PPTA

Access to plasma-derived medicines

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CONFERENCE: THE SUPPLY OF PLASMA-DERIVED MEDICINAL PRODUCTS IN THE FUTURE OF EUROPE

23-24 April 2024, Rome

PDMPs are often the only, life-saving treatment in many rare and orphan diseases and conditions

ILLUSTRATIVE/ NOT EXHAUSTIVE

PDMP class	Conditions Treated
Coagulation factors: *Essential for blood clotting, used to treat genetic bleeding disorders and surgical bleeding.*	• Bleeding Disorders I. Hemophilia A and B II. Von Willebrand disease (VWD) III. Rare clotting factor deficiencies - Bleeding from trauma, Liver disease
Immunoglobulins: *Proteins used to neutralize foreign objects such as bacteria and viruses.* *Used to treat primary and secondary immunodeficiencies and autoimmune disorders.*	• **Immunodeficiencies** **I. Primary (PID)** **II. Secondary (SID)** • **Neurology: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) , Multifocal Motor Neuropathy (MMN), Guillain-Barré Syndrome (GBS), Autoimmune Encephalitis** • **Idiopathic Thrombocytopenic Purpura (ITP)** • **Dermatology: e.g. Blistering Disease, Pemphigus, Scleroderma**
Hyperimmune Globulins: *Prevention and treatment of specific infections and other indications.*	- Rabies, tetanus, hepatitis B, cytomegalovirus, varicella-zoster virus - Rh negative pregnancy - Liver transplant and surgery
Alpha-1 Proteinase Inhibitors: *Protects tissues from enzymes of inflammatory cells.*	• Alpha-1 Antitrypsin Deficiency (AATD) (genetic emphysema)
Albumin: *The major plasma protein, regulating blood volume and providing many essential functions.*	- Cardiac surgery - Liver disease - Severe infections - Emergency and Surgical Medicine (shock, severe burns and during surgery)
C1-esterase inhibitor (C1-INH): *A protein found in the fluid part of blood. It controls a protein called C1, which is part of the complement system. This system is a group of proteins that move freely through bloodstream.*	• Hereditary angioedema (HAE)

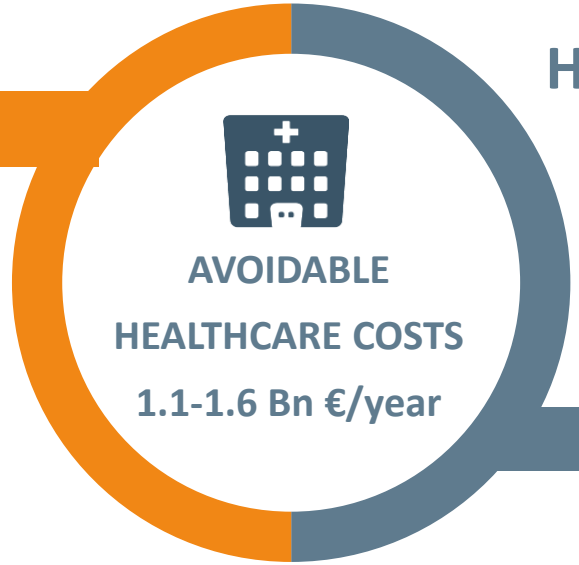
PDMPs not only treat debilitating and life-threatening diseases but also translate into high socio-economic value and substantial health gains

HEALTH GAINS AND AVOIDABLE HEALTHCARE COSTS (PID & HAEMOPHILIA IN EUROPE)

PIDs: treated with IgGs

PID≈1 Bn €/year

PDMP eligible population in Europe: ~44,000
Survival rate 1979 = 30 % vs. 2010 = ~100%
65% reduction in infections



