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)

IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

21th PID Forum | Medicine shortages in the EU: the case of immunoglobulin and PIDs

Welcome and opening remarks by MEPs István Ujhelyi (S&D, Hungary) & Kateřina Konečná (GUE/NGL, Czechia)

Setting the scene by Johan Prevot
IPOPI Executive Director

September 8th, 2022

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Programme

How are immunoglobulin therapies developed?
Dominika Misztela, PPTA

The European Commission proposal for the revision of the BTC legislation: impact on plasma collection
Deirdre Fehily, European Commission

IPOPI presentation on the study results on immunoglobulin shortages from a PID patient perspective
Leire Solis, IPOPI

Panel Discussion and Q&A on AMR and PID Medical Care

Closing Statements
MEP István Ujhelyi (S&D, Hungary)

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21st PID Forum

How is an Immunoglobulin developed?

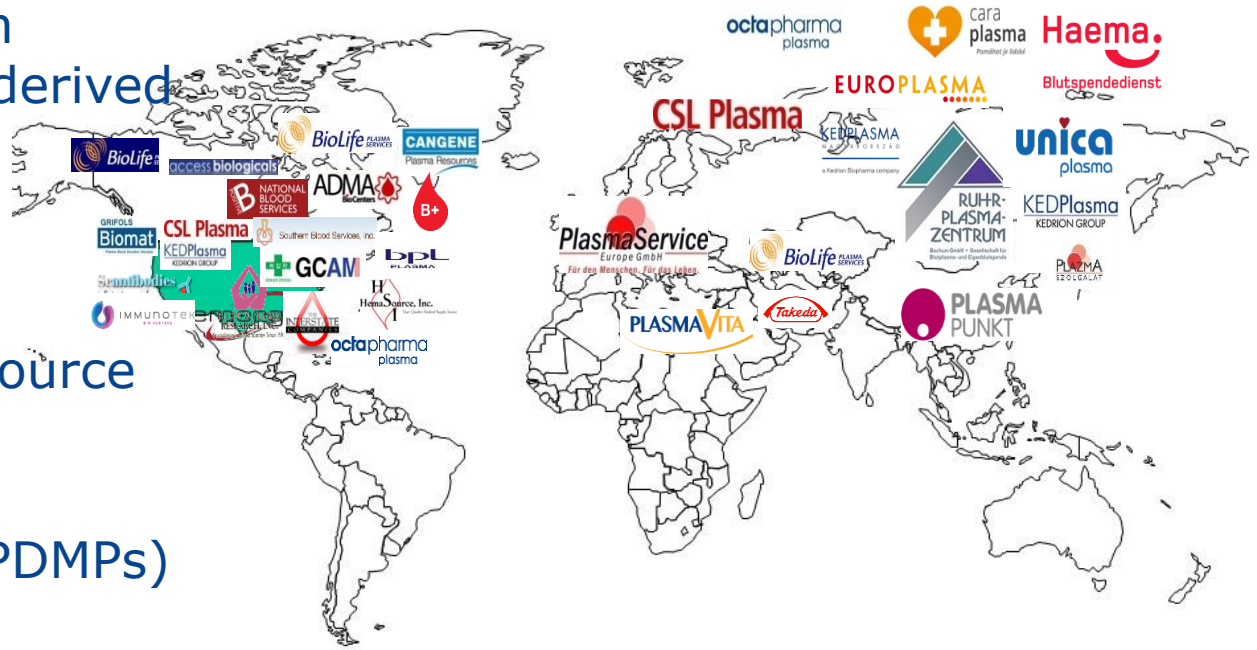
Dominika Misztela, PhD

Senior Director, Head of Global Regulatory Policy

dmisztela@pptaglobal.org

Plasma Protein Therapeutics Association

Industry trade and standards-setting organization representing private sector producers of plasma-derived and recombinant biological therapies.



PPTA's global and regional members:

- Provide more than 60% of world's needs for Source Plasma (plasma for fractionation)
- Provide majority (60-80%) of world's safe and effective plasma-derived medicinal products (PDMPs)

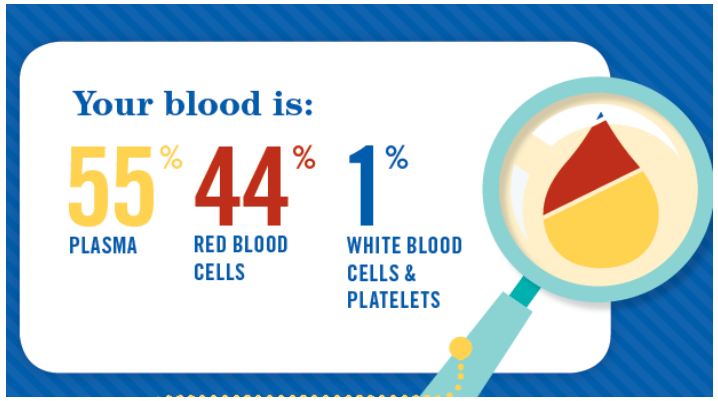
Mission:
'As a trusted partner to health systems, PPTA drives broad and reliable access to high-quality plasma protein therapies, with a focus on the wellbeing of patients and plasma donors'

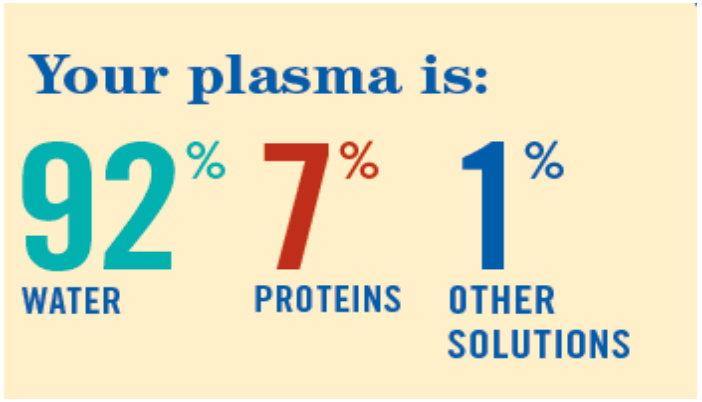
1041 North America PPTA plasma collection centres

153 EU PPTA collection centres

****current December 2021 (1)***

What is Plasma and where does it come from?





Plasma

- **Key blood component** (55% of total blood volume), carries water, salts, and proteins
- Clear straw-coloured liquid left after removing red and white blood cells, platelets and other
- **Unique, indispensable starting material** for manufacture of plasma-derived medicinal products (PDMPs) (1, 2, 3)
- Donated by **healthy human volunteer donors**
- **Plasma & PDMPs can only be obtained from healthy donors**
- Only **four EU countries** (Austria, Czech Republic, Germany, Hungary) **contribute ~ 55 % of total plasma for manufacturing in EU** (3)
- Europe relies to **~40 % on U.S.A for plasma for manufacturing** (3)

Plasma donation

- **Donor commitment**: Plasma donation takes ~ 1-2 hours, can be donated more often than whole blood
- **Plasma donation is very safe**: Minimal/ no side effects, just like whole blood donation

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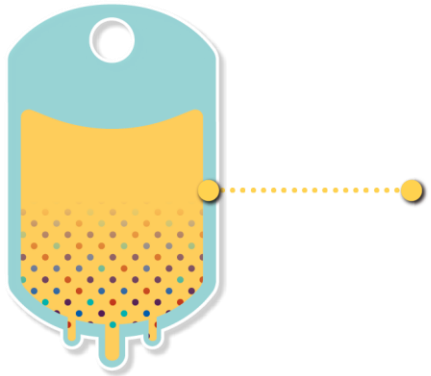
What are Plasma-derived Medicinal Products?

PDMPs

- **Essential medicines** according to WHO, needed by ~ 300,000 EU patients [2,3]
- ~ 17 unique proteins identified up to date
- Treat wide range of **rare, chronic, and life-threatening** conditions, often **genetic**
- Without PDMPs, many **patients might not survive or have diminished quality of life**
- Carry out **critical functions**, e.g.: blood clotting, regulating immune system, homeostasis



PROTEINS IN YOUR PLASMA:

- ALBUMIN
- ALPHA-1 PROTEINASE INHIBITOR
- C1 ESTERASE INHIBITOR
- CLOTTING FACTORS
- IMMUNOGLOBULINS (ANTIBODIES)

EVERY YEAR IT TAKES MORE THAN:

1200: Plasma donations to treat ONE PATIENT for HEMOPHILIA.

900: Plasma donations to treat ONE ALPHA-1 PATIENT.

130: Plasma donations to treat ONE PATIENT with a PRIMARY IMMUNE DEFICIENCY.

