, focusing on areas of higher risk and greater need. This is important for the plasma industry as the existing backlog of inspections, particularly of plasma collection centres in the US, has a direct impact on availability of plasma and PDMPs for EU patients. Thus, the EMA should have available resources to adequately manage inspection oversight and strengthen inspection capacity and harmonise inspections across the EU.

RECOMMENDATIONS

- Promote and support the harmonisation of GMP inspection conduct, best practices, and resources sharing, as well as mutual audits among EU Member States and inspection capacity building.
- Changes to GMP inspection rules, such as issuance of the provisional certification of new manufacturing facilities, re-certification of existing manufacturing facilities and alignment of plasma collection centres and manufacturing site inspections.
- Based on lessons learned from the inspection conduct during the COVID-19 pandemic, maintain flexibility and the possibility for remote/hybrid inspections for plasma collection sites.

3. ADAPTING REGULATORY REQUIREMENTS AND REDUCING ADMINISTRATIVE BURDEN

A revised EU framework for pharmaceuticals needs to accelerate, refine, and improve standard regulatory processes. Manufacturing of PDMPs from human plasma is a complex, multi-stage, and multi-factorial process, which is conducted on a global scale. Increasing regulatory efficiency through harmonisation of requirements for the plasma industry with relevant third country jurisdictions which provide plasma for PDMPs would make the system more resilient in crisis situations. Regulatory convergence would also 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.

PPTA welcomes the Commission's proposal for simplifying and streamlining regulatory provisions and its efforts in promoting digitalisation, through mandatory electronic submissions for variations and marketing authorisation. However, existing regulatory processes related to the variations and EU Plasma Master File (PMF) could be further improved by diminishing the administrative burden and adapting regulatory provisions based on the latest scientific knowledge and considering advances in the safety and quality of PDMPs

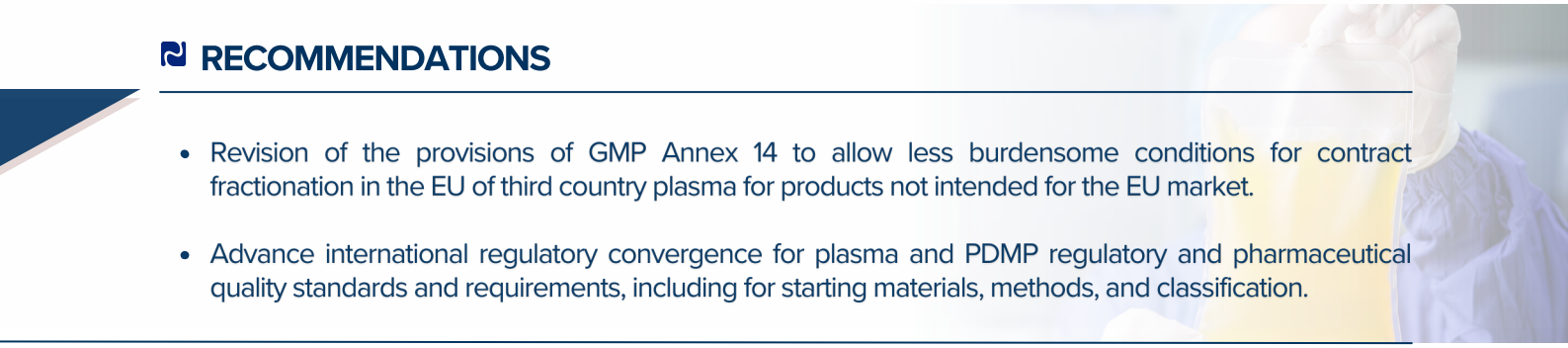
RECOMMENDATIONS

- Encourage revision of technical provisions applicable to the plasma industry, including variations guidelines and EMA Plasma Master File (PMF) guidelines as well as the requirements for the addition of new plasma collection centres.
- Remove redundant administrative procedures such as the PMF second step procedure, which have no impact on the quality, efficacy, and safety of medicinal products, but uses limited resources of national regulatory authorities and manufacturers.
- Facilitate the administrative requirements for the use of recovered plasma that is collected by blood establishments and is compliant with EU safety and quality requirements to manufacture PDMPs

4. NEED FOR A STRONG EUROPEAN PLASMA INDUSTRY

A strong European plasma industry is a prerequisite to fulfilling the key aims of the EU pharmaceutical framework revision. The EU remains a major actor in global plasma fractionation, advancing research, and manufacturing techniques to meet the growing need for PDMPs, while maintaining the highest standards of quality, safety, and efficacy. While the US supplies more than 60% of the starting material (plasma for fractionation) for PDMPs globally, Europe remains at the forefront of PDMP manufacturing with the highest number of fractionation facilities and product output globally [1], despite its dependence on US plasma for about 40% of its plasma need.

Amid the increasing global competition, the revision of EU pharmaceutical legislation presents a unique opportunity to improve regulatory efficiency and further strengthen Europe's competitiveness by enabling a robust and innovation-friendly environment for the plasma industry to address unmet medical need and ensure continuous supply. The revised framework should focus on strengthening regulatory convergence and international cooperation to help ensure resilience of the global PDMP supply chain. This will require a collaborative effort between industry stakeholders, regulatory bodies, and European and international governments.



RECOMMENDATIONS

- Revision of the provisions of GMP Annex 14 to allow less burdensome conditions for contract fractionation in the EU of third country plasma for products not intended for the EU market.
- Advance international regulatory convergence for plasma and PDMP regulatory and pharmaceutical quality standards and requirements, including for starting materials, methods, and classification.

A strong and sustainable plasma industry for the EU and EU patients is critical. The plasma industry plays a pivotal role in providing life-saving treatments, improving the quality of life for countless patients in the EU. PPTA calls upon EU policymakers to recognise the essential role of the plasma industry in the global PDMP supply and work collaboratively to create an environment that is conducive to its growth and continued manufacturing excellence, while ensuring that patients in the EU and beyond have access to life-saving treatments. PPTA is committed to working with the European Commission, European Parliament, and the Council of the EU to ensure that the revised EU pharmaceutical legislation creates a cohesive regulatory environment and supports the needs of patients for safe and efficacious PDMPs.

[1] MRB (2018) https://marketingresearchbureau.com/wp-content/uploads/2021/09/Hotchko-MRB-website-presentation.pdf