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REPORT

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Plasma collection and supply in Europe: Proceedings of an International Plasma and Fractionation Association and European Blood Alliance symposium

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Abstract

At the symposium organized by the International Plasma and Fractionation Association and European Blood Alliance, experts presented their views and experiences showing that the public sector and its blood establishments may strengthen the collection and increase the supply of plasma using the right strategies in plasma donor recruitment, retention and protection, scaling-up collection by increasing the number of donors within improved/new infrastructure, supportive funding, policies and legislation as well as harmonization of clinical guidelines and the collaboration of all stakeholders. Such approaches should contribute to increased plasma collection in Europe to meet patients' needs for plasma-derived medicinal products, notably immunoglobulins and avoid shortages. Overall, presentations and discussions confirmed that European non-profit transfusion institutions are committed to increasing the collection of plasma for fractionation from unpaid donors through dedicated programmes as well as novel strategies and research.

Keywords

fractionation, patients' needs, plasma, plasma-derived medicinal product, supply

Highlights

- Plasma donation continues to be the only source from which to prepare plasma-derived medicines (immunoglobulins, albumin and coagulation factor concentrates).
- The supply of plasma-derived medicines in Europe depends on plasma collected both within Europe (approximately 63%) and outside Europe (approximately 37%).

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- Implementing best practice regarding voluntary unpaid donor recruitment and plasma collection, scaling-up collection capacity and providing a supportive legislative and financial framework are key parameters for achieving European strategic independence in plasma supply.

INTRODUCTION

The International Plasma and Fractionation Association (IPFA) and the European Blood Alliance (EBA) organized a symposium 'Plasma Collection and Supply' on 15 and 16 March 2022 in Amsterdam, the Netherlands to discuss how the public sector and its blood establishments (BEs) can strengthen the collection and increase the supply of plasma to meet European patients' needs for plasma-derived medicinal products (PDMPs).

After the opening address by **Leni von Bonsdorff (IPFA), Pierre Tiberghien (EBA)** welcomed the participants and emphasized that reaching an adequate level of self-sufficiency in plasma for fractionation (PfF) to ensure European strategic independence is a key factor in sustaining the long-term supply of PDMPs to meet the needs of patients in Europe. The current dependence on PfF collected outside Europe is not sustainable and is associated with potential disruptions related to geopolitical or infectious threats and competition for the resource. During the waves of the COVID-19 pandemic, the high prevalence of the disease in the population, physical distancing measures and other restrictions on mobility led to a decline in PfF donations due to reduced donor availability and absenteeism of plasma collection staff. The increasing demand for convalescent plasma for COVID-19 for investigational therapies has posed an additional challenge to the plasma supply, particularly in the United States [1]. The PfF supply can be augmented by very frequent plasma donations per donor or by increasing the number of donors who donate plasma less frequently. High-frequency plasma donation, necessarily remunerated, relies on a narrow donor base and mostly on donor financial uncertainty and vulnerability. Such a donation may pose a risk to donor health, a risk of acute disruption in plasma collection in the presence of unforeseen adverse effects and a risk to the availability of blood products by erosion and/or fragmentation of a community-based donor population and competition for resources [2]. Lastly, plasma collected from high-frequency donors will be of lesser quality as it contains reduced protein concentrations including immunoglobulins (IGs). Low-frequency plasma donations, feasible without financial incentives/remuneration, rely on a large donor base with reduced individual donor burden and are more protective regarding health and ethics. It is based on a single integrated donor base supported by not-for-profit BEs across Europe, the same safety setting, management and donor haemovigilance.