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Immunoglobulins (IG) and their use

- **Immunoglobulins (IGs) = antibodies**
  - Essential proteins found in plasma [2,3]
  - **Mainly IgG** class, others: IgA, IgM, IgE, IgD, different functions in body
- **IG therapies**
  - **Not interchangeable:** Not biosimilars, **different IG brands - different tolerability**
  - Treat, amongst others

Immunodeficiencies

- Primary (PID), Secondary (SID)

Neurological diseases

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Acute inflammatory demyelinating polyneuropathy (Guillain Barré)
- Multifocal motor neuropathy (MMN)

Haematological diseases

- Primary immune thrombocytopenia/ Idiopathic thrombocytopenic purpura (ITP)

Inflammatory diseases

- Kawasaki disease

Hyperimmune Immune Globulins [4]

IG therapy: Donation – manufacturing - use

- **7-12 months** from plasma donation until IG therapy ready for use
- **1 month** to produce small molecule pharmaceutical medicine

1. **'Plasmapheresis': Plasma donation by healthy volunteer donors**
   - **PPTA Qualified Donor Standard ®**
   - Plasmapheresis: Larger volumes ~ 450–880ml plasma, more frequent donations, depending on country; Europe: 24 – 60x/ year
   - **PPTA Donor Health Standard – PlasmaVigilance ®**
   - Recovered plasma: From whole blood, yield varies, approx. 3-5x/ year

2. **Rigorous testing**
   - Each plasma donation and minipool
   - HIV, HBV, HCV and in-process HAV and B19V NAT (PPTA standard)
   - Inventory Hold (lookback/ traceability to single donation)

3. **Fractionation: Industrial pooling and processing**
   - Cohn, 1940s: 'Fraction 2' contains IGs [7]
   - **Pathogen inactivation and removal: Very high safety margins** [8]

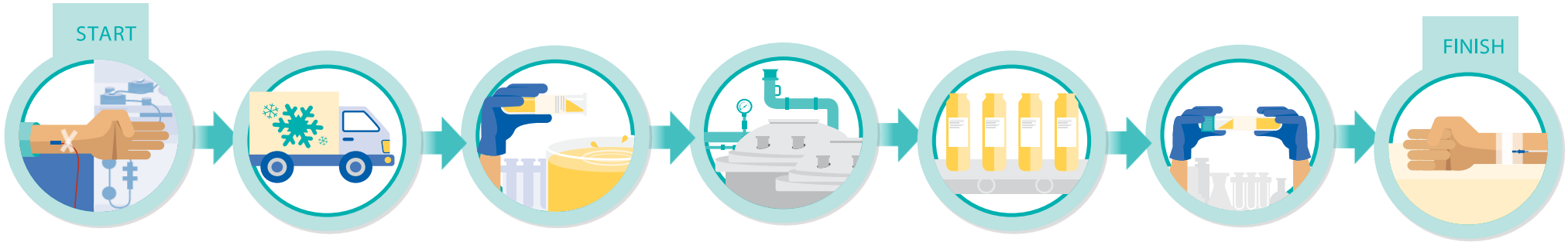
IG therapy: Donation – manufacturing – use (cont.)

4. Regulatory review and approval

- **Product safety & efficacy assessment** before market entry
- Post-marketing surveillance
- Also for plasma collection centres, testing labs, storage, manufacturing facilities

5. PPTA voluntary industry standards

- Go beyond international regulatory requirements
- Collection, incl. donor health, processing and testing of plasma for manufacturing by fractionators
- **IQPP ® - International Quality Plasma Program** (9)
- **QSEAL ® - Quality Standards of Excellence, Assurance and Leadership** (10)



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Regulatory/ clinical approval and use (3)

- **IG therapy approval/ authorisation**

  Regulatory review, based on evidence and data
  - Manufacturer must demonstrate IG therapy **safety and efficacy for particular disease**
  - Manufacturer must regularly submit data

- **IG therapy prescription: Should be clinician-led**
  - Based on evidence and recommendations (scientific societies) and approvals from regulatory agencies

- **IG therapy use varies globally/regionally** (9)
  - Not every IG therapy is used and approved for each indication in each region

	European Medicine Agency (EMA)	US FDA[a,b]
Primary immunodeficiency syndromes (PID) with impaired antibody production	X	X
Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of less than 4 g/l	X	
Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count	X	X
Guillain–Barré syndrome	X	
Kawasaki disease (in conjunction with acetylsalicylic acid; see 4.2)	X	X
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	X	X
Multifocal motor neuropathy (MMN)	X	X
Hypogammaglobulinemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contraindicated.	X	X
Hypogammaglobulinemia and recurrent bacterial infections in multiple myeloma (MM) patients	X	
Hypogammaglobulinemia in patients pre and post allogeneic haematopoietic stem cell transplantation (HSCT)	X	

[a]US Food and Drug Administration. Immune Globulin Intravenous (IGIV) Indications. Available online: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulin-intravenous-igiv-indications (accessed on 15 June 2020).
[b]US Food and Drug Administration. Immune Globulins. Available online: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins (accessed on 15 June 2020).

CURRENT OPINION IN ALLERGY AND CLINICAL IMMUNOLOGY

IG therapies: Some data

IG therapy use increased over past decade due to advances in identification, treatment, and diagnosis of many diseases, thanks to

IPOPI
Jeffrey Modell Foundation
Immune Deficiency Foundation
GBS|CIDP Foundation International

Conditions treated with IG therapies often experience delays in diagnosis due to rare nature!!!

- **More conditions identified** (10,11)
  - Number of distinct immunodeficiencies in **2004 – 100**
  - Number of distinct immunodeficiencies in **2020 – 400**

- **More clinicians understand IG therapy benefits** (10)
  - Twice in number of medical personnel with PID expertise
  - Better education of medical personnel on IG clinical benefits

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IG therapies: Some data (cont.)

- **Better and earlier diagnosis of conditions requiring IG therapies**
  - Increase in PID diagnosis = 8.5%[12]
  - New diagnoses = 130% increase in IG therapy in past 10 years [12]
  - Use of advanced diagnostic tools (newborn screening, genetic sequencing [13]

- **Individuals who use IG therapies live longer**
  - Overall longer lifespan
  - IG therapies = lifelong treatments decreasing morbidity and mortality
    e.g., 10-year survival rate for one PID type increased from 38% to 78% [14]

- **More individuals receive correct, individualized IG therapy**
  - More patients on optimal dose > fewer infections in immunodeficiency settings [15, 16, 17]
  - Dose adjustments also due to mode of administration (i.v. vs. s.c. vs. f.s.c. IG) [18]

- **Need to address global imbalance in IG therapy** [19]
  - Significant variation in plasma collections regionally (U.S.A vs. EU vs. RoW, …)
  - Significant variation in diagnosis, treatment
  - Impact of emerging (new) infectious diseases; past: ZIKV, current: COVID-19, MPXV

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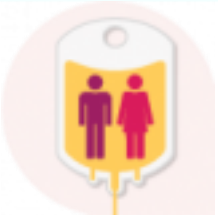
Summary



- **Plasmapheresis is safe and the most efficient way to collect plasma**.
- **IGs therapies are made from plasma** donated by healthy human volunteer donors in a process called '**fractionation**'. They cannot be made in the laboratory.

- **IG therapies** are **essential medicines.** They treat a range of rare and serious medical conditions. They are not interchangeable.

- **Manufacturing of IG therapies is lengthy**. It takes ~7-12 months from a donation to be available as IG therapy on the market.
- **IG therapies** are assessed for **safety and clinical efficacy for each indication and monitored long-term.**

- Use of **IG therapies** has been **increasing due to advances in diagnosis and treatment**.

- **The most effective way to assure adequate access to essential IGs for EU patients who need them is sufficient plasma collections.** Currently the EU does not collect sufficient plasma to meet their needs

Thank You
to all donors who donate plasma to save and improve lives

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4) CoVIg Alliance: https://www.takeda.com/newsroom/newsreleases/2021/covig-19-plasma-alliance-announces-topline-results-from-nih-sponsored-clinical-trial-of-investigational-covid-19-hyperimmune-globulin-medicine/ (Accessed 02 September 2022)
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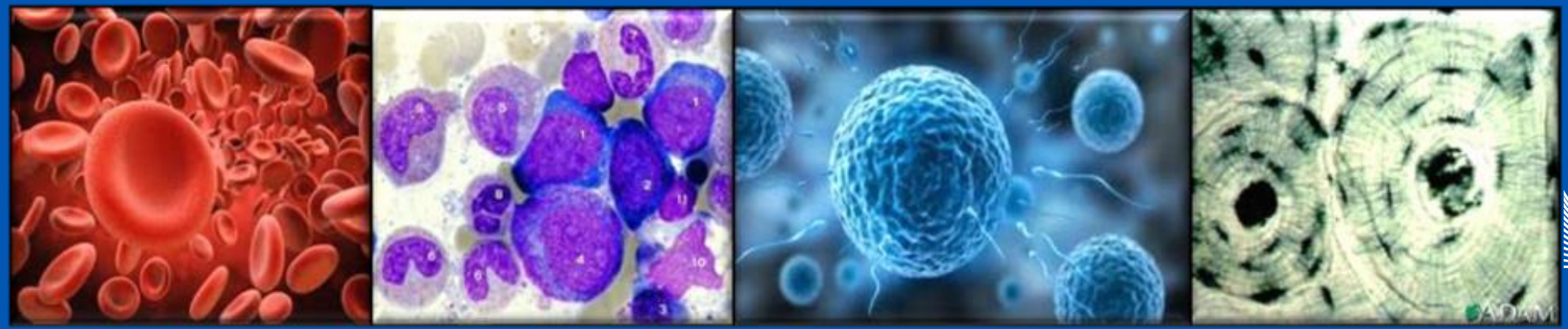
European Commission proposal for the revision of the blood, tissues and cells (BTC) legislation: impact on plasma collection

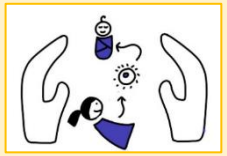
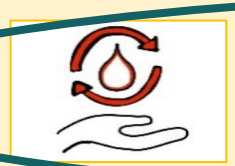
08.09.2022



European Commission

Evaluation of the BTC legislation found the legislation had been effective – increased safety and quality

However, it identified 5 shortcomings:

