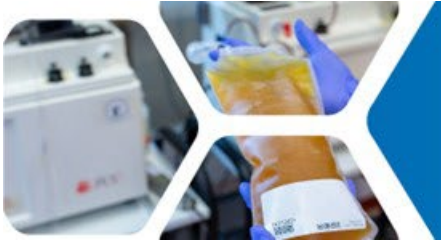


Position Paper on SoHO Regulation

PPTA Plasma Protein Therapeutics Association

PPTA's position on the European Commission's proposal for an EU Regulation on standards of quality and safety for substances of human origin intended for human application (SoHO Regulation)

PPTA welcomes the EU Commission proposal on a SoHO Regulation and considers it as a great opportunity to improve patient access to life-saving, high-quality plasma-derived medicinal products (PDMPs), with the health and safety of patients and plasma donors at the heart of it.

Medicines made from human-donated plasma are essential for some 300,000 patients across the EU who rely on these therapies every day to treat a variety of rare, chronic, and life-threatening conditions.[1] Without these treatments, many patients would have a substantially diminished quality of life, and some may not survive.

In many cases, PDMPs are the only treatment option for these rare diseases. New indications, improved diagnostic techniques, greater access to treatment in other regions of the world, and increased use in cancer treatment-induced secondary immunodeficiency, continue to contribute to the growing clinical need for PDMPs.

With Europe's current reliance on the U.S. for almost 40% of the plasma it requires for the manufacture of PDMPs to treat its citizens, it is vital that the new legal framework is fit for purpose to help increase much-needed plasma collection in Europe.

300,000

EU patients rely on life-saving plasma therapies

Only treatment option

for many rare diseases

1. Ensure health and safety of plasma donors

The safety of plasma donors is of paramount importance to the plasma industry. PPTA therefore welcomes and supports measures and standards that protect donor health and safety.

PPTA's well-established commitment to donor health has been and continues to be demonstrated by the implementation of the International Quality Plasma Program (IQPP), a voluntary industry standard programme. One of these standards assesses DAEs in plasma donors: "IQPP Standard for Recording Donor Adverse Events – 'PlasmaVigilance''[2]. Since 2016, it provides a common set of definitions to assess and monitor DAEs across the plasma industry.

Ensuring that assessment of Donor Adverse Events is harmonised across the EU

Considering the plasma industry's expertise in the monitoring, evaluation, and assessment of plasma DAEs, any new system should be streamlined across the EU (data collection, reporting, evaluation) to allow harmonisation, and should consider the specificities of plasmapheresis[3]. It is important to distinguish donor health requirements applicable to plasma donors (who donate via plasmapheresis) from those applicable to donors of whole blood and

[1] More patients across the EU are diagnosed every year with life-threatening plasma protein-related disorders, such as immune deficiencies, immune-mediated peripheral neuropathies, hereditary angioedema, alpha 1-antitrypsin deficiencies, haemophilia and other bleeding disorders.

[2] PPTA: IQPP Standard for Recording Donor Adverse Events, version 2, April 2018: https://www.pptaglobal.org/images/IQPP/Standards_Revisions/2018/IQPP_DAERS_V2.pdf

[3] With Plasmapheresis, there is no pre-treatment required. The medical intervention (i.e. phlebotomy) is identical to blood donation, however, plasmapheresis is an extracorporeal lab technology. The donor's blood cells are then returned to the body. This is not the case for blood donors. In addition, the amount of time it takes for plasma donors to recover and replace the extracted plasma proteins is shorter for plasma donors, when compared with the amount of time it takes blood donors to recover and replace blood components.

other blood components. There are also different apheresis types[4], which require different methods of donor (and donor health) management.

Plasma donation is safe

PPTA is concerned to see the statement that plasma donation is "considered to imply a significant risk" as it can be misleading with scientific data proving that the risk of donor adverse events (DAEs) in plasma donation is low and similar to blood donation. A recent study of more than 12 million plasma donations, which is one of the largest studies conducted on plasma donors to date, has shown that adverse events related to the donation of plasma are very rare (approximately 16 events per 10,000 donations), and most of them are mild: 90% are hypotension or bruises at the injection place. They represent a low risk to donors and are similar to DAEs when donating whole blood.[5] Comparable results have been identified in many other scientific studies.[6,7,8,9]

Safe for donors

Only 0.16% of plasma donors experience adverse events,

2. Increase plasma collection in the EU

Differentiating between plasma and blood and ensuring clear definitions

PPTA welcomes the differentiation of plasma from blood components for transfusion, including the new definitions of 'plasma for fractionation', 'plasma for transfusion' and 'apheresis' in the SoHO Regulation Proposal by the European Commission (COM/2022/338 final).

