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Position Paper on Distribution of PDMPs coming from EU/national plasma

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INTRODUCTION

SUPPLY is a project co-funded by the European Union's EU4Health Programme that aims to increase and strengthen the resilience of plasma collection by the Public health sector in the EU to enable a stable, appropriate, and sufficient supply of Plasma-derived medicinal products (PDMPs) for patients both in a general situation as well as in times of crises. Along the project life-cycle, strategic items were timely and properly assessed: plasma donor recruitment and retention, donor health assessment, plasma collection, plasma processing and quality requirements definition; as well as demand, use, and distribution of PDMPs.

The initiative will result in the development of recommendations, tools, and best practices to support national and EU efforts to define/improve common policies and legal frameworks to achieve a greater strategic independence in its needs for PDMPs.

BACKGROUND

1. PDMPs Supply in Europe: Where are we now?

For decades plasma has been used as a primary material for the production of plasma derivatives through industrial fractionation, to varying degrees in each Member State (MS). This plasma comes from the integral processing of whole blood donations and specific plasma donations through apheresis. The adoption and development of alternative approaches throughout the plasma value chain across Europe has resulted in the significant heterogeneity of plasma systems which exists today.

Europe, as a whole, is suffering a significant and persistent plasma deficit. Considering immunoglobulins G (IgG), the main reference product, Europe is consuming 25% of the whole world production, but its contribution, as measured in litres of Plasma for Fractionation (PfF), is estimated to be less than 15% of what is needed to cover global IgG consumption. It is worth noting that work is on-going, including within the SUPPLY project, to determine the actual contribution of European plasma to IgG availability globally, as there is uncertainty in to what extent the higher IgG content in plasma sourced in EU is actually accounted for. It has become very clear from the SUPPLY project that Europe has more low-frequency donor plasma and thereby a higher content of IgG compared to paid, high-frequency US donor plasma.

Now, however, and with an enhanced focus due to the major impact of the COVID pandemic, the possibility of a more integrated policy on the availability of PDMPs in Europe, with the ultimate aim of achieving strategic independence, is being explored.

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2. Position Paper. Overview

This Position Paper gives insights on how products derived from European plasma are distributed and how they contribute to national and European strategic independence.

The intention is that this Position Paper will contribute to the final SUPPLY recommendations for future actions and benefits from the information and conclusions included in key SUPPLY project surveys and reports including, *inter alia*:

- D4.2 Analysis report: policies and/or legal frameworks on plasma collection and PDMPs management;
- D4.5 Assessment report on Plasma and PDMPs economics and tenders;
- D6.1 Report on the results of: "A comparative analysis on the current use of immunoglobulins in individual countries: A clinical programme";
- D3.3 Report on the results of the "characterization of the waste of recovered plasma and missed opportunities for plasmapheresis in European Union";
- D3.6 Recommendations on plasma donation quality ;
- Specific interviews with chosen EU and non-EU countries.

This Position Paper focuses on the following aspects:

a. Degree of **commitment in obtaining PfF** as a strategic priority for the EU, its MS, and European blood establishments (BEs).

b. **Level of collaboration** amongst all stakeholders when developing strategies, including their involvement in the definition of agreements and tenders for the selection of fractionators and/or plasma management procedures.

c. **Modes of supply of available products from national and European plasma**, as well as the procedures that define the needs and assess the contingency plans in force.

3. Factors influencing the availability of PDMPs

The availability of PDMPs, in particular of IgG and albumin, depends largely on plasma collection, but it is also directly related to the involvement of different stakeholders identified at different steps of the provision process.

Firstly, regional, national, and European authorities are central in defining legal frameworks for national plasma source procurement. These can be effectively translated into practical arrangements, such as: realistic needs assessment, specific resources allocation for plasmapheresis programmes, evidence-based use scenarios, efficient management of surpluses, and adequate contingency plans in the event of shortages. However, very few MS do so on an ongoing basis (e.g. only 36% of MS declare having an active plasma collection programme defined in national policies or legislation, and only 45% of MS declare having a shortage management programme in place). Therefore, the transmission of information to donors and citizens is inconsistent and insufficient for BEs to implement efficient apheresis plans.