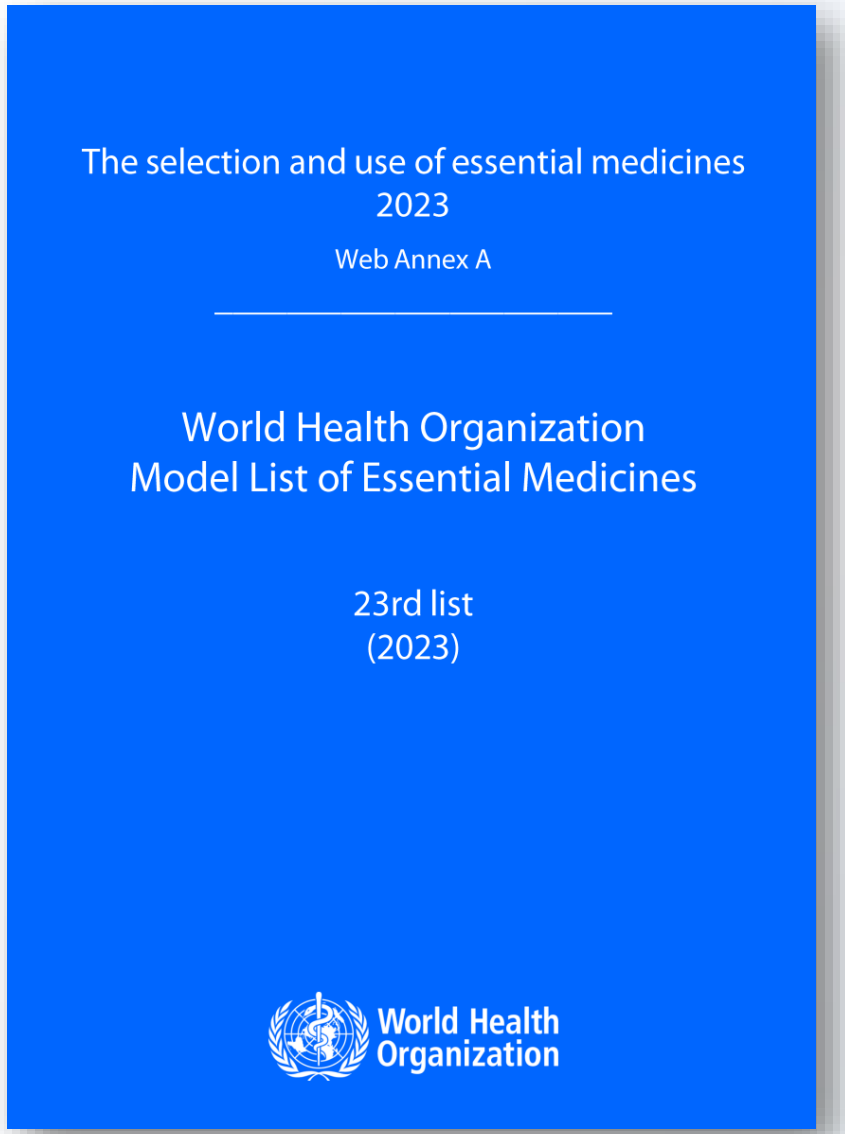
Haemophilia: Coagulation Factors

PDMP eligible population in Europe: ~47,000
Life expectancy prior 1955 = 19 years vs. 2001 = 71 years; 80% reduction in bleeds

Haemophilia ≥ 1 Bn €/year

Limiting access to PDMPs often equates with denying Patient Access to the only effective therapy and reduces the concomitant socio-economic benefits.

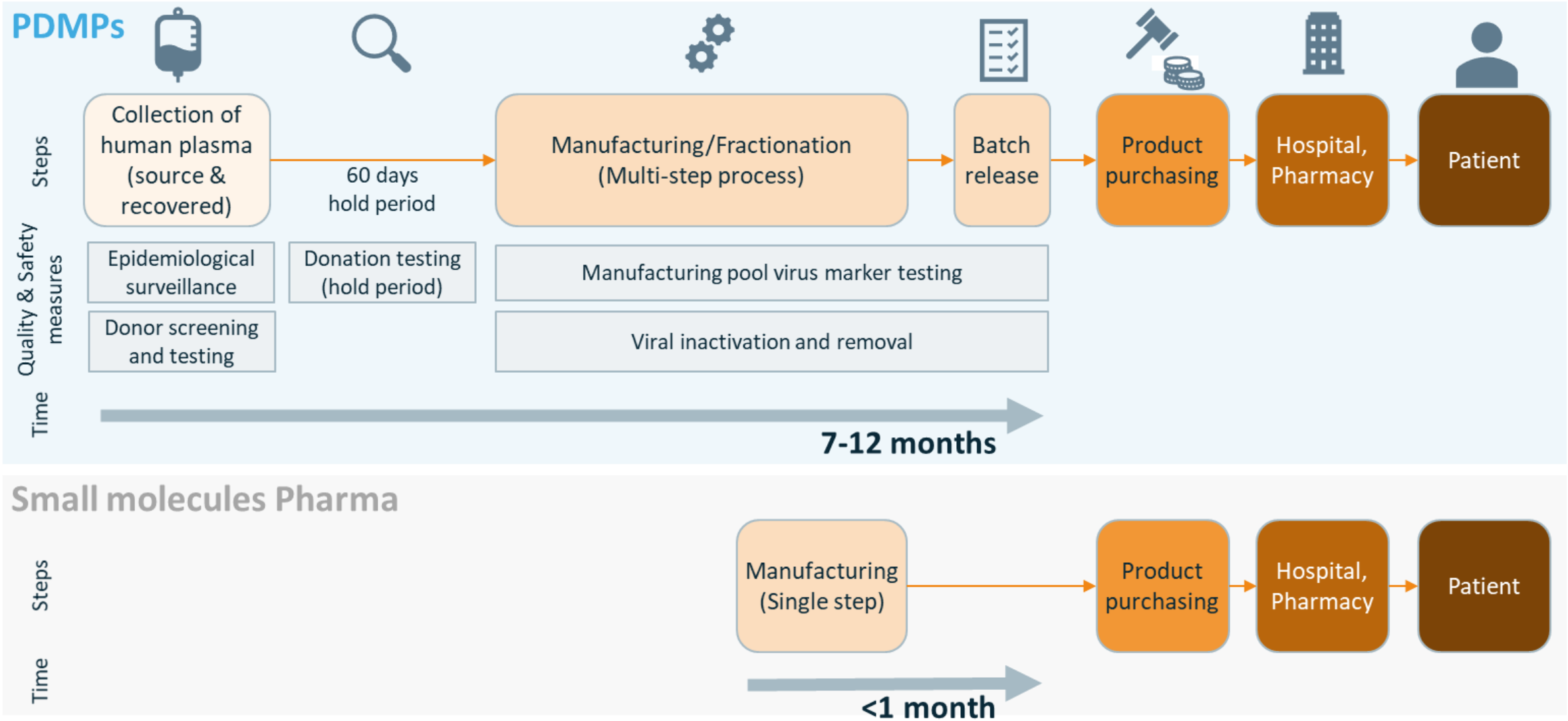
- Health Gain = Recovered DALY * VOLY
- DALY is the sum of the Years of Life Lost (YLL) due to premature death and the Years Lost due to Disability (YLD)
- Key DALY component for PID is # of severe infections per year and for Haemophilia: key DALY component is 3 of bleeds per year
- VOLY (Value of a Statistical Life Year) is estimated at €40,000
- Avoidable indirect healthcare costs for PID based on reduction of hospitalization days due to severe infection



