IPOPI 21st PID Forum

Medicine shortages in the EU: the case of immunoglobulin and PIDs

Virtual Event

8th September 13:30 – 15:00 CET

Hosted by MEPs István Ujhelyi (S&D, Hungary)
& Kateřina Konečná (GUE/NGL, Czechia)

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Introduction

On 8 September 2022, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) organized its 21st PID Forum entitled "**Medicine shortages in the EU: the case of immunoglobulin and PIDs**". The online event was co-hosted by Members of the European Parliament (MEPs) **István Ujhelyi (S&D, Hungary) & Kateřina Konečná (GUE/NGL, Czechia)** and moderated by **Johan Prevot,** IPOPI's Executive Director.

During the event, the panellists carefully considered the challenges posed by medicine shortages for primary immunodeficiency (PID) patients. Specifically, participants were informed about immunoglobulin replacement therapies (Ig) and the impact shortages or tensions in the access to these therapies have on PID patients. Accordingly, the myriad of stakeholder perspectives present all proposed concrete actions that could be taken to alleviate this challenge, which was particularly interesting and relevant for the policymakers that attended the event.

The event and its content were endorsed by MEPs István Ujhelyi & Kateřina Konečná, both confirming their political support for the PID community when it comes to promoting their needs and tackling medicine shortages in the EU.

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Welcome & Opening Remarks

Opening the 21st PID Forum, MEP István Ujhelyi (S&D, Hungary) welcomed all speakers and participants and expressed his gratitude to be able to support the PID patient community. He emphasised that medicine shortages are constituting a growing concern for patients, but also for doctors, pharmacies, and healthcare providers. **MEP Ujhelyi started his speech** by giving an overview of the impressive work he conducted over the last three years as a devoted member of the European Parliament's Environment, Public Health and Food Safety (ENVI) Committee, as well as his involvement in improving the Commission's European Health Union initiative.

He explained that in the case of immunoglobulin replacement therapies, it is crucial to guarantee that patients have continued access. Any delays in shortages or changes in medicine stocks will likely cause harm to patients. For that reason, he highlighted the need to further elaborate on how these therapies are being developed, and particularly the importance of plasma collection, the pharma industry as well as hospitals within this process. To conclude, Mr Ujhelyi expressed the key role of this Forum in addressing the problem of immunoglobulin shortages from the perspectives of each stakeholder: the patients, the medical professionals, the industry, and also the policymakers.

Co-host **MEP Kateřina Konečná (GUE/NGL, Czechia)** followed MEP Ujhelyi's introductory remarks by likewise expressing her support for the event and to IPOPI while greeting all the guests and experts present. She pointed out her appreciation for having been invited to the Forum and was keen to learn more about the issue of medicine and immunoglobulin shortages and PID patients.

She expressed that recent initiatives of the European Commission, such as the new proposal for a Regulation on substances of human origin (SoHO), are steps in the right direction. However, there is still much work to be done, which is why awareness of the importance of plasma collection, in particular, is important. Ms. Konečná also added that it is relevant to understand how notification systems and research can support the development of new solutions for the impact on shortages of immunoglobulin therapies.

The MEP concluded by noting that it is crucial to improve the situation for PID patients and make access to their much-needed therapies easier. Ms Konečná emphasised that the correct path to achieve this is by carefully considering the voice of all the different actors involved in the topic, as this will facilitate the efforts of policymakers in ensuring better access to these essential medicines.

Setting the Scene by IPOPI: PIDs and medicine shortages

Mr Johan Prevot, IPOPI's Executive Director, began by thanking the MEPs for their political support, as well as IPOPI's sponsors who made this event possible. He introduced IPOPI and explained that immunoglobulin replacement therapies are derived from human plasma. He also reiterated the messages from the MEPs by highlighting the essence of these therapies for patients with PIDs. He proceeded by explaining that many people with PIDs require Ig therapies throughout their entire lives as prescribed by the treating physician. Accordingly, unstable access to immunoglobulin therapies is a growing concern for those patients in many countries. Mr Prevot concluded his intervention by stating that the objective of the Forum was to shed more light on immunoglobulins, how their access relates to plasma collection, and how they are developed. He then provided an overview of the afternoon's agenda and gave the floor to the next speaker.