PLASMA COLLECTION AND FRACTIONATION IN EUROPE: PAST, PRESENT AND FUTURE

Paul Strengers asserted that most of the plasma collected in Europe until 1993 was obtained from whole blood donated by local voluntary non-remunerated blood donors and fractionated largely by public organizations. PDMPs produced from European plasma covered largely the patients' needs. Prior to 1989, PDMPs were exempted from medicinal regulations and were licensed and overseen only by national authorities. In 1989, PDMPs have become medicinal products and hence followed the related regulations and authorization systems. In 1993, 20 not-for-profit and 11 commercial fractionation plants were active in Europe. By 1993, cases of viral transmission via plasma and PDMPs increased necessitating improvements in their quality and safety. An open market for PDMPs was established, while plasma collection remained the responsibility of national authorities. The introduction of regulatory and quality requirements increased the cost of plasma fractionation and raised liability risks, leading to the closure of many public fractionation plants. In the period 1990–2000, only three public and six commercial fractionators could survive in Europe. The European Commission (EC) adopted directives governing blood and blood components including source plasma. In an open European Union (EU) market, PDMP producers faced financial pressure because some products were considered generic and could be marketed when market protection had expired, prices were reduced by competition, there was insufficient financial compensation due to limited product pipelines and there were high costs and risks of developing new products. Moreover, the use of PDMPs has been hampered due to increasing pressure on healthcare costs. Small companies could not compete with larger ones active in international markets. As a result, between 2000 and 2022, only one public and six private fractionation companies remained active in Europe.

Currently, PDMPs are unevenly distributed globally, and their prices are rising. Two products—IGs and albumin—determine the demand for plasma. In addition, there are also concerns about the lack of regulatory harmonization of plasma supply and PDMP manufacturing worldwide and finding ways to cover the 15%–20% plasma shortage due to the COVID-19 pandemic and to improve plasma wastage and the limited access to PDMPs for all patients.

The worldwide growth of the PDMP-dependent patient population and the development of new therapeutic options will dictate the evolution of PDMP treatment in the future. A new generation of known recombinant products with an extended shelf life and less immunogenicity, as well as new recombinant substitutes and products, are expected to be developed. Global markets for polyvalent IGs are expected to continue to grow, highlighting the need for harmonized and updated guidelines for their clinical use. Many guidelines [3–6] recommend the use of IGs based on the evidence of clinical effects in diseases with often unknown pathology where the mechanism of action of IGs is mostly unclear or hypothetical when it comes to immunomodulation. However, the relatively small

number of manufacturers might imply a future risk of PDMPs supply such as unforeseen production collapse, reduced availability of products, monopolistic behaviour, higher prices, less innovation in production technologies and the risk of non-introduction/withdrawals of PDMPs in selected markets. There is also a risk of inadequate management of plasma supply resulting from the increasing requirements and growing discrepancies between the supplies of recovered and source plasma. The impact of the COVID-19 pandemic has highlighted the need for a balanced plasma supply, which will increase significantly.

MARKET LANDSCAPE FOR PLASMA AND IMMUNOGLOBULINS

As presented by **Matthew Hotchko**, the global plasma protein market has shown steady growth of 7.4% per year from $4.8 billion in 1996 to $26.6 billion in 2020. Sales of IGs achieved the fastest growth in the last 5 years in both volume and price, Albumin sales also grew, but at a slower pace, reflecting steady volume growth driven by China, although prices declined. Demand for plasma-derived Factor VIII and IX has decreased due to the presence of recombinant and non-factor therapies and growing competition showing a large decline in high-income countries but an increase in emerging markets. Sales also decreased for PDMPs with competition from recombinant or non-plasma-derived products but increased for those without competition or those prescribed for acute blood loss.

Since the 1990s, IGs have been the main driver of the global plasma market, so manufacturers balance plasma needs according to forecasts of IGs sales. The only way to increase (or decrease) their supply is to collect and fractionate more (or less) plasma. Albumin demand grew more slowly while the demand for IGs grew the fastest of all PDMPs. To meet the expected demand for IGs in the last decade, companies have been collecting plasma with an average growth of 8%–9% per year which was severely affected by the COVID-19 pandemic. Global plasma volume fell from 69 million litres in 2019 to 59 million litres in 2020, which is a 14.7% decrease.