1. Human Immunoglobulin (IgG): Used for various immune deficiencies and autoimmune disorders.
2. Coagulation Factors (e.g., Factor VIII, Factor IX) Essential for the treatment of hemophilia and other bleeding disorders.
3. Albumin: Used for the treatment of hypovolemia, hypoalbuminemia, and burns.
4. Anti-D Immunoglobulin: Used for the prevention of Rh isoimmunization in Rh-negative individuals.
5. Intravenous Immunoglobulin (IVIg): Employed in the treatment of autoimmune diseases, immunodeficiency disorders, and certain neurological conditions.

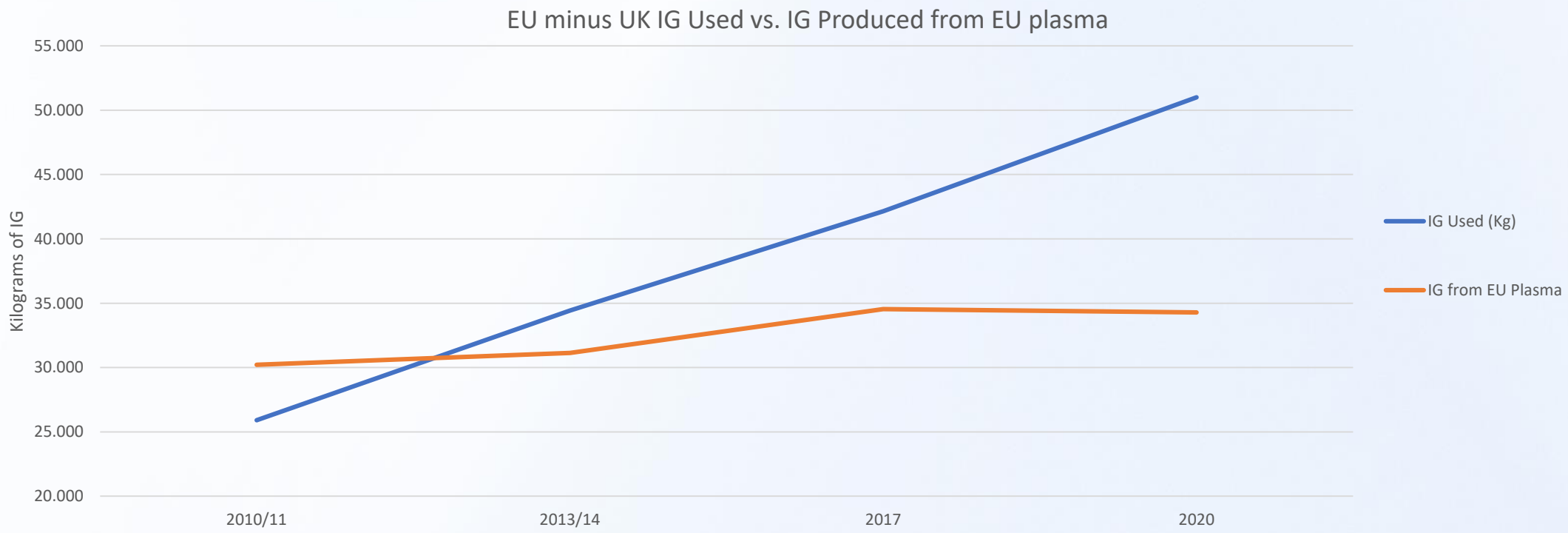
The PDMP value chain from Donor to Patient is extremely complex, lengthy and highly regulated