How are immunoglobulin therapies developed?

Ms Dominika Misztela, Head of Global Regulatory Policy at Plasma Protein Therapeutics Association (PPTA), started her intervention by explaining what plasma is and where it comes from. She noted that it constitutes an essential material for the manufacturing of plasma-derived medicinal products (PDMPs). However, it was highlighted that in Europe there are two issues when it comes to plasma collection. Firstly, Europe relies to almost 40% on plasma coming from the United States as it does not collect sufficient plasma. Secondly, a significant donor commitment, when compared to whole blood donation, is required – a plasma donation can take up to two hours. Ms Misztela emphasised the importance of plasma donation given that without PDMPs, many patients might not survive or experience a significant impact on their quality of life. She added that PDMPs carry out critical functions in the body, such as regulating the immune system, and others.

She then explained that immunoglobulins are antibodies that are essential proteins found in plasma. It is mostly immunoglobulin G which is developed into Immunoglobulin (Ig) therapies to treat diseases such as PIDs and secondary immunodeficiencies (SIDs), but also other conditions such as neurological and autoimmune diseases, chronic inflammatory demyelinating polyneuropathy (CIDP) as well as a range of haematological diseases. Ms Misztela added that it takes an average of seven to twelve months from plasma donation until an Ig therapy ready-for-use. This compares to an average of one month to produce small-molecule (chemical) medicine.

Ms Misztela concluded her intervention by outlining the regulatory review and approval process for Ig therapies. Ms Misztela described that once a medicine or medical therapy is approved for a certain indication, it needs proof of evidence on safety and efficacy in the form of data to be approved for another indication. As such, each manufacturer of an Ig therapy has to clearly demonstrate specific requirements for each particular indication to the relevant regulatory authority; as part of post-marketing surveillance obligations, the manufacturer is also obliged to regularly submit data on safety and others, once a medicine is on the market.

European Commission proposal for the revision of the SoHO legislation: impact on plasma collection

Ms Deirdre Fehily, policy officer in the European Commission's DG SANTE Substances of Human Origin Team, shared her insights on the latest Commission proposal for a Regulation on Substances of Human Origin (SoHO). She highlighted how this new piece of legislation is putting forward changes as compared to existing legislation and how it establishes a new perspective on vulnerabilities in the supply of SoHO's and the lack of tools to prevent shortages.

Ms Fehily explained the different problems that have led to the revision of the Blood, Tissues, and Cells (BTC) legislation. Safety and quality standards were considered not up-to-date and donors, as well as children born from medically assisted reproduction, were not adequately protected by the previous legislation. Moreover, there was evidence that the legislation did not

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sufficiently facilitate innovation, due in many cases to novel methods of preparing SoHO's that have been introduced since the legislation was adopted 20 years ago. As a main point of attention, she emphasized that previously there were certain vulnerabilities in the supply of critical SoHO's, notably plasma for the manufacture of medicinal products, and a lack of tools to prevent shortages. Accordingly, the new proposal aims to provide the Member States with tools to act on this issue when necessary. The proposal also works toward improving harmonisation between Member States, facilitating cross-border exchange and improving patients' access to the therapies they need. In light of this, mechanisms such as joint inspections, joint authorisations and data sharing on a new EU platform have been introduced as elements to support Member States in their efforts to ensure an adequate and safe SoHO supply.

The next element touched upon was the *Voluntary and Unpaid Donation (VUD)*, a principle upheld by the Council of Europe's Bioethics Committee Recommendations. Ms Fehily noted that the revision of the legislation considers, firstly, that compensation or reimbursement of donation-related losses is admissible and that it could be based on a flat-rate compensation within a ceiling set by each Member State. Secondly, she added that compensation should be financially neutral and consistent with the standards of VUD.