However, the origin of plasma did not change globally. In 2020, most of the plasma (67%) was from North America (99% from the United States), 18% from Asia-Pacific (75% from China), 14% from Europe and the remaining 1% from Latin America, the Middle East and Africa. North America and Asia-Pacific produced enough plasma for their internal use [7]. In Europe, the need for additional amounts of IGs produced from PfP collected outside Europe, mainly in the United States, arises from an imbalance in which Europe consumes 25% of the world's IG supply but collects only 14% of the world's PfF. In 2020, a total of 8.3 million litres of plasma were collected in Europe which was 9.4% less compared to 2019, while IG use and demand continued to rise. Consequently, the self-sufficiency of Europe dropped by 8% from a deficit of 32% in 2019 to 40% in 2020. The required increase in plasma collections to meet the IG needs in Europe was 4.3 million litres in 2019 and grew to 5.6 million litres in 2020.

DONOR RECRUITMENT, RETENTION AND PROTECTION

Karin Magnussen reported that donations of whole blood or plasma have some common but also different positive and negative effects elicited during the donation. From the perspective of both types of donors, the overall atmosphere with welcoming, kind, respectful and attentive professional staff acknowledging donors and their donations is perceived as positive.

Some plasma donors perceive plasma donation as being less physically demanding compared to whole blood donation and are associated with a lower likelihood of deferral due to certain aetiologies (e.g., travel history to malaria-endemic country). Donors understand that there is a need for plasma to help patients and sometimes the increased donation frequency helps to make donations a routine. Increased frequency also eases social interaction with staff and fellow donors. Donors appreciate easy accessibility to the donation facility with the possibility to park a car and access to drinks and snacks. The donors, however, do experience some negative effects, including time constraints due to the longer duration of plasmapheresis compared to whole blood donation. They also can experience adverse events such as citrate toxicity, needle injury and fainting. It is, therefore, crucial to take into account the donor's blood volume when assessing their suitability for plasma donation in order to prevent circulatory adverse reactions. As donors are expected to donate more often, they can sometimes feel exploited. Unavailable car parking is also indicated as a negative point. Donors enjoy being helpful and personalized handling of donors is recommended to improve the plasma donation experience.

Christian Erikstrup showed previous studies indicating that frequent plasma donation may be associated with decreased levels of proteins, IGs and changes in other biochemical parameters in the blood [8, 9]. There is, however, a lack of data on the clinical effects of plasma donation on the donor's health. One study concluded that long-term intensive plasmapheresis was safe when donors were monitored according to the study protocol, although 16% of donors were excluded when laboratory parameters fell below cut-off values [9]. It is unknown what constitutes an acceptable decrease in blood IG levels and whether a simple deferral of donors with low IG/protein levels is a sufficient measure. When analysing donor health in studies, one of the challenges is to mitigate the 'healthy donor effect' that can introduce selection bias due to the health criteria that donors must meet for plasma collection. Another study showed that a personalized approach to the collection of increased plasma volume does not increase the incidence of hypotensive adverse events [10].

Is it adequate to solely consider acute or subacute events, such as hypotensive reactions, in order to evaluate the safety of donor health [11]? Plasma donation may lead to long-term effects (e.g., increased risk of infection or cardiovascular disease) not captured by the standard monitoring of acute and subacute adverse events [12]. Adequate research is needed to determine the long-term effects of donating plasma on the health of the donor. To obtain relevant donor data for such analyses, the databases of blood and plasma

centres and digital health data in public health registries must be linked. The lack of comprehensive surveillance of donor health performed at the European level indicates a need to improve European plasma donor vigilance.

Marloes Spekman asserted that in 2020, Sanquin, the Netherlands opened a proof-of-concept plasma-only donation centre in Utrecht (the Powerbank), where they started recruiting donors directly for plasma donations. Unlike most traditional Dutch donation centres, the Powerbank is in a highly visible location (shopping mall) and is designed to create an efficient and hospitable experience for donors. A survey showed that both Powerbank's plasma donors and plasma donors from a nearby traditional donation centre were similar in terms of gender, education and household composition. However, Powerbank donors were slightly younger on average and had a higher proportion of working donors and fewer students and retirees. Results from qualitative focus group discussions showed that donors liked the look and atmosphere of the Powerbank, as well as its accessibility, service level, food, efficiency and loyalty programme. Preliminary conclusions are that the Powerbank attracts a population of donors similar to those in traditional blood centres, though with a higher proportion of the younger and actively working population. New generations of plasma donors could benefit from highly visible locations, efficiency (i.e., more donor-focused processes), high service levels and a non-clinical atmosphere at the donation centre.