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Secondly, the types and volumes of PDMPs obtained from the fractionation of the plasma collected by the BEs vary depending on the characteristics of tenders and agreements in place in every country. These tenders and agreements are managed by a range of different bodies: BEs and/or hospitals themselves, central national purchasing agencies for health materials, or specific agencies for the provision of pharmaceutical products. Only in a few cases are organisations in charge of both plasma donation and primary processing of the plasma obtained involved in the management of the related tenders and agreements, and/or in the distribution of the final PDMPs. Tenders and/or agreements may be local, regional, or national in scope, and do not always take into account important factors such as protein yields or recovery percentages. Far from all PDMPs are returned to the country of origin of the plasma. When they are, albumin and IgG are always included, and some other PDMPs may be added, such as: subcutaneous IgG, Prothrombin complex, Factor (F) VIII, FVIII / von Willebrand F, FIX, Antithrombin III, Alpha1-Anti-trypsin, Fibrinogen, etc.

Finally, other factors having an impact on the availability of PDMPs are those related to their use. There are numerous local hospital initiatives and contingency plans, but still very few agreed as regional or national guidelines, which, if in place, could support common policies and strategies.

In those countries where a close relationship exists between the prescribers of Ig and other stakeholders in the plasma value chain, there is better management and insight on their use. This is a very important aspect in achieving self-sufficiency[1] and sustainability.

Tender Models

An overview of tender models used in Europe is presented below. The two generic models implemented in Europe are presented. However, each of them has different variants observed in each country where it is currently in place. Information gathered throughout the SUPPLY project, as referenced above, is used to provide a synopsis of the perceived strengths and weaknesses of each model.

1. Direct Sales Model

The main aims are defining a price for the sale of plasma. PDMPs are, on the other hand, typically purchased through the country´s specific mechanisms for purchase of pharmaceuticals. The price for the purchase of the PDMPs can, in some cases, include the specification or link the percentage of return of PDMPs from the original local plasma.

Direct sales of plasma is a simple and quick model to implement and ensures that the plasma is used for manufacturing of PDMPs and not wasted. The revenue received through the plasma sales typically covers costs for plasma collection and may bring financial support to those hospitals or BEs collecting the plasma. However, direct sales of plasma without any arrangement or link to return of PDMPs to the country of origin, or even to the European market, is not guaranteed to have a positive impact on strengthening domestic or European strategic independence, and it can result in the loss of public

[1] WHO Expert Group. Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD). Vox Sang. 2012 Nov;103(4):337-42. doi: 10.1111/j.1423-0410.2012.01630.x. Epub 2012 Jun 13. PMID: 22690746.

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control of a raw material considered as critical for the market. Another weakness of the direct sales of plasma without link to return of PDMPs is the difficulty to explain with transparency to donors and citizens the complex procedure and implications of the sale. A secondary effect is that if plasma is sold as a commodity in this way, the price will be set according to supply and demand and may, in some instances, especially when demand is high, result in even higher purchase prices for PDMPs to cover the increasing cost of plasma. Some countries following this model report a dissatisfaction with this model based on the price of plasma being too low and not regularly updated, as well as a lack of inclusion of relevant stakeholders, specifically BEs, in the tender process.

2. Toll Fractionation Model / Contracted Service Model

This is based on payment for fractionation of domestic plasma and the subsequent return of PDMPs obtained. This is frequently reported as a preferred high-value model, as tenders that enable the return of PDMPs to the country or region of origin ensure traceability, motivate citizens to donate plasma for the implicit local benefit, and may demonstrate epidemiological benefits. It can have a positive impact on social cohesion through its transparency, and on sustainability if economic savings are achieved or whether a significant impact on market prices is reached. Weaknesses include: difficulty in obtaining contracts for smaller plasma volumes, limited availability of some PDMPs depending on the contracted fractionator, which can also impact the management of surpluses to improve the global efficiency and availability. It involves additional work for BEs, and the allocation of more resources aimed to handling the agreements for the fractionation process. The complexity of these kind of tenders makes litigations a risk that can delay the awarding procedure.