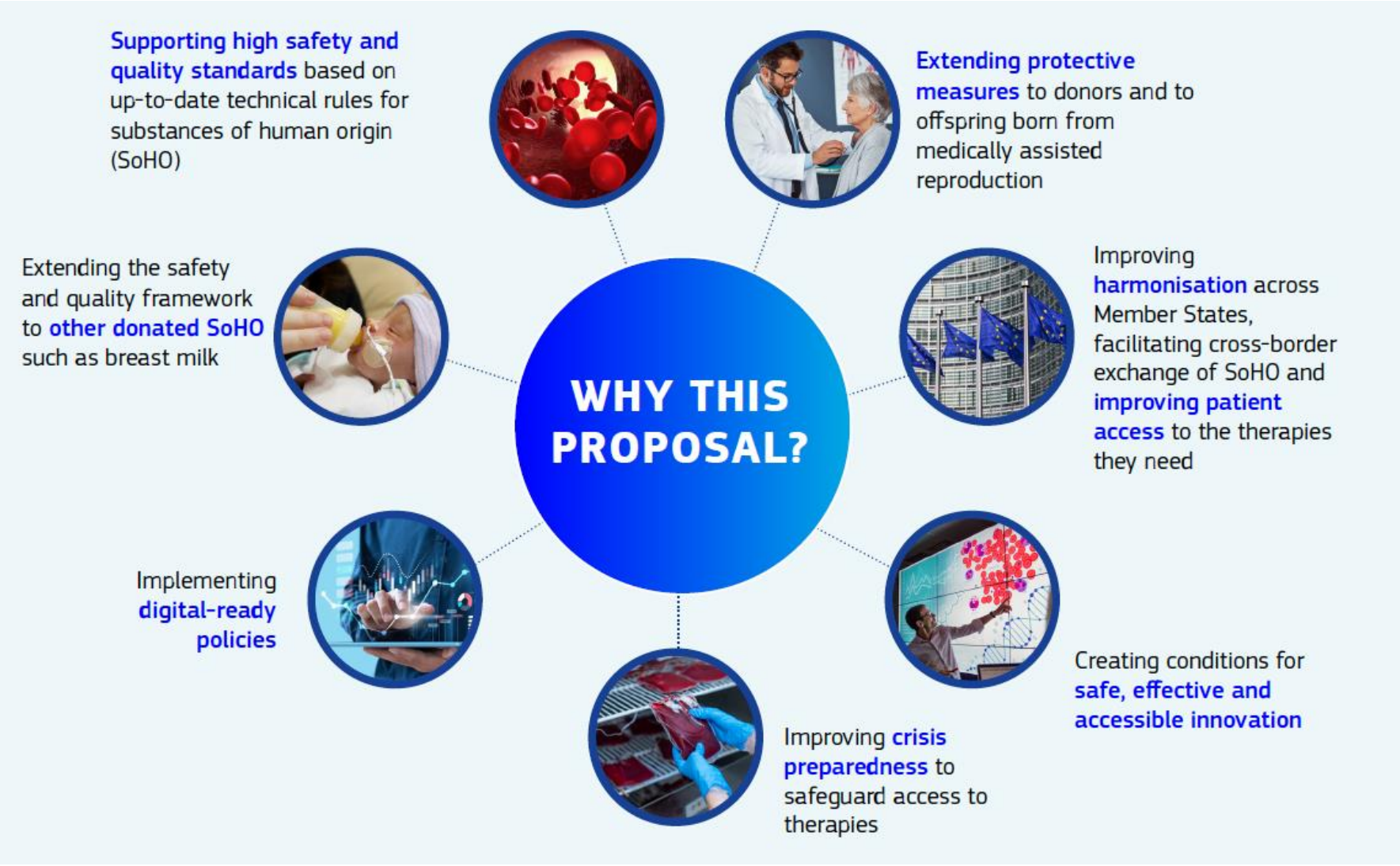
1. 
   Patients can be even more protected from avoidable risks and BTC not covered should be included
2. 
   BTC donors and children born from donated eggs, sperm, or embryos should be further protected from new risks (monitoring, reporting, testing etc)
3. 
   Divergent approaches to oversight between MSs make cross border solidarity across the EU difficult
4. 
   BTC legislation not able to capture new innovative BTC based therapies ; not enough future proof
5. 
   Vulnerability of BTC supply chains and need to prevent shortages

Evaluation of the BTC Framework, 2019

European Commission

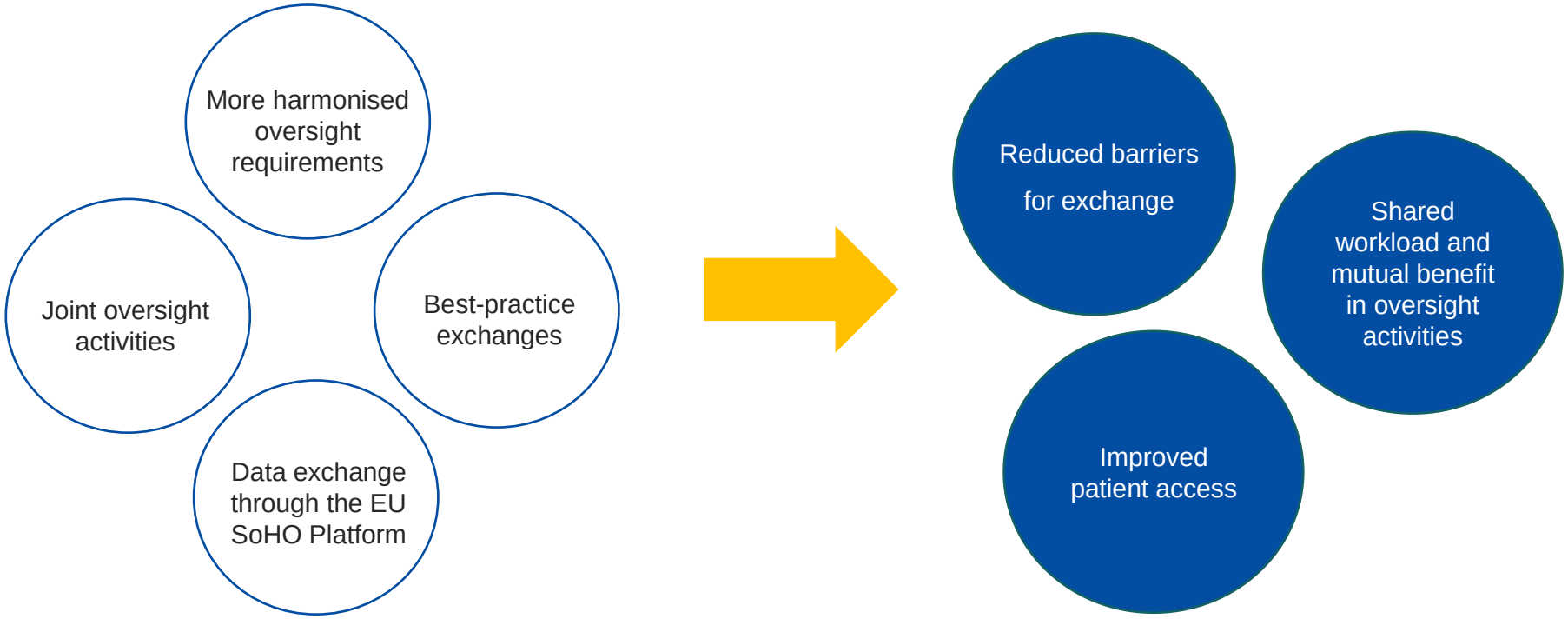
A proposal to address the issues published in July 2022

– A Regulation to replace the current BTC directives



European Commission

The proposal aims to improve harmonisation across Member States, facilitating cross-border exchange and improving patient access to the therapies they need



Voluntary & Unpaid Donation

Principle maintained
Based on Recommendations of Council of Europe Committee on Bioethics

"SoHO entities shall not provide financial incentives or inducements to SoHO donors or their relatives or any persons granting authorisation on behalf of the prospective donors, in accordance with national legislation" (Art. 54)

"SoHO entities may compensate or reimburse SoHO donors as provided for by their competent authorities (…)"

- **Compensation** or reimbursement for losses related to donation are permissible
- Based on fixed-rate allowances **within an upper limit set by Member State**
- Allowances must be **financially neutral** and consistent with standards for VUD

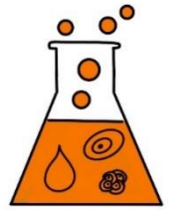
In addition, new measures to protect donors will increase public trust in donation programmes

European Commission

‘Critical SoHO’

“‘critical SoHO’ means SoHO that, if not available in sufficient quantities, will result in serious harm or risk of harm to patients” (Art. 3(41))