INFRASTRUCTURE AND SCALING-UP PLASMA COLLECTION

Stuart Chesneau indicated that **the Australian Red Cross Lifeblood** has set a fast-track donor panel target to achieve plasma collection targets of approximately 1300 tonnes by 2025 and to provide a cushion against the ongoing impacts of COVID-19. The panel growth target is from 502,000 to 600,000 donors in 2022–2023. Some existing blood collection sites have been refurbished or relocated, and a small number of fixed sites are new. Optimization goals at some locations are to increase both whole blood and plasma collections by extending business hours and increasing staffing and appointment availability. Regional sites will increase predominantly plasma collections and efficiency within existing staffing at fixed sites. Mobile and pop-up sites will help to increase whole blood donation. In terms, 50% of fixed sites in metropolitan and suburban areas will provide 70% of the collection with a donor panel that can support plasma growth. Donor awareness and marketing are improved with a strategy of 'brand behaviour' to reframe blood donation as a community activity. The plasma donation 'game-changer' campaign has been launched highlighting that donated plasma can help more people more often than donated whole blood. In Australia, a newly implemented programme aims to provide a personalized customer experience by focusing on 'the moments that matter'. This approach aims to make a significant impact on a donor's decision to donate again while prioritizing donor retention and reducing the number of lapsed donors. Tools based on machine learning and artificial intelligence are also evaluated to deliver communications via the donor's preferred channel and to propose a tailored approach to the donor journey/donation lifecycle stage. Currently, self-service makes up 70%+ of total appointments predominantly done via the mobile phone app.

Judy Jones showed that in 2019, the **Canadian Blood Services** (CBS) developed a strategic plan to 'Ensure a secure supply of Canadian plasma for immune globulin' [13]. At that time, the rate of usage for IG products had increased by 111% over the past 10 years, with the IG consumption rate of approximately 219 g per 1000 population. The COVID-19 pandemic has further elevated the risk of plasma supply sufficiency by exposing domestic vulnerabilities. In 2022, the Canadian plasma sufficiency rate for the demand of IG was 15%. The changing dynamics in Canada with the growth of commercial parties in a competitive market have added pressure to the system. Supply constraints in the early stages of the pandemic were mitigated through the pre-emptive purchase of additional inventory. With the elevated risk-increasing pressure on the Canadian security of IG supply, a refreshed risk-based decision-making exercise was conducted. Risk modelling suggests a target of at least a 50% level of self-sufficiency that balances the supply risk and ensures sufficient IG to meet all needs of critical patient groups. In that perspective, CBS started over 3 years ago a plasma division for stand-alone plasma locations. The objective is to establish 11 specialized locations for collecting source plasma by March 2024, with each site collecting a total of 20,000 L of plasma. Additionally, CBS plans to extend the collection capacity within the current mixed centres. To support these goals CBS developed a donor recruitment strategy based on recruiting whole blood donors to donate source plasma, recruiting directly to plasma donation, retaining source plasma donors and increasing the donation frequency.

According to **Bjarne K. Møller**, the challenges to attaining or enhancing self-sufficiency in the supply of PDMPs in **Denmark** stem from various factors. These include navigating through turbulent periods of heightened clinical demand and market economy, volunteer-based donor recruitment, ensuring a balanced geographical distribution of apheresis sites, managing the complexities of political decision-making in the development of national tenders for contract fractionation, as well as navigating political, legal and financial constraints. Therefore, it is essential to enhance the national structure and professional organization of blood centres, while also implementing 'professional recruitment practices'. Currently, volunteers are recruiting donors at blood centres that are not evenly geographically distributed over the country but are placed in five regions. There are only two plasma-only centres in Denmark. The national contracts for fractionation place political, economic and legal constraints on plasma collections. Right now, most of the Danish donors are between the ages of 30 and 40 and men, indicating the possibility and need to include donors from other age and sex groups in the plasma donor pool. In addition, focusing on the quality of plasma donation drives helps retain donors, whereby communication about why donations help patients is the key to success, the frequency of donations decreases. In the future, Denmark is planning to build more plasma-only centres and disperse them geographically.