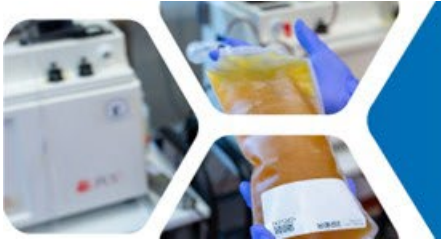
These definitions are crucial to improve the clarity of the Regulation and legal certainty in the field of SoHOs while ensuring a common understanding of the scope, applicability, and technical concepts of the Proposal. Recognising the differences between 'plasma for fractionation', 'plasma for transfusion' and 'apheresis' lays the foundation for policies to support the increased availability of plasma in Europe for the manufacturing of life-saving plasma-derived medicinal products.

As such, PPTA expresses concern regarding the discussion around the potential removal of key definitions as highlighted in progress report of the Council of the European Union on the SoHO Regulation (Interinstitutional File (2022/0216(COD)), dated December 1st, 2022. PPTA stresses the importance of keeping the definitions as outlined at the beginning of the Proposal, laying the foundation for common understanding of the operative articles of the Regulation.

Compensating donors by using a fixed-rate allowance covering expenses and inconveniences related to the donation

PPTA welcomes the clarification that compensating donors with a "fixed-rate allowance" – for which Member States set the conditions – is compatible with the principle of "Voluntary Unpaid Donation". PPTA believes, however, that it would be more appropriate to keep in the SoHO Regulation the wording of the EU Tissues and Cells Directive, which clarifies that "donors may receive compensation, making good the expenses and inconveniences related to the donation". This wording also encompasses the interpretation of the Nuffield Council on Bioethics, which states that compensation can cover financial and non-financial losses.[10] In this context, the EU Commission's Evaluation of the Blood Tissue and Cell Directives notes that the degree of inconvenience and the time required for different types of donations can differ considerably[11], including between a blood and plasma donation.

[4] These include red blood cell apheresis, platelet apheresis, granulocyte apheresis (with medical treatment at time of apheresis), lymphocyte apheresis, monocyte apheresis, stem cell apheresis, and plasmapheresis
[5] Schreiber GB, Becker M, Fransen M, Hershman J, Lenart J, Song G, et al. 2021 "Plasmavigilance – Adverse events among U.S. source plasma donors." Transfusion 2941-57
[6] Gustafson M. Source Plasma Donor Hemovigilance Activities and Results. Available from: https://www.pptaglobal.org/images/presentations/2017/Gustafson_PlasmaVigilance100817.pdf (Pilot study).
[7] Hartmann J, Ragusa MJ, Burchardt ER, Manukyan Z, Popovsky MA, Leitman SF. Personalized collection of plasma from healthy donors: a randomized controlled trial of a novel technology-enabled nomogram. Transfusion. 2021;61:1789–98.
[8] Cho JH, Rajbhandary S, van Buren NL, Fung MK, Al-Ghafry M, Fridey JL, et al. The safety of COVID-19 convalescent plasma donation: a multi-institutional donor hemovigilance study. Transfusion. 2021;61(9):2668–76
[9] Cho JH, Hiskey M. Plasmavigilance: Source plasma joins the call to arms. Transfusion. 2021 Oct;61(10):2803-2805. doi: 10.1111/trf.16668. PMID: 34605562.
[10] The Nuffield Council on Bioethics - Human bodies: donation for medicine and research - https://www.nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf
[11] Commission Staff Working Document - Evaluation of Union legislation on blood, tissues and cells {SWD(2019) EN376 final}



Position Paper on SoHO Regulation

PPTA
Plasma Protein Therapeutics Association

Ensuring sustainable collection of plasma in the EU by dedicated plasmapheresis programmes

The proposed EU Regulation foresees that Member States must proceed to a mandatory "establishment of national SoHO emergency plans"[12], which include some regulatory and monitoring measures to be taken. However, the EU Commission Study on "supporting the Impact Assessment of the Revision of the BTC legislation" confirmed that a "monitoring system and foreseen regulatory measures would not be sufficient to reduce the EU's dependence on U.S. plasma".[13]

The EU's reliance today on U.S. plasma is almost 40% (or about 5 million litres).[14] Moreover, data demonstrate that "recovered" (indirect) plasma collection levels from whole blood have declined over time because of decreasing demand for blood and the implementation of Patient Blood Management programmes.[15,16] PPTA believes therefore that the EU should be more ambitious and recommend that Member States also establish proactive national plans, addressing the need to collect more plasma through plasmapheresis.[17] This call supports the objectives of the Pharmaceutical Strategy for Europe, to reduce dependency on starting materials for critical medicines.