3. Challenges common to tenders

Overall, the participation of relevant stakeholders, e.g. BEs, in the definition of tenders and agreements is poor and ambiguously defined. This causes, on the one hand, the distancing from clinical practitioners, and on the other hand, it hinders the possibility of fractionating plasma more efficiently so to obtain more useful products and optimise the use of surpluses.

Litigations are quite common at some stages of tender procedures making the organisation of PDMPs provision even more complicated. This litigation frequently delays the award of contracts, negatively impacts the availability of local products, and increases the overall costs.

Legal uncertainty due to different interpretations of certain court cases, related in most cases to aspects such as competition within the free market, can negatively impact the management and effectiveness of tenders and agreements.

Tenders and/or agreements do not always take into account important factors such as protein yields or recovery percentages. IgG content differs significantly between donations, and should be taken into account when tendering, noting that IgG content in European plasma pools with different background in donation frequency could differ by over 10% and 20-30%more IgG can be recovered from high IgG concentration recovered plasma than from very high frequency (US) source plasma.

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Strategies for the appropriate allocation and usage of IgG need to be based on best practice evidence, and real-world experience. Relevant research needs to be supported and conducted. Clinical guidelines are an important part of this allocation framework, but are mostly based on efficacy assessed through clinical trials on limited populations. Real-world experience, drawing on larger post-registration surveys, assessments of patient Health Related Quality of Life (HRQoL) and estimates of latent demand[2,3] are needed to construct a holistic picture of the real and projected demand for the various indications of IgG. All the above should be accompanied by health technology assessments taking into account current and future alternatives to Ig.

In those countries where a close relationship between the Ig prescribers and other stakeholders exists Ig , there is better management and insight on the use of Ig as well as on the planning of their provision both from domestic plasma and/or market purchases. This is a very important aspect in achieving strategic independence and sustainability.

[2] Farrugia et al Vox Sang. 2022; 117(2): 208-219, Stonebraker JS Vox Sang. 2018 Apr 20. doi: 10.1111/vox.12651
3 Brand A, De Angelis V, Vuk T, Garraud O, Lozano M, Politis D; European Mediterranean Initiative for Transfusion Medicine. Review of indications for immunoglobulin (IG) use: Narrowing the gap between supply and demand. Transfus Clin Biol. 2021 Feb;28(1):96-122. doi: 10.1016/j.tracli.2020.12.005. Epub 2020 Dec 13. PMID: 33321210.

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European strategic independence for PDMPs

1. An achievable goal in the short term.

The **contribution of European plasma** to the availability of PDMPs in Europe has been historical and significant, but uneven across countries. During the last decades some events, such as the opening to the global market, have caused a certain **"detachment",** in some countries, from playing an appropriate role in the supply of PDMPs.

The European blood donation system is fundamentally based on Voluntary and Unpaid Donation (VNRBD). This system has proved to be very strong, rooted and effective for many years, as well as being a phenomenon of high social cohesion for many millions of European citizens. More than 20,000,000 whole blood donations are collected in Europe yearly being self-sufficiency for blood components an unquestionable reality for many decades. It is also worth noting that the volume of source plasma collected by the public sector in the EU increased by a **strong 15.6%** per year between 2000 and 2021 while the volume of source plasma collected by the private sector grew by **10.6% annually** over the same time period[4].

This is in clear contradiction with the frequent statement that only a paid-based plasma donation system can guarantee the continued supply and self-sufficiency of PDMPs. The overall European background, and the individual experience of some MS at different historical moments, including the current one, shows that achieving a high degree of sufficiency to get the strategic independence through VNRBD is achievable; maintaining thus a long, successful, and proudly embraced behavior by citizens.