Peter Verheggen indicated that **the Netherlands** has set up a target to increase plasma collections to 450,000 kg in 2025. To achieve this goal, it is necessary to reduce plasma production costs and bring them closer to selling prices. The collection has to increase to 20,000 donations in their plasma-only centre and to 15,000 donations in the hybrid centres per year. The demand for whole blood of about 400,000 units per year is expected to remain stable. The goal of the Powerbank (plasma-only centre) set up in 2020 was to reach a donation frequency of 5 annual donations per donor, by 4000 unpaid donors to achieve a total of 20,000 source plasma donations. Several process modifications have been implemented, such as conducting post-donation haemoglobin measurements and eliminating the determination of blood groups. Additionally, process automation has been introduced, including online appointment scheduling and questionnaire submission. Costs reduction is highly dependent on the number of donors and the donation frequency, as was also observed in the pilot Powerbank. It looks that recruiting new plasma-only donors and thereby increasing the number of donations is essential to lower the costs. During the pandemic, it was not possible to recruit the desired number of donors, only online recruitment was possible. The regular recruitment programme started again in 2022 as the online activity oriented to the recruitment of the non-Western local population. The loyalty programme enhances the plasma donation frequency (7.0 donations/year) when compared with donors who do not participate in this loyalty programme (2.6 donations/year).

Gerard Gogarty outlined how the National Health Service Blood and Transplant (NHSBT) in **England** built a completely new plasma operating system from scratch when it began collecting COVID-19 convalescent plasma (CCP) in 2020 to support trials of its use as a therapeutic option to treat the disease. To collect and process the CCP an infrastructure with more than 40 collection sites was built and the supply chain was updated. Some of these CCP collection sites started collecting PfF by NHSBT in 2021 when the United Kingdom lifted its ban on the collection of United Kingdom-source plasma for the preparation of PDMPs, particularly IGs. NHSBT is committed to delivering a world-class plasma service to support patients in England with an initial target of 20% IG self-sufficiency, building a foundation to meet the future ambition of 30% self-sufficiency and beyond. Today, the United Kingdom consumes a significant quantity of IGs, all of which are derived from plasma collected in Europe and the United States. As the United Kingdom builds self-sufficiency in IG medicine, it can reduce the amount it needs to purchase on the international market. The NHSBT, along with its European partners, holds the perspective that the United Kingdom's reintroduction of plasma for medicinal purposes can yield mutual benefits. It can enhance the United Kingdom's self-sufficiency in IG supply while simultaneously decreasing the reliance of European nations on plasma imports. NHSBT is aiming to collect around 1 million litres of plasma between 2022 and 2026, which will ease the pressure on the European plasma supply.

Polonca Mali said that **Slovenia** entered a contract for the fractionation of plasma with a manufacturer that performed viral inactivation of PDMPs in 1991. Since then, the national toll fractionation of mainly recovered plasma (95%) is ongoing. During 2004–2021, the number of plasmaphereses increased, but self-sufficiency remains challenging. IGs are the main driver of plasma supply, though evidence-based medical indications for Ig therapy are missing and the late COVID-19 effects on plasma supply can be expected. A capacity-building 2 years programme for BEs has recently been launched, which foresees among others: adjusting opening hours and ensuring effective collection and equipment utilization. This programme has been enabled through the Emergency Support Instrument (ESI) funds made available by the EU to support countries facing the COVID-19 crisis and to collect CCP [14].

According to **Mazen Elzaabi**, Laboratoire français du Fractionnement et des Biotechnologies (LFB) in **France** fractionates recovered and source plasma collected by the civilian and military transfusion public services (Etablissement Français du Sang—EFS and Centre de Transfusion Sanguine des Armées—CTSA, respectively). LFB distributes PDMPs produced from this plasma primarily on French territory. Although 75% of patients are treated with LFB PDMPs, the market share of LFB for IGs in France is 35%. During the COVID-19 pandemic, France also experienced a drop in plasma collection, resulting in a decrease in IGs production and supply to French hospitals (11% decrease in December 2021), followed by increased competition between EU Member States (MS) for IG supply. Due to the impact of production timelines linked to industrial constraints and multi-years hospital contracts, this situation is likely to persist. By opening a new fractionation plant LFB will triple its production capacities. However, there is an ongoing challenge to increasing PfF collections in France. To cope with supply tensions, the EFS and the French Ministry of Health are preparing a 'plasma plan'. This plan is likely to mark a major change in the institution's mission. Linked to this supply tension situation, the National Agency for the Safety of Medicines and Health Products has published a list prioritizing the immunoglobulin indications and has provided 'temporary import authorization' for unregistered IGs.