In addition, Ms Fehily added that there are many new measures to protect donors, as this is key for increasing public trust in donation programs, and accordingly for increasing the possibility of citizens donating. As regards the issue of supply adequacy, she said that the concept of Critical SoHO is defined within the Proposal. This definition implies that responsible entities need to have contingency plans in place to be prepared for any kind of shortage.

Finally, she addressed new measures in the proposal related to sudden shortages of SoHO such as plasma for the manufacturing of PDMPs. Ms Fehily stressed that, in the event of a sudden fall in supply, it will be a requirement for responsible entities to launch an alert to their competent authorities. Following that, competent authorities should implement measures to mitigate the risks of shortages and take into account any relevant information in the regular view of their emergency plan. Moreover, she insisted that it is essential to examine further the operational aspects involved in changing the activities of the blood service, as this could lead to an increase in plasma collection. This latter approach is outside of the legislative competence of the EU but is being supported by EU funding for collaborative efforts such as the SUPPLY project that has just been launched and will work to support blood services to significantly increase their plasma collection.

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IPOPI's presentation on the study results on immunoglobulin shortages from a PID patient perspective

Ms Leire Solis, IPOPI's Health Policy and Advocacy Senior Manager, presented the study results on immunoglobulin shortages across EU Member States from a PID patient organisation perspective.

She presented a survey that IPOPI launched among its national patient organisations in July 2022. She noted that two-thirds of respondents stated that patients in their country experienced an Ig shortage in the past year. For a majority of countries (56%), the situation after the COVID-19 pandemic has worsened. 7 out of 15 countries reported an Ig shortage of more than 7 months.

The study also looked into the routes of administration that were affected by shortages. 40% of countries report a shortage affecting subcutaneous Ig, nearly 27% affected intravenous Ig and 20% of countries reported a shortage affecting both intravenous and subcutaneous.

With regards to the measures given to patients while experiencing the shortage, most of the patients were asked to delay their infusion (28%), lower the dosage (nearly 19%) or change routes (nearly 19%). Changing brands within the same route or not accepting new patients was the case in 9% of cases. The reasons alleged for the shortage were mainly related first to a drop in plasma collection and then to issues relating to the tender system in place in the countries. Poor forecasting of the needs of patients and supply chain problems came third.

The study also showed that only half of the patient organisations have been contacted by the manufacturer or distributor of Igs in the country. On the other hand, 2 out of 3 patient organisations have engaged with public authorities on the topic of shortages. In both areas, the level of engagement was very uneven and Ms Solis made a call for a meaningful engagement with patient organisations to discuss and work together to tackle the shortage

Finally, Ms Solis elaborated on the data collected from organisations on how plasma collection has evolved over the past two years. The results showed that only in 7% of the countries, plasma collection had increased, remaining stable in 47% of countries or decreasing in 33%. This showed an urgent need to increase plasma collection in order to meet patients' needs.

Panel Discussion and Q&A

All speakers came together for the panel discussion following the presentations, during which they shared their perspectives on how the impact of Ig shortages on the PID patient community could be alleviated. Apart from the speakers, the following other panellists were welcomed for the discussions:

- **Ms Otilia Stanga**, Romanian PID patient organisation (ARPID)
- **Prof Siobhan Burns**, Chair of European Society for Immunodeficiencies (ESID) Clinical Working Party
- **Ms Leni von Bonsdorff**, IPFA

The need for immunoglobulin deficiency treatments and innovative models to develop new ones was discussed from both a research and industry perspective, with the important consideration that the

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process of changing treatments or having them delayed can have substantial impacts. All speakers recognized the importance of acknowledging the different perspectives when discussing this issue, especially when it comes to patients, better treatments in order to guarantee good mental health, as well as positive long-term health outcomes for PID patients.

Ms Otilia Stanga, President of the PID Association in Romania *ARPID*, presented a clear example of how shortages could seriously impact patients. In 2017 and 2018, Romania experienced a dramatic situation of shortages in Ig therapies due to defective pricing mechanisms and lack of communication between the parties involved, which had a huge negative impact on the physical and mental health of Romanians PID patients. Many lessons were learnt from the dramatical situation the country went through in those years, the main one being that there was a wide range of reasons for the shortage, but also showing the areas for improvement, such as patient registries, guidelines, prioritisation and demand management plans, easy to use reporting systems regarding shortages as well as a courageous policy for the collection of plasma for manufacturing of PDMPs so as to ensure that, at least, the needs of the current identified patients can be met.