2. Understanding Regional and National differences

According to the Marketing Research Bureau, in 2020 Europe contributed 8.3 million litres of plasma to the total estimated 14 million litres of PfF required by Europe, based on current usage of IgG as the driver for the plasma need. Of these, 3.4 million litres came from recovered plasma and 1.4 million litres came from source plasma from public centres, and 3.5 million litres are classified as source plasma from the private sector. Based on these figures, additional 5.7 million litres of PfF are required by Europe: of which 4.5 million litres are required by the EU27 MS. Based on current national IgG demands (estimated range 20-200 g/1,000 population), this means that 11-13 litres of European public source plasma /1,000 inhabitants are required.

[4] Data & Analysis of Immunoglobulin Supply and Plasma Requirements In Europe 2010-2021.Marketing Research Bureau 2023 MRB Accessed Nov 26 2023

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It is of critical importance that national commitments to collect sufficient volumes of plasma to meet the optimum plasma-related requirements of populations are accompanied by sufficient control/monitoring over the collection-PDMP production-utilisation chain, ideally through legislative guarantees, to ensure that the patient population needs are met. This commitment and control should be built on an EU legislative framework which enables European strategic independence.

Currently the degree of commitment of public centres in collection of PfF is variable, and in many cases insufficient, ranging between 1.5 and 23 litres / 1,000 inhabitants / year for the different MS.

A very significant fact is that 95.7 million European citizens (from 17 European Countries, including 10 EU Member States) do not have active plasmapheresis programmes. Besides that, there are still some MS that do not utilise the plasma collected in fractionation programmes for different reasons (low volume, epidemiological reasons, etc.). Their inclusion in fractionation policies would also have a positive effect on the overall European sufficiency.

The efficiency with regards recovered plasma is positive (in most cases the volume of plasma obtained from each unit of whole blood collected in Europe is between 250 and 280 ml). One of the negative aspects is the progressive, but appropriate, decrease in whole blood donation due to the lower use of red blood cells, making the accurate estimation of its future supply uncertain.

In the SUPPLY project report on: "*Characterisation of the waste of recovered plasma and missed opportunities for plasmapheresis in European Union",* a range for improvement in the recovery of plasma from whole blood has been estimated at around 2%, which even though quite marginal is still positive**.** The collaboration between/among different countries to ensure the correct management of plasma, which is often difficult for smaller MS, is another point to be taken into account in improving European sufficiency.

The final result of all activities and discussions held during the SUPPLY project life-time is not questionable: the absolute priority of increasing the collection of plasma by plasmapheresis from voluntary and unpaid donations in Europe to attain strategic independence.

When arranging plasma donation programmes, some other points should be taken into account:

- In almost all cases there is an important commitment from the BEs to obtain sufficient PfF and a positive willingness to donate from the citizenship. The most successful countries, in terms of plasma donation recruitment programmes, are those that already had a significant number of whole blood donors who are referred to plasma donation as appropriate depending on the needs for red cells components.

- Transparency in communicating to citizens about the terms and conditions of tenders and agreements, and the foreseen, or already in place, formats of public-private collaboration is essential. In this sense, the appropriate training of staff involved in both the recruitment of plasma donors and plasma donation itself is essential to ensure accurate information is communicated to donors in order to build and maintain trust and loyalty.

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- Despite their critical role in the plasma value chain, BEs do not always receive the necessary support or commitment from their authorities, often translated into insufficient economic resources specifically allocated to plasma donation. Given the inherent value to patients and citizens, and the sound economic reasons underpinning decisions to fund BEs appropriately, the reasons for this lack of support are difficult to justify or specify. However, they appear to be linked to differences of opinion, interpretation, and knowledge among the stakeholders rather than based on economic assessments. Conversely, the countries providing sufficient resources for public plasmapheresis programmes to meet targets are achieving very positive results (e.g. Denmark, Belgium, and The Netherlands).