POLICIES AND LEGISLATION FAVOURING PLASMA COLLECTION

Vincenzo de Angelis highlighted that the EU blood legislation, transposed into national blood laws, regulates the collection of plasma in BEs and plasma collection centres, while EU pharmaceutical legislation is covering the production of PDMPs. The standards within the European Directorate for the Quality of Medicines & HealthCare (EDQM) Guide for the preparation, use and quality assurance of blood components define the collection and quality of plasma, while its properties as source material are defined in the EU pharmacopoeia. Finally, Good Practice Guidelines should be followed during plasma collection and Good Manufacturing Practice during fractionation. The definition of 'voluntary non-remunerated donation' and the compensation for plasma donors remains to be delineated in the EU legislation. Twenty-five EU countries provide some form of compensation for donors covering expenses incurred and recognizing the

inconvenience related to donating. In four EU countries (Austria, Czech Republic, Germany and Hungary), private plasma centres apply for compensation as a fixed rate allowance. Key characteristics of national policies and laws in France, Spain, Germany, Portugal, the Netherlands, Belgium, Slovenia, Hungary, Poland and Italy, show a diversity also in the regulation of plasma collection and fractionation models, remuneration and self-sufficiency. In addition, a lack of infrastructure and cooperation between EU bodies and national authorities are obstacles to achieving strategic independence for plasma collection.

There is a need for supporting EU MS to set up plasmapheresis programmes and to better inform citizens of the critical importance of PDMPs and therefore the need for plasma donations. **Fabio Candura** presented the environment of decentralized, regional-based healthcare governance divided into 16 regions and five autonomous provinces in Italy. Each of them is responsible for the organization and delivery of health services at their local level. The national blood law has made 'national self-sufficiency' a key priority and has been constructed to facilitate the implementation of agreements between the regions and fractionation companies, by including agreement models and procedures. Since 2015, Italy has revisited the number of interregional agreements, moving from two to four agreements with a wider range of fractionators. This made it possible to achieve adequate volumes of PfF collected and further increase PDMP availability while remaining cost-effective. While Italy's plasma system is regarded as one of the most self-sufficient among the EU countries, the regional tendering process is very time-consuming but has resulted in a very significant decrease in costs for fractionating domestic plasma allowing savings that are reinvested in plasma collection.

Françoise Rossi pointed out that a significant amount of plasma collected worldwide, including in both the EU and the United States, is being discarded due to non-compliance with quality standards to enter the fractionation chain [15]. The shortage of PDMPs mostly impacts low- and middle-income countries (LMIC) due to insufficient domestic supply of PfF. Given PDMPs are considered essential medicines, PfF is valued and considered a strategic resource. Small EU MS facing a shortage of PDMPs may decide to either sell plasma to a fractionator or establish a contract for fractionating national plasma into PDMPs in return. Irrespective of the fractionation strategy, BEs should meet several conditions: minimum volume and quality requirements set by the authorities and fractionators and following the EDQM Good Practice Guidelines as the reference in Europe.

The WHO has developed the guidance intended to provide an overview and recommendations for actions to be taken by all stakeholders of the blood systems as a roadmap towards reducing the wastage of plasma and thus increasing access to PDMPs in LMIC [16]. The guidance further highlights the benefits for both the plasma collectors and fractionators of establishing national/regional plasma fractionation programmes. However, this requires, among other things, the engagement of governments, strengthening national/local capacity building and knowledge and close cooperation between plasma collectors and fractionators. Ways to avoid plasma wastage are to be explored, for instance, allowing small EU countries bilateral and regional cooperation in pooling plasma.