~ 40%

of plasma needed in the EU comes from the U.S.[14]

Growth in plasma collection in the EU over the past twenty years has been possible mainly due to the contribution of the private sector in order to meet the growing clinical need for PDMPs of patients in Europe.[18]

growth in EU plasma collection has come mainly from the private sector[18]

Currently, only four EU Member States (Germany, Austria, Czech Republic, and Hungary) permit plasma collection models in which both the public and the private sectors can operate together. These four countries contribute 44% (around 4,3 million litres in 2020) of the total EU plasma volumes collected.[19]

44%

of the total EU plasma volumes collected comes from only four EU countries[19].

The proposed Regulation suggests that Member States should make "all reasonable efforts to promote public participation in SoHO donation activities, in particular for critical SoHOs". In this context, combining efforts of public and private sectors to increase plasma collection in Europe is crucial to address the growing patient needs.

3. Optimise, clarify and align roles of designated technical expert bodies (EDQM, ECDC, EMA, SoHO Coordination Board) in plasma-related regulatory decision-making

Involving industry stakeholders in the consultation process for the development of guidance on the safety of donations and donor health

PPTA welcomes the new SoHO Coordination Board together with the enhanced role of the European Centre for Disease Prevention and Control (ECDC) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) in the provision of technical guidance to assure the safety of donations and maintain donor health. However, further clarification needs to be provided on the individual remits and responsibilities of the different bodies involved. There must be a clear delineation of authority and responsibilities with as little

[12] Art 62.1: "Member States shall draw up national SoHO emergency plans, setting out measures to be applied with-out undue delay when the supply situation for critical SoHOs presents or is likely to present a serious risk to human health"
[13] Study supporting the Impact Assessment of the Revision of Directive 2002/98/EC and of Directive 2004/23/EC - https://health.ec.europa.eu/publications/study-supporting-impact-assessment-revision-directive-200298ec-and-directive-200423ec_en
[14] The Marketing Research Bureau, 2021 data
[15] The Marketing Research Bureau, 2021 data
[16] Commission Staff Working Document-Evaluation of Union legislation on blood, tissues and cells {SWD(2019) EN376 final}
[17] The EU Commission recognised in its Evaluation Report that apheresis plasma collection (or plasmapheresis) is the most efficient method of collecting plasma.
[18] The Marketing Research Bureau, 2021 data
[19] The Marketing Research Bureau, 2021 data

overlap as possible and the provision of a limited and restricted view of what is applicable for plasma for fractionation as opposed to for whole blood/ blood components for immediate transfusion.

It is key that any provisions and guidelines that will be developed, are based on the latest evidence and science. We look forward to sharing our expertise with these bodies in full transparency, to ensure that provisions for plasma donation and plasmapheresis practice take into account the substantial differences, including in the areas of donor deferrals, mandatory testing, manufacturing, and storage when compared with whole blood or transfusable blood components, PPTA thus calls for the implementation of stakeholder engagement principles by the designated Expert Bodies, similar to the stakeholder engagement principles of the EMA [20,21,22], and a rigorous scientific review process as it is already in place at both EMA and the European Pharmacopoeia Commission of the EDQM for the issuance of monographs, including for plasma for fractionation. This will ensure an open and constructive dialogue, with the involvement of stakeholders with relevant expertise and understanding of plasmapheresis practice.

Specifying which scientific guidelines should be used by SoHO entities to comply with technical standards of plasma collection and manufacturing

The draft Regulation foresees that scientific guidance set out by the EDQM and ECDC for SoHO entities "should be considered as a means to demonstrate compliance with technical standards". However, the draft Regulation also foresees that "SoHO entities should be permitted to follow other guidelines, provided they achieve the same level of quality, safety and efficacy". PPTA would like to emphasise that, while the relevant EDQM Blood Guide[23] provides useful parameters and standards for transfusible blood components, it currently does not adequately address important differences between whole blood and blood components for transfusion, and plasma for fractionation for (manufacturing) PDMPs. To ensure regulatory certainty for SoHO entities and other stakeholders, clarification is thus needed about when alternative guidance to EDQM and/or ECDC provisions can be applied.

Finally, PPTA remains committed to an open and constructive dialogue with all policymakers and relevant stakeholders to achieve an EU SoHO Regulation that will help, via its provisions appropriately implemented across the EU, to preserve the health and safety of donors, to increase plasma collection in the EU and, ultimately, to improve the patient access to essential life-saving PDMPs in the EU.

[20] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf
[21] https://www.ema.europa.eu/en/documents/other/framework-interaction-between-european-medicines-agency-industry-stakeholders_en.pdf
[22] https://www.ema.europa.eu/documents/presentation/presentation-module-2-engagement-stakeholders_en.pdf
[23] EDQM Blood Guide: https://www.edqm.eu/en/blood-guide