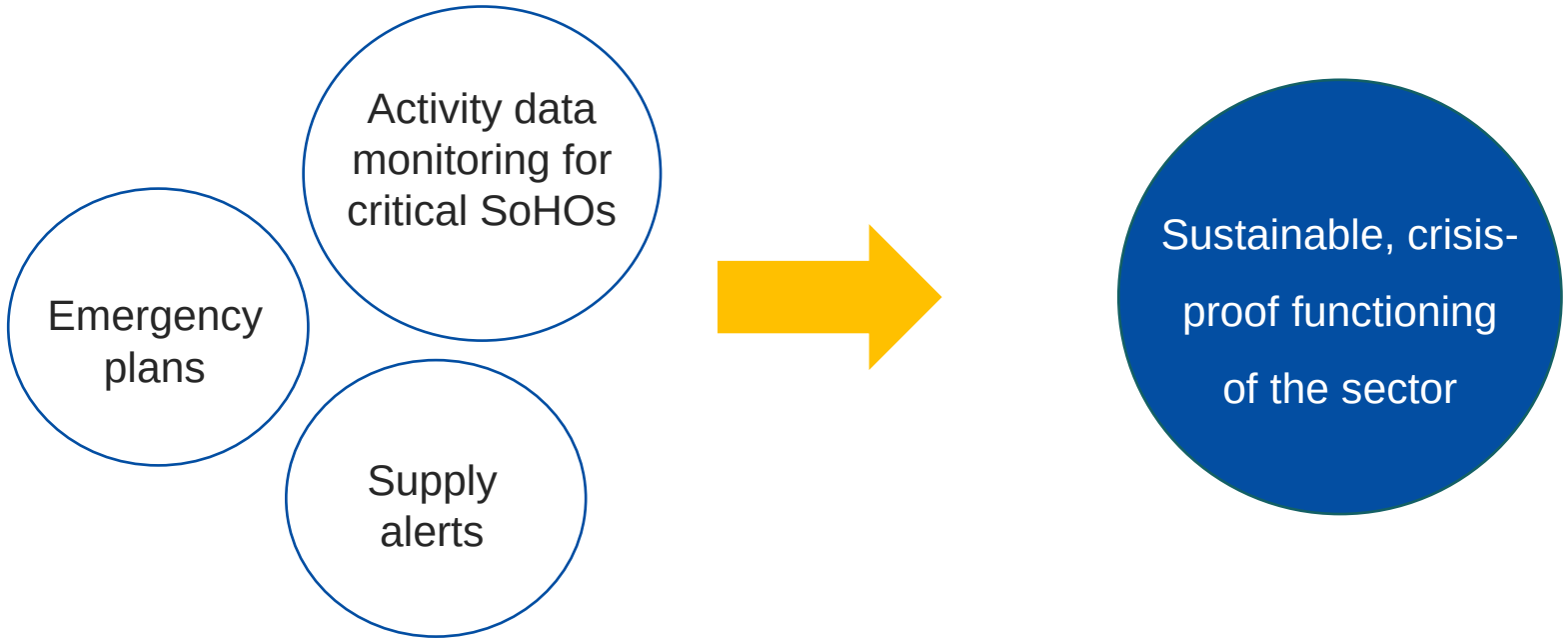
“‘critical SoHO entity’ means a SoHO entity that carries out activities contributing to the supply of critical SoHOs and the scale of those activities is such that a failure to carry them out cannot be compensated by activities of other entities or alternative substances or products for patients” (Art. 3(42))



Supply of critical SoHO is supported by:

- National SoHO emergency plans & SoHO Entity emergency plans (Art. 62 & 66)
- Supply alerts (Art. 63)
- Additional emergency measures by Member States (Art. 65)
- Activity data collection and reporting (Art.44)

Monitoring of supply to inform national policies for the prevention and management of shortages.



Supply Alerts

"Critical SoHO entities shall without undue delay launch a SoHO supply alert to their competent authorities in case of a significant interruption (…)" (Art. 63)

Significant interruptions: "application of a critical SoHO is cancelled or postponed due to unavailability and this poses a serious risk to health"

Contents of alert: underlying reason, expected impact, any mitigating measures taken, possible supply channels (if appropriate)

Responsibilities of competent authorities receiving such an alert (Art. 63)

- Communication of the SoHO supply alert to the SoHO National Authority
- Implementation of possible measures to mitigate the risk
- Take into account any relevant information in the regular review of their national SoHO emergency plan

Communication to the EU SoHO Platform: possible in any cases where the interruption may affect other Member States or where the interruption may be addressed through cooperation

Legislation is just part of the tool box – other EU initiatives will increase supply

- During the Covid crisis, the **Emergency Support Instrument** funded increased plasma collection capacity across the EU - 13 Member States, 67 blood establishments, over EUR 20 Million Euros, 35 new plasma collection centres, almost 300 new plasma collection machines and over 70,000 plasma collection sets as well as extended freezer space.
- **EU4Health** grant signed with the European Blood Alliance to run the **SUPPLY** project. Working towards making the EU more strategically independent in its need for plasma medicines, EUR 1.13 Million. Recommendations for non-profit blood institutions, competent authorities, medical societies and other professional stakeholders to help them grow plasma collection and achieve a resilient supply in the EU. https://europeanbloodalliance.eu/strengthening-plasma-collection-in-europe/
- Collaborative grant agreement between the Commission and the **Council of Europe. Plasma Supply Management Symposium** was held in 2019. The conference developed a series of Recommendations for Stakeholders that provide expert views on how those involved **at all levels** can work together to increase plasma supply in the EU. https://www.edqm.eu/en/w/recommendations-to-stakeholders-on-plasma-supply-management

Ensuring availability and addressing shortages of medicinal products – watch this space!

Pharmaceutical Strategy for Europe and European Health Union

Secure the supply

- Revision of the legislation to ***to enhance security of supply and address shortages through specific measures including stronger obligations for supply and transparency, earlier notification of shortages and withdrawals, enhanced transparency of stocks and stronger EU coordination and mechanisms to monitor, manage and avoid shortages***
- Structured dialogue to ***identify and address vulnerabilities*** in the global supply chain
- **Joint Action on Shortages -** Member States to develop guidelines, measures and tools through funding provided by EU4Health

Crisis preparedness and response mechanisms

- Proposal for an **EU Health Emergency Response Authority** [HERA established]
- **Regulation 2022/123,** the regulation reinforcing EMA's role in crisis preparedness and management for medicinal products and medical devices

European Commission

Immunoglobulin shortages in the EU from a PID patient perspective

IPOPI 21st EU PID Forum

8 September 2022, 13h30 – 15h CEST, virtual

Leire Solis

Health policy and advocacy senior manager, IPOPI

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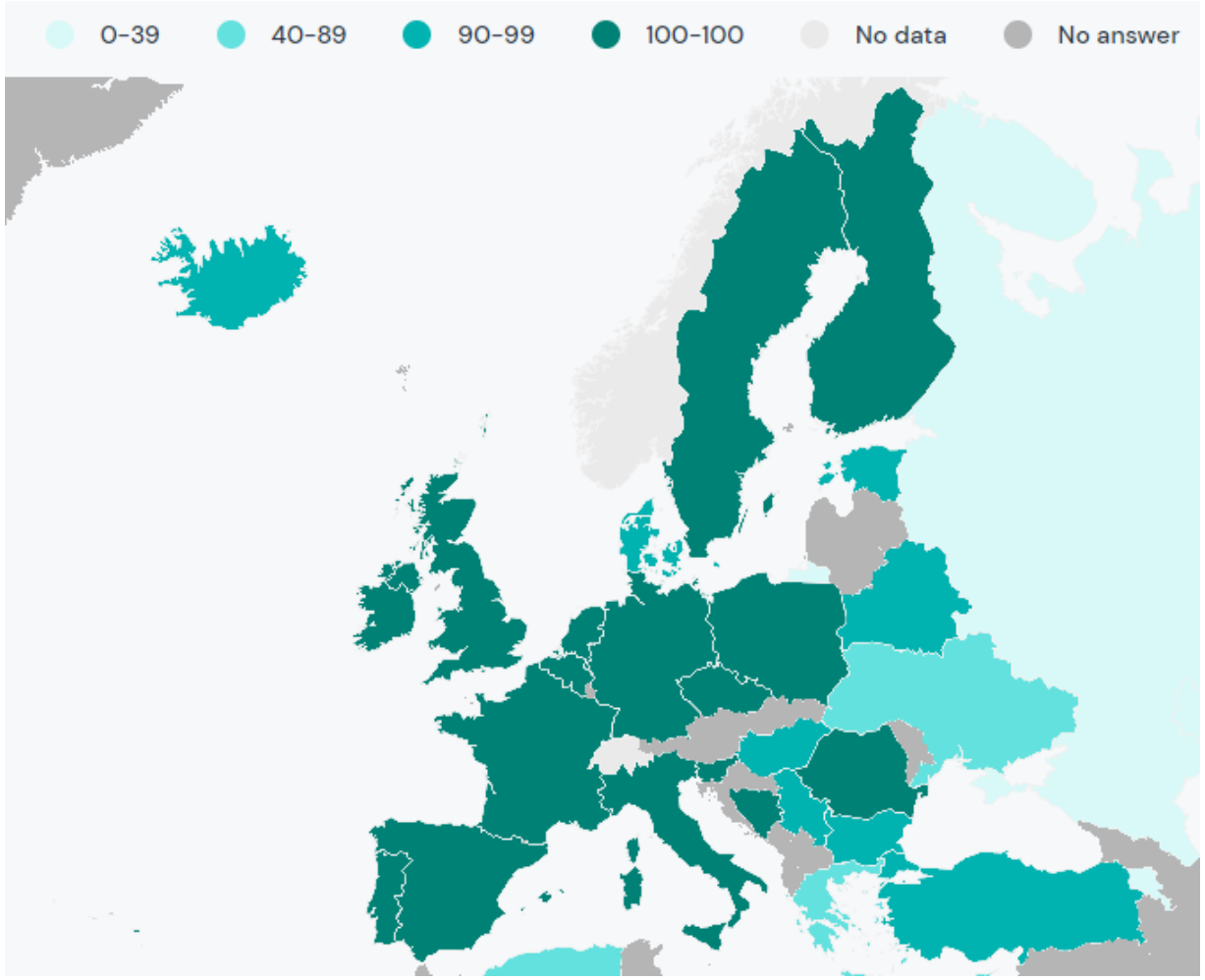
Ig availability reported by PID national patient groups



What matters to you?

WHAT PRINCIPLE ARE YOU INTERESTED IN?