Bernardo Rodrigues said that the Services of General Economic Interest (SGEI) are defined as economic activities that public authorities identify as being of particular importance to citizens and that would not be supplied (or would be supplied under different conditions) if there were no public intervention. When the government of an EU MS designates plasma collection as an SGEI and provided it complies with EU competition law, public authorities can provide support to improve plasma collection activities, including dedicated public funding (under specific conditions) or other forms of support such as attributing exclusivity to specific operators. However, these options need to be individually evaluated as they may not be suitable for every EU MS. This applies to all EU MS although other European countries outside the EU may have similar regimes.

MANUFACTURER'S APPROACH

Ramune Sepetiene presented an '**Abbott** Transfusion Health Institute' designed to support BEs and plasma centres in their practical and scientific activities. **Thomas Lenzen** emphasized that **Haemonetics** offers the integration of plasmapheresis devices with donation centre software to overcome risks of errors, non-compliance and safety associated with the manually completed documentation systems in blood and plasma centres. **Stephan Walsemann** presented the **Scinomed** offers of high-quality products and services to plasma collection facilities including plasmapheresis machines and disposables, supporting the validation of machines at customers' facilities and enhancing GMP compliance by connecting apheresis machines to BEs computer systems.

SUPPLY AND USE OF IMMUNOGLOBULINS IN TIMES OF CRISES

The European Medicines Regulatory Network aims to minimize the impact of medicine shortages by working with pharmaceutical companies to resolve manufacturing and distribution issues, sharing information with international partners about alternative sources of supply, seeking input from patients and healthcare professionals on the impact of medicine shortages and supporting decision-making on taking measures to allow alternative medicines or suppliers to be used [17]. EMA publishes information on shortage when it affects more than one EU MS. The Heads of Medicines Agencies and EMA task force on the availability of authorized medicines are designed to function as a 'supply and availability hub' that is tracking progress on the medicine availability and shortage-related activities.

Jean-Philippe Plançon stressed that the shortages of PDMPs, particularly IGs, directly impact patients' quality of life through suboptimal medical care or, sometimes, instant treatment with second-line drugs (e.g., immunosuppressants or corticosteroids). For some patients, absence or delay in access to treatment can mean a loss of

autonomy that might be irreversible. The prioritization of indications for IG treatment places patients in competition with each other, as physicians choose to treat some patients and not others simply because treatment is unavailable.

There is no plasma programme in Romania, and access to PDMPs is also very limited. Patients' organizations in Spain have information on a shortage of IG starting from September 2020, causing delays in treatment, reduced dosages and transfer from IG therapy to plasma exchange (with difficulties in albumin access). The Immunoglobulin Observatory (OBSIG) survey conducted among French patients with autoimmune peripheral neuropathies treated with IGs in early 2022 by the French Association Against Peripheral Neuropathies showed that 30% of patients have problems satisfying their needs [18]. European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN) believes that the rights and ethical principles of both the patients and the donors are equally important and that the protection of plasma donors guarantees the protection of patients using PDMPs.

Cynthia So-Osman presented the BEST# 160 study that started on 1 March 2022 and aims to create clinical awareness of Ig shortage and to gain insight into decision-making on how IGs are used within hospitals. This qualitative study involves the development of surveys targeted to hospital professionals, including conducting semi-structured in-depth interviews on the use of Ig in hospitals (demand side). The study seeks answers to the questions of which clinical specialties most often use IGs and in what way (appropriateness and cost aspects); whether changes in their use are observed; what are the possible causes for reduced IG use; and which strategies are used to reduce the use of Ig in inpatients and outpatients. Aiming for a representative sample from different settings and regions, the survey will interview hospital pharmacists/blood bank providers (Phase I), end users (clinicians [Phase II]) and in the semi-structured interviews (Phase III) selected key persons.