Prof. Siobhan Burns, Chair of the ESID Clinical Working Party, further emphasised that when Ig shortages occur, there is no equally adequate alternative to these therapies particularly if patients are affected by a severe form of immunoglobulin deficiency. She also talked about the challenges for nurses and the whole immunology team in managing continuity of immunoglobulin therapy for their patients and how shortages affect the treatment of patients at the hospital.

The discussion was then followed by Ms Leire Solis, who remarked that medicine shortages are causing patients to change treatment, not for medical reasons, but only because there is a problem with the supply of therapies, which is unacceptable. For this reason, she explained that it is essential to have a meaningful engagement with manufacturers, distributors and authorities at national level, so as to jointly identify the most appropriate solutions to the shortages and find solutions for them.

The discussion then proceeded with Ms Deirdre Fehily on the importance of the Commission's proposal in changing the existing legislation on substances of human origin for the better. Specifically, she noted that the new proposal aims to increase the capacity of Member States in improving their plasma collection and increasing it at least to the level where patients' needs can be met.

Ms Leni von Bonsdorff, Executive Director of the International Plasma and Fractionation Association (IPFA) added that in order to prevent shortages, it is very important that the public sector holds and applies a clear vision of plasma procurement strategies both at the country and EU levels. Ms von Bonsdorff stressed the importance of using different public sector mechanisms to avoid medicines shortages, such as reimbursement systems established in different countries or a precise definition of tendering conditions to allow public purchasers to obtain a competitive price and guarantee of supply. Moreover, she emphasised that there is still much work to be done in terms of demonstrating to the public sector that plasma collection is of great relevance to treating patients.

Ms Dominika Misztela touched upon how the COVID-19 pandemic has negatively affected plasma donations in both Europe and the U.S. She remarked that the impact of COVID-19 has been significant in the U.S because plasma collection has fallen by around 20% in 2020; collections were also lower in 2021. Various measures were put in place to increase collections during this time, including longer opening times for plasma collection centres. Regulators, such as the U.S. Food and Drug Administration (FDA) have also issued specific provisions during the pandemic to release more plasma for manufacturing by updating their plasma donor deferral criteria. The European Medicines Agency and the European Commission worked together to allow remote inspections of plasma collection facilities in the U.S so the U.S plasma can be used in the EU for manufacturing of PDMPs for European patients.

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Closing Statements & Next Steps

MEP István Ujhelyi began his closing remarks by stating that the lack of access to tailored treatments should never leave a patient behind. He acknowledged the urgent need for alternatives to current options on the market to ensure that patients have access to effective novel treatments at all times, as well as for patient-centred pharmaceutical innovation. Taking into consideration that each person and condition is different, he added that legislation must support a *no-one-size-fits-all* approach.

MEP Ujhelyi emphasized that medicine shortages are one of the current key challenges, underpinning the desire of the European Parliament and other EU institutions to represent the interests of patients when engaging on this issue. Moreover, he stressed that the institutions have already taken various steps in the right direction to address shortages, but that they are at present insufficient for future implementation. For that reason, he expressed his willingness to work on this and be useful to patients with PIDs to ensure that their needs are respected in any policy dossiers that may affect them.

Mr Johan Prevot provided the final remarks of the event and thanked all speakers and participants, particularly those representing PID patients, for taking part in the 21st PID Forum. He emphasized that IPOPI is excited to build on the awareness raised and recommendations put forward throughout the Forum. He noted that the discussions had shown how important ongoing and future EU initiatives, such as the work of the EMA, the Pharmaceutical Strategy or the SoHO future regulation could have an impact on patients' access to their Igs. He further expressed IPOPI's willingness to work in collaboration with MEPs on the different dossiers to ensure that patients with PIDs have access to their Ig as prescribed by their treating physician.

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