Treatments

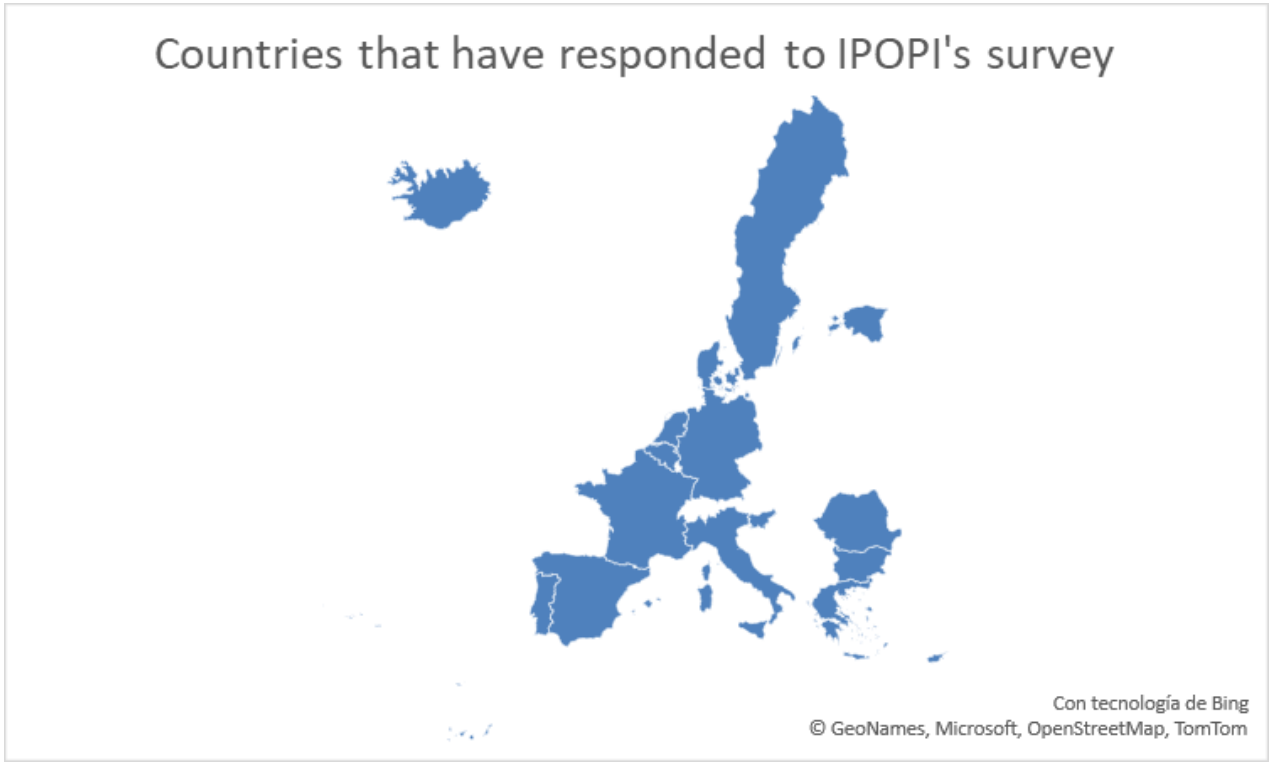
WHAT CRITERIA ARE YOU INTERESTED IN?

Ig availability

Source: https://pidlifeindex.ipopi.org/#/

IPOPI's survey on Ig shortages

- Survey sent to our national patient organisations.
- Responses received from 1st – 25th July 2022.
- 16/22 responses received.



IPOPI's survey on Ig shortages
- study results -

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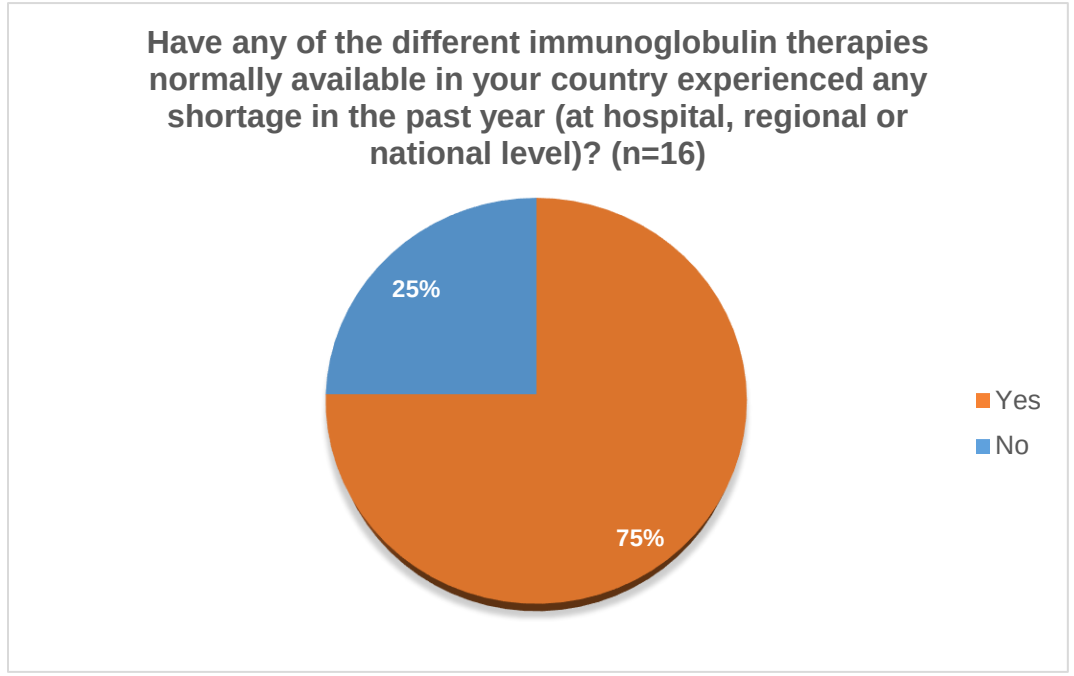
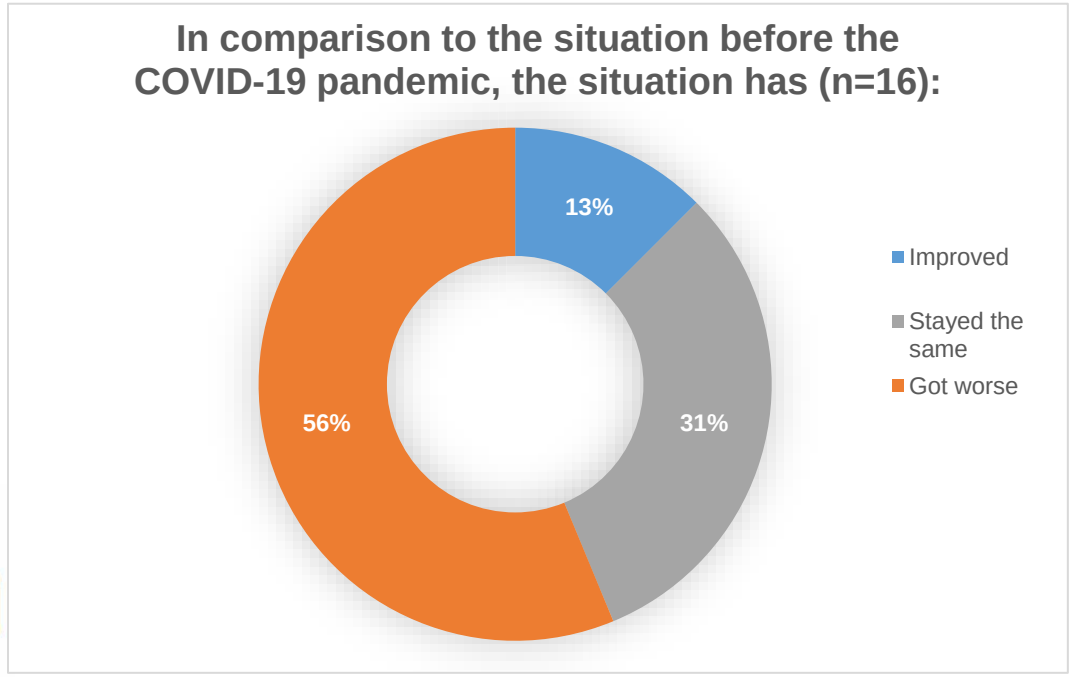
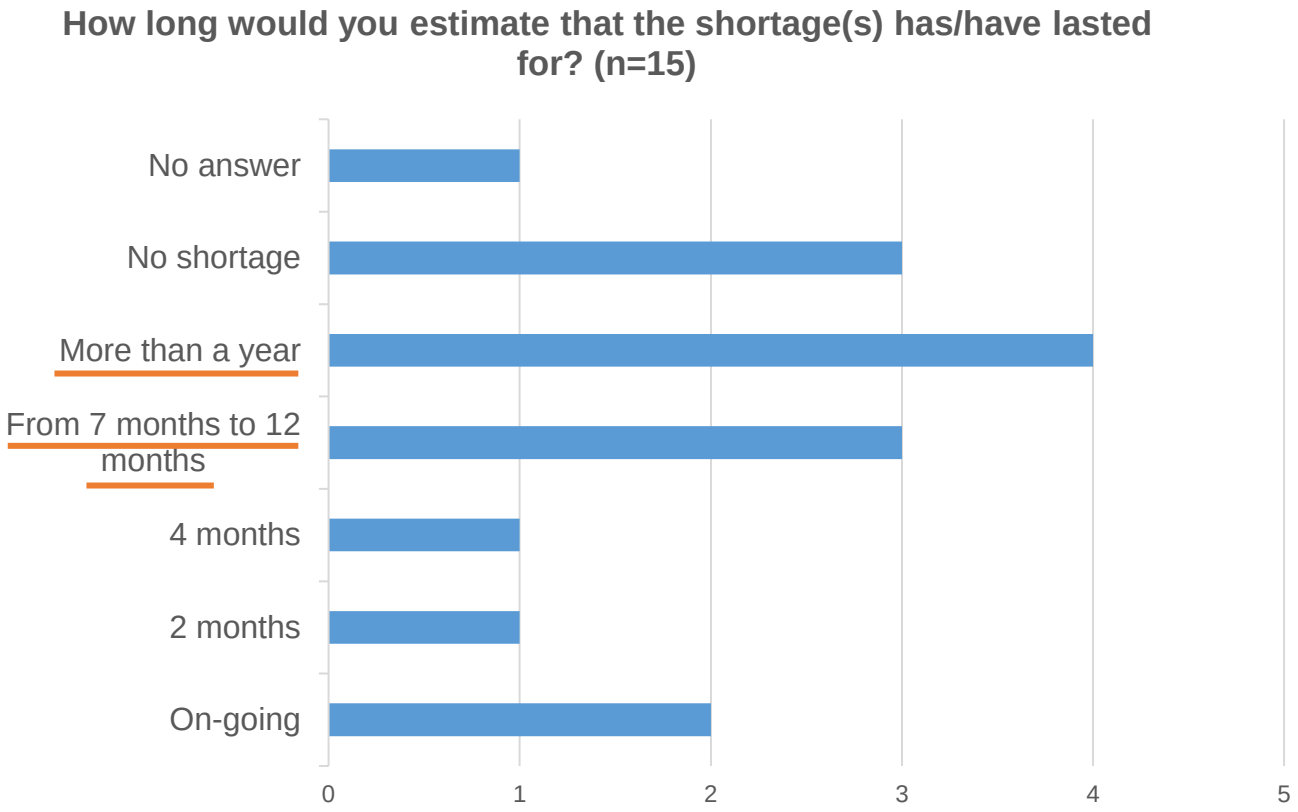


- In 12 out of 16 countries, patients with PIDs report experiencing Ig shortages.