- The document issued in October 2023 and prepared by the Presidency of the EU, *"Resilient EU2030: A future oriented approach to reinforce the EU's Open Strategic Autonomy and Global Leadership",* considers plasma as a critical product. The pivotal importance of this consideration may represent the beginning of the inclusion of PfF within the essential products that respond to a different legal definition within the global market.

CONCLUDING REMARKS

In conclusion the core of debate lays on the necessity to **increase the donation of plasma of public origin to achieve the strategic independence for PDMPs provision.** The majority of the countries consulted within the project deem it a feasible and achievable goal. In fact, several countries are close to accomplishing this, so it is reasonable that others with similar development and cultural environments can be similarly successful. The proposal for a new Regulation of the European Parliament and of the Council of the European Union also encourages a strong public and non-profit involvement in the provision of Substances of Human Origin (SoHO).

In addition, the SUPPLY consortium highlights the following pivotal considerations to be taken into due account at national and European levels:

- Plasma is a **critical medical raw material and a public resource** that requires strategic management. The fact that PDMPs from plasma collected in EU MS have to be used first in Europe, especially when far from self-sufficiency, must be unquestionable. It must therefore be guaranteed that this can be done within forthcoming European legal frameworks and that no obstacles in this regard are present.

- A partial but significant amount of the PDMPs made from national plasma return **to the country itself.** Different types of agreements between Public plasma collectors and fractionators are in place, a disparity which directly influences both the efficiency of plasma fractionation procedures and the real return of PDMPs to their countries of origin. One of the reasons for this disparity in agreements is the lack of clarity and transparency around the management of these fractionation agreements. It must therefore be ensured the provision

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of legal clarity and transparency to these agreements including the involvement of all stakeholders.

- European countries should offer equitable health service to citizens. In order to support its sustainability, increases in both the levels of products derived from public plasma and the participation and responsibility of medical professional experts should be fostered and supported. In particular, in order to significantly contribute to sustainability and to clearly avoid prescriptions differences, it must therefore be ensured that clear indications are defined in terms of products distribution, use, and monitoring. .

- In some European jurisdictions, commercialising public plasma is not leading to an enhanced and evidence-based usage of the products involved. Moreover, it can have negative implications for establishing a commitment by donors and other community stakeholders in the plasma procurement process. Therefore, it is fundamental to introduce measures which link plasma collected domestically by BEs and other institutions to the usage by the Public health sector of products manufactured from this plasma.

- Litigation is a major obstacle to developing efficient tender procedures. Legal challenges can delay the availability of PDMPs from European plasma and can have a negative impact on sufficiency. It is time to assess and implement general agreements in public-private collaboration avoiding unnecessary and dangerous competition, which help to establish equitable procedures to guarantee the timely distribution of these products in a fair and just way for both parts. Therefore, a framework agreement would help the resolution and smooth development of further specific tenders and agreements.

- The European public donation system has faithfully fulfilled the needs of citizens in recent decades regarding blood and blood products for direct transfusion. It could not be otherwise in the case of plasma donation if public blood systems are awarded that confidence with the appropriate resources and the efficient functional frameworks. The argument that blood donation and plasma donation should be considered under a different prism has been proven unrealistic. In most cases donors do not differentiate their feelings when helping patient, and the effectiveness of regular donors moving between different types of donation according to the needs of patients has been demonstrated. The donor base should be increased by facilitating plasma donation in a similar way to other types of donations.

- Transparency about the private-public agreements when it comes to inform and recruit plasma donors. This topic should be taken into consideration in staff training to contribute to strengthening donors trust and loyalty (for example, through material such as: IPFA donor information standard).

- The motivation of donors can also be increased if the beneficiaries of the donation are closer to their natural environment. The implementation of measures able to help ensuring the

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return of PDMPs to the national or European scenarios can have a positive impact on citizens' willingness to donate plasma.

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