Isabelle Durand-Zaleski emphasized that currently, IGs are the most expensive pharmaceutical products utilized in hospitals, exhibiting an annual increase in usage of 10% in recent years [19]. Spain reported a pharmaceutical expenditure of €92 M in 2012 for IG-authorized indications only [20]. The retrospective survey from 2019 showed that the daily practice of French neurologists with IG treatment for multifocal motor neuropathy and chronic polyneuropathies followed the guidelines from 2010 [21]. In 2012, IG replacement therapy used for secondary immunodeficiency (SID) accounted for 18% of polyvalent IGs use in the Ile de France region with a total expenditure of €9.7 M out of a total of €54 M for all indications. Although the study population did not fully represent patients with all the SID indications, 75% of patients received IG treatment outside the EMA guidelines and the estimated cost of the misuse was €8.2 M for the entire region [22]. Data from Spanish hospitals show a huge variability of IG use for the same indications among the different regions [23]In 2007, IGs administered in Belgian hospitals constituted 17% of hospital drug expenditure where 50%–60% of the IG use was associated with approved indications and 40%–50% was off-label, occurring in unspecified conditions (surgery, orthopaedics and oncology). The study demonstrated a rapid change in indication for investigational IG use, which may account for the high percentage of 'off-label' use and poor documentation on the decision process for compassionate use and obtaining informed consent [24]. Computerized decision support for IG prescriptions showed 74 unique indications included in the final list of appropriate use and the appropriate dosages for each indication were programmed into the final order set, allowing a reduction in dose deviation [25]. The use of IGs represents a typical condition where rapid access to a full Health Technology Assessment is applicable because all the elements of a crisis are present: limited supply, increasing demand, high variability in adherence and high costs [26].

MECHANISMS TO SUPPORT EFFORTS TO INCREASE PLASMA COLLECTION

At the time of the symposium, the revision of the EU legislation on blood, tissues and cells was at the final stage. It was expected that the new EU legislation would strongly focus also on the better management of supply issues including donor protection as well as protecting EU patients from the risk of shortages or sudden supply disruption.

Giuseppina Facco presented that the European Support Instrument (ESI) Grant Project for 'Increasing Capacity for COVID-19 Convalescent Plasma Collection' financed 20 projects in 13 Member States and the United Kingdom, starting from 1 September 2020 and ending between 30 June and 15 October 2021. A total of 67 BEs received funding under this scheme. The overall objective of the granted projects was to improve the ability of public and non-governmental blood services in the EU to collect plasma by plasmapheresis from donors recovered from COVID-19. PDMP This had a secondary long-term benefit of creating conditions for the growth of PfF collection by increasing the pool of plasma donors, opening new collection sites and improving the quality of plasma storage that meets PDMP production standards.

Daphne Thijssen-Timmer stipulated that the COVID-19 pandemic demonstrated the need for coordinated EU-level action to respond to health emergencies and it revealed gaps in foresight, including demand/supply dimensions, preparedness and response tools. The main goal of such a response is to achieve European strategic independence in plasma supply by establishing an equitable, low-risk balance between source plasma collected in the EU by public suppliers and commercial non-EU suppliers to meet domestic demand for IGs and avoid shortages. EBA is working to raise awareness of the need for plasma and is organizing webinars for BEs on how to increase their plasma collection. Together with IPFA, which supports the public sector for plasma strategies internationally, EBA organizes symposia on plasma collection and supply in Europe. Finally, the EBA conducts regular research and exchange of best practices among transfusion institutions. A 2020 EBA internal survey showed that 66% (3%–100%) of the total fractionation plasma requirements for self-sufficiency in the EBA members is collected by BEs or other non-profit facilities. At the time of the symposium, the EBA submitted for EU funding for a project named SUPPLY to analyse the whole plasma

supply chain, aiming to increase non-paid plasma collection and strengthen the resilience of plasma collection by BEs throughout Europe to ensure optimal availability of PDMP's both in the current situation as well as in times of crises. To reach EU strategic independence, especially during times of crisis, all stakeholders including EC, BEs and National Competent Authorities for blood and blood components, need to work together.

We may conclude from the presentations and discussions at the symposium that European non-profit transfusion institutions are committed to increasing the collection of PfF from unpaid donors through dedicated programmes as well as novel strategies and research.

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CONFLICT OF INTEREST STATEMENT

I.D.-Z. reports fees for speaking and taking part in advisory boards from Amgen, BMS, MSD, Pfizer and Takeda.

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