- For a majority of countries, the situation after the COVID-19 pandemic has worsened.
- 1/3 countries report that the situation has remained unchanged.
- Only in 2 countries, patients with PIDs report an improvement in their access to Igs.

Source: IPOPI's survey on Ig shortages in the EU

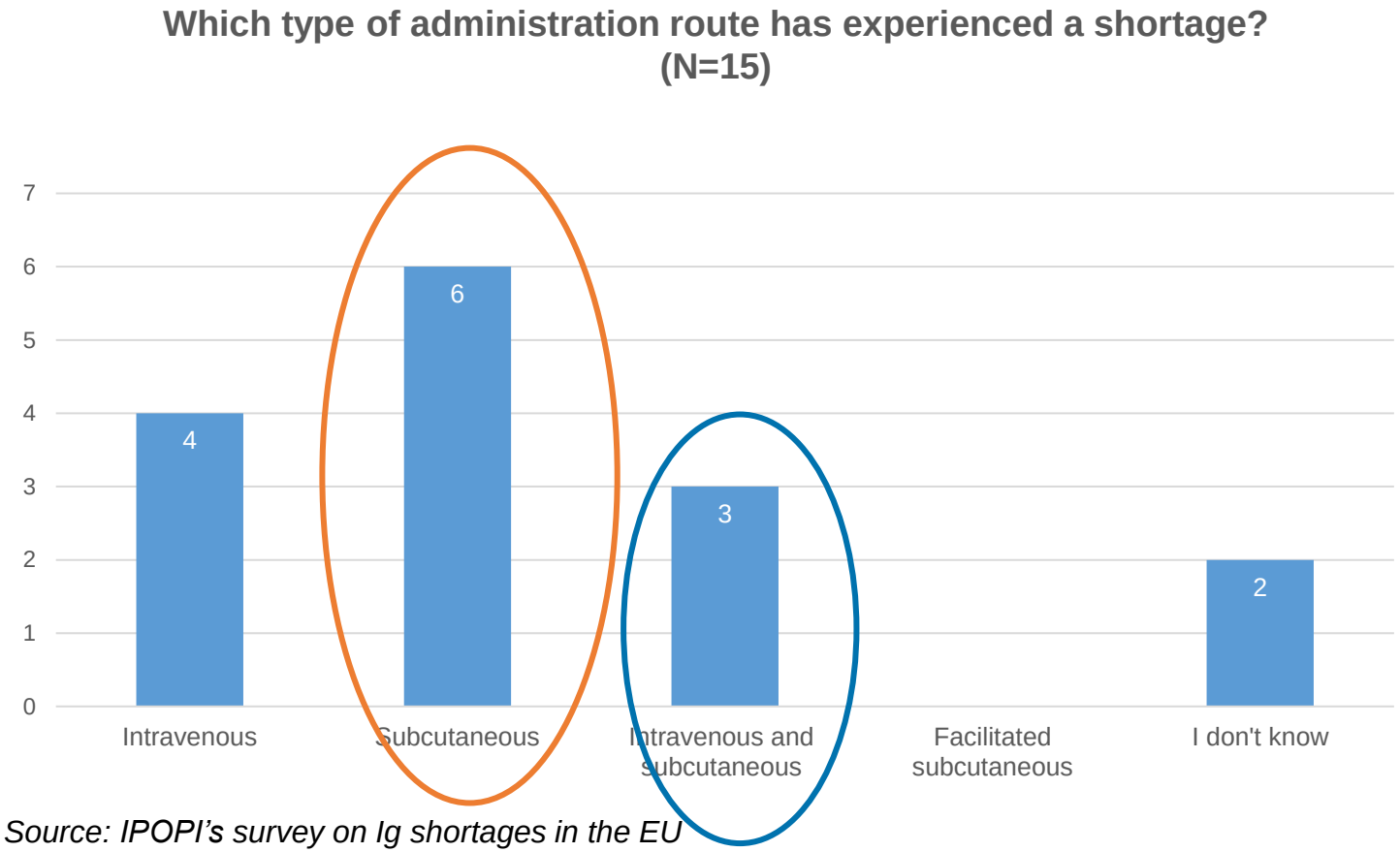


Source: IPOPI's survey on Ig shortages in the EU

Disclaimer: "on-going" means that the shortage was still on-going at the time of the survey and was hard to assess the duration of the shortage

- 7 out of 15 countries report an Ig shortage of more than 7 months.

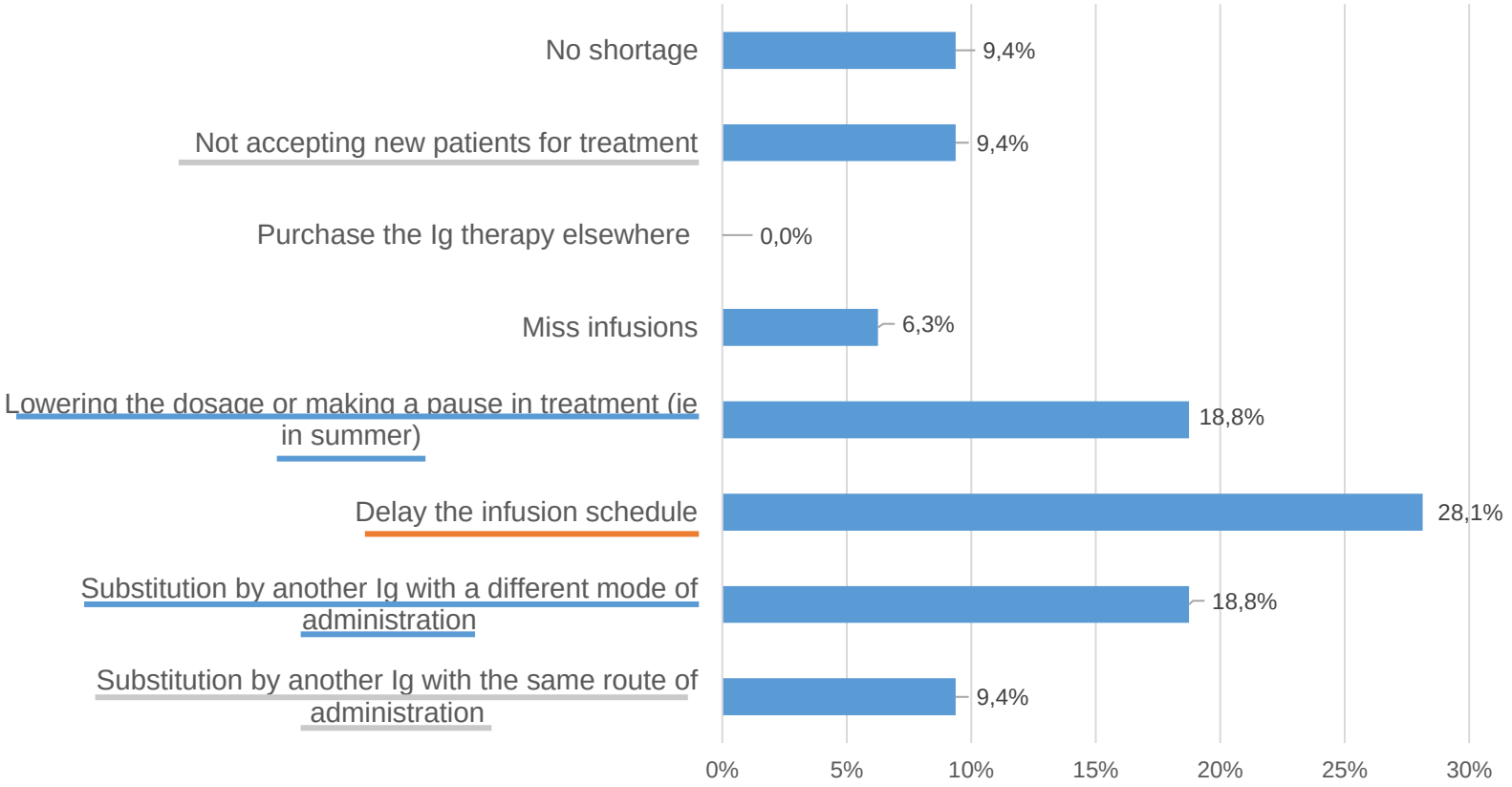
Note: in one country the Ig shortage has been reported by nurses, but the patients have not felt such availability problems.



Source: IPOPI's survey on Ig shortages in the EU

- 40% of countries report a shortage affecting SCIg (6 out of 15)
- 26,66% of countries report a shortage affecting IVIg (4 out of 15).
- 20% of countries report a shortage affecting the 2 most common routes of administration (3 out of 15)

What measures were given to the patients?

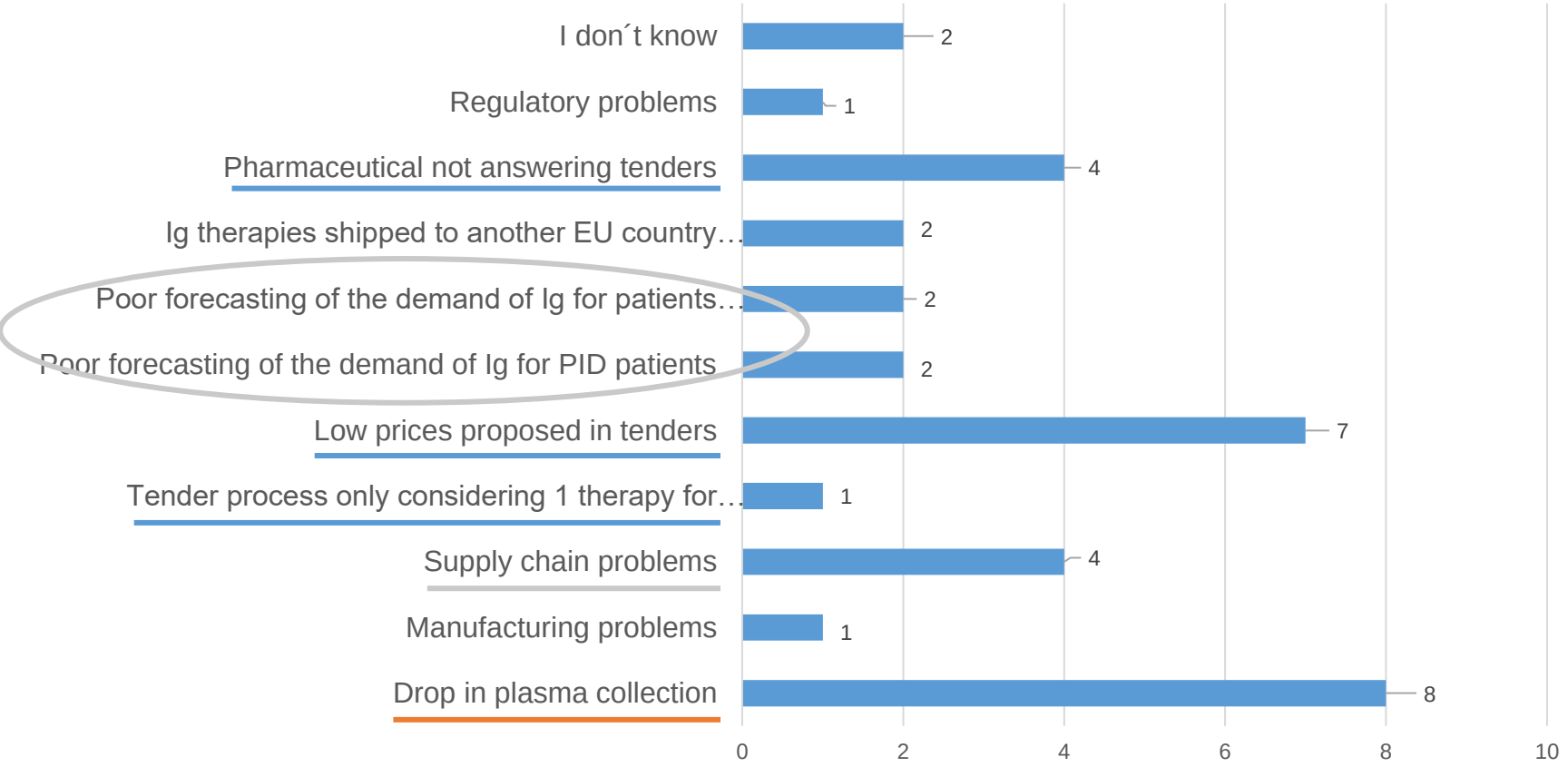


Source: IPOPI's survey on Ig shortages in the EU

The most common measures given to patients with PIDs:

- Delay in infusion schedule (28,1%)
- Lowering dosage & changing routes (18,8%)
- Changing brands (same route) & not accepting new patients (!) (9,4%)

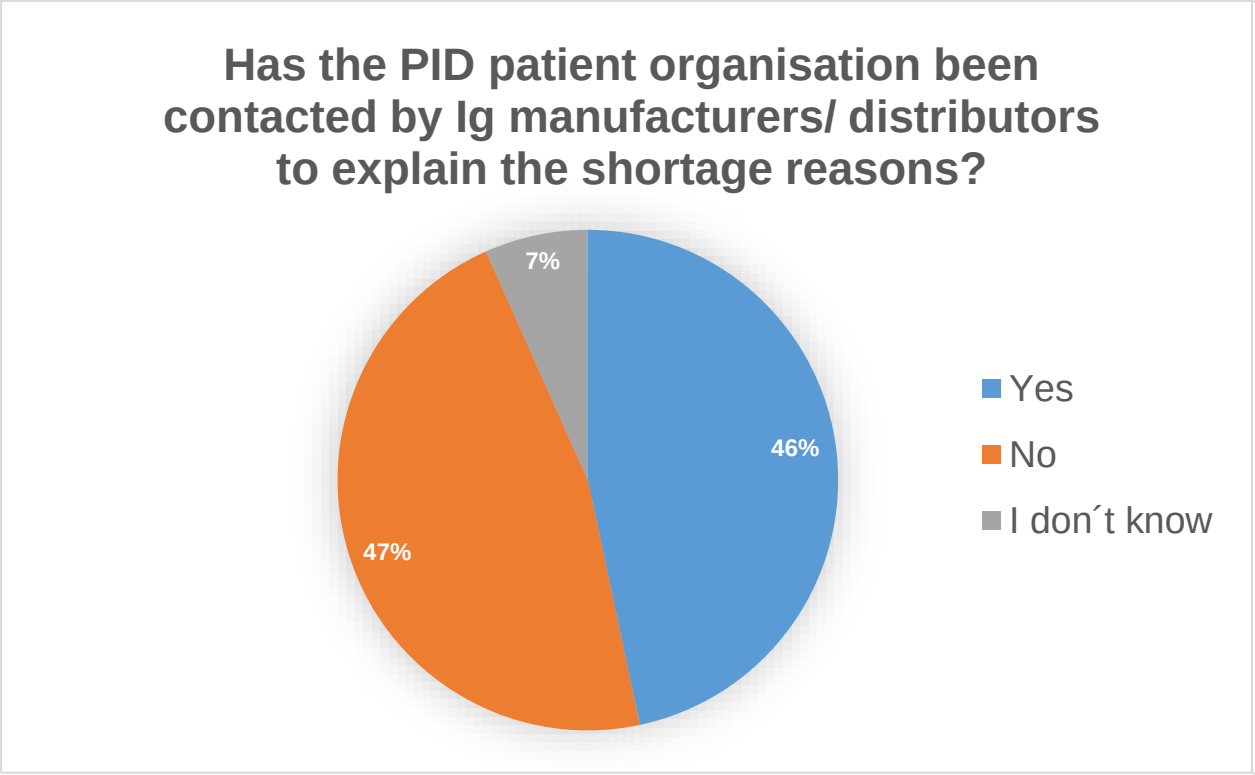
What were the reasons for the Ig shortage(s) in the past year?

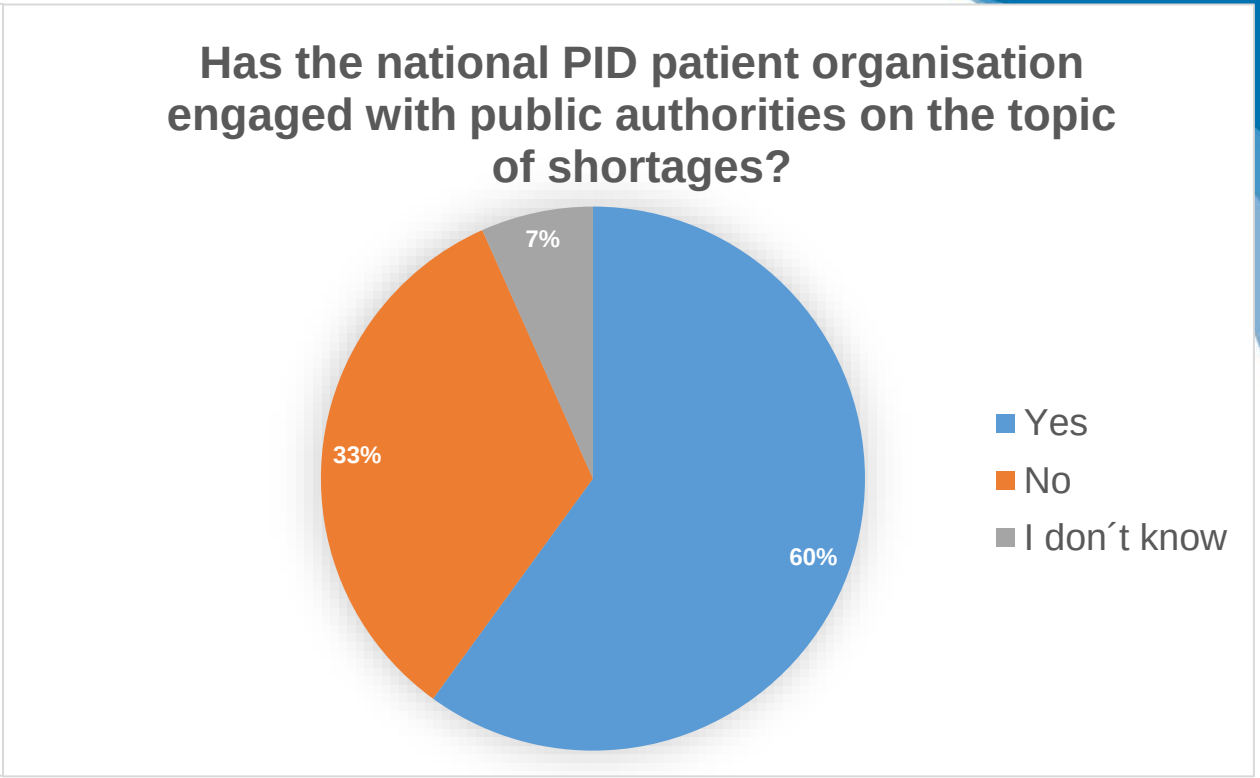


Source: IPOPI's survey on Ig shortages in the EU

Main reasons related to:

- Drop in plasma collection
- Tenders
- Poor forecasting of needs of patients & supply chain problems

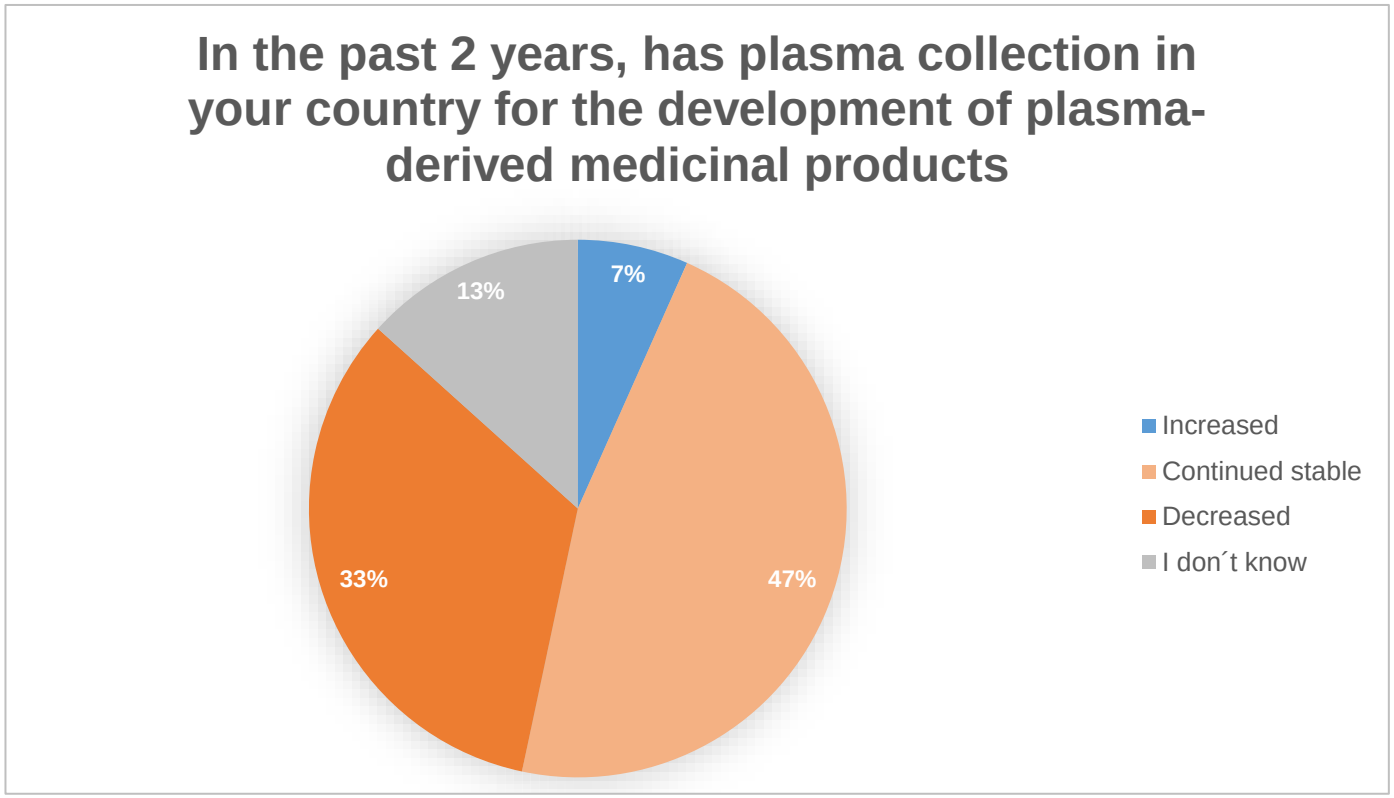




Source: IPOPI's survey on Ig shortages in the EU

- Only half of the patient organisations have been contacted by the manufacturer/distributor.
- Uneven type of engagement:
  - "*The answer was we are trying to do our best*"
  - "*the main brands contacted us to explain the reasons and helped us to tackle the issue*."

- 2 out of 3 patient organisations have engaged with public authorities on the topic of shortages.
- Uneven type of engagement:
  - "*We participate in the task force with the ministry (…) and other stakeholders*"
  - "*written letters*"



Source: IPOPI's survey on Ig shortages in the EU

- 33% of countries, plasma collection has decreased in the past 2 years.
- 47% of countries, plasma collection has remained stable.
- Only in 7% of countries has plasma collection increased.

→ What happens with newly diagnosed patients in need of Igs?

Concluding remarks

- Ig shortages for patients with PIDs affect/have affected most of EU countries.
- The situation since COVID-19 has worsened.
- Both routes of administration are affected.
- Alternative measures proposed to patients (change in administration frequency, dosage, route, brand) are not optimal solutions.
- Reasons reported for the shortage relate to drop in plasma collection and issues with tenders.
- Call on manufacturers, distributors and national authorities for a meaningful engagement with patient organisations.
- Need for increased plasma collection to meet patient needs.

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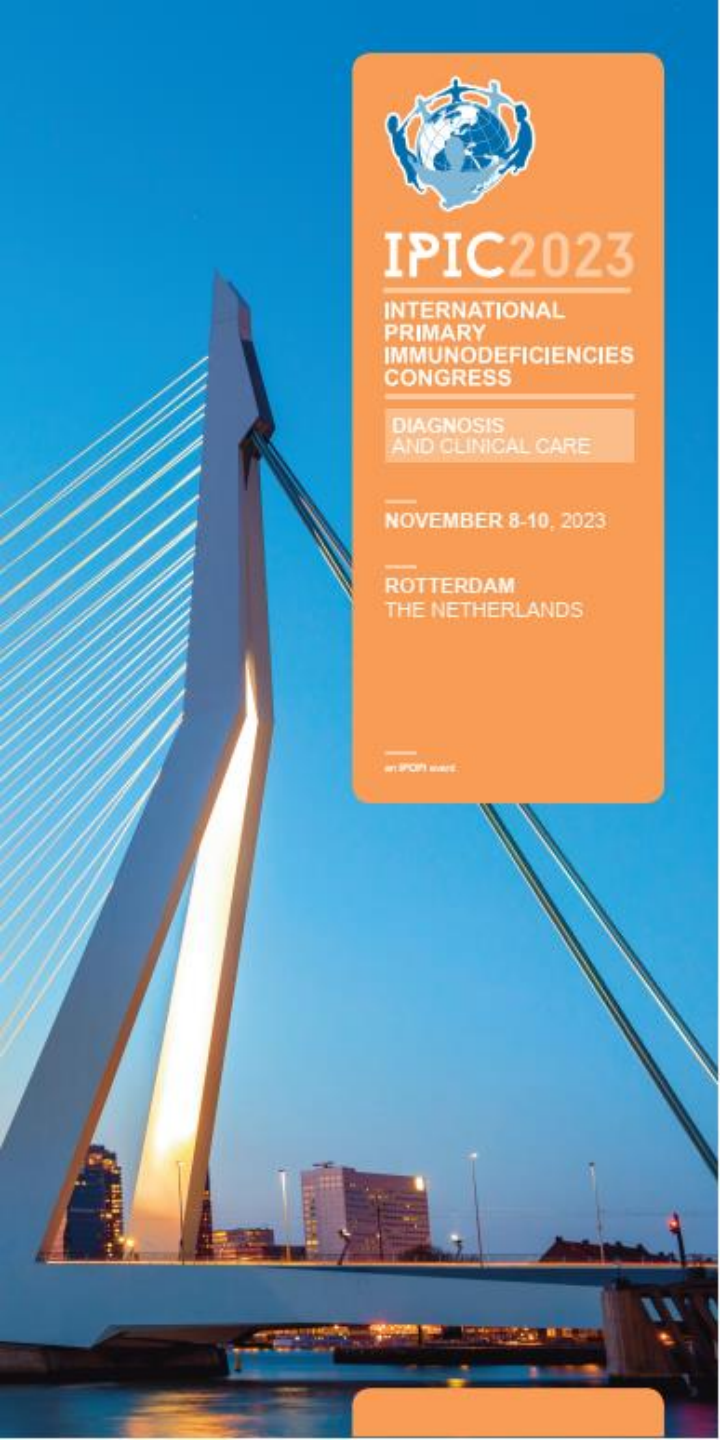

Thank you for your attention!

Panel discussion

Leni von Bonsdorff, IPFA

Prof Siobhan Burns, Chair of ESID Clinical Working Party

Deirdre Fehily, European Commission

Dominika Misztela, PPTA

Otilia Stanga, Romanian PID patient organisation (ARPID)

Leire Solis, IPOPI

Concluding remarks by MEP István Ujhelyi (S&D, Hungary)

Event closure by Johan Prevot, IPOPI Executive Director

Thank you for your attention!

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