COMPARISON OF PDMP VALUE CHAIN WITH SMALL MOLECULES



Source: Burnouf: An overview of plasma fractionation Ann Blood 2018;3:33, PPTA analysis, Vintura analysis

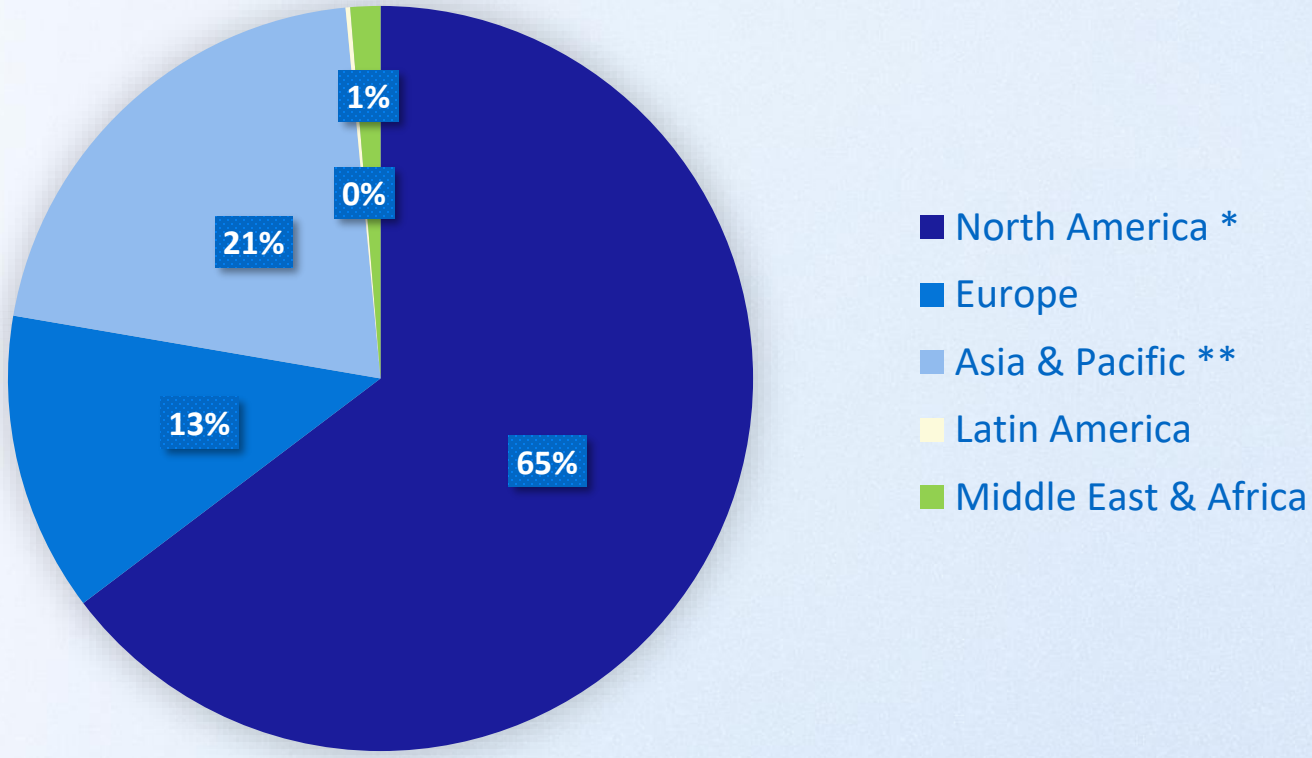
The volume of IG used in the EU has grown much faster than plasma collections in the region



Source: The MRB data, 2023

Plasma is still dominated by United States after the pandemic, so countries still rely on US plasma

Origin of Plasma for Fractionation – 2021 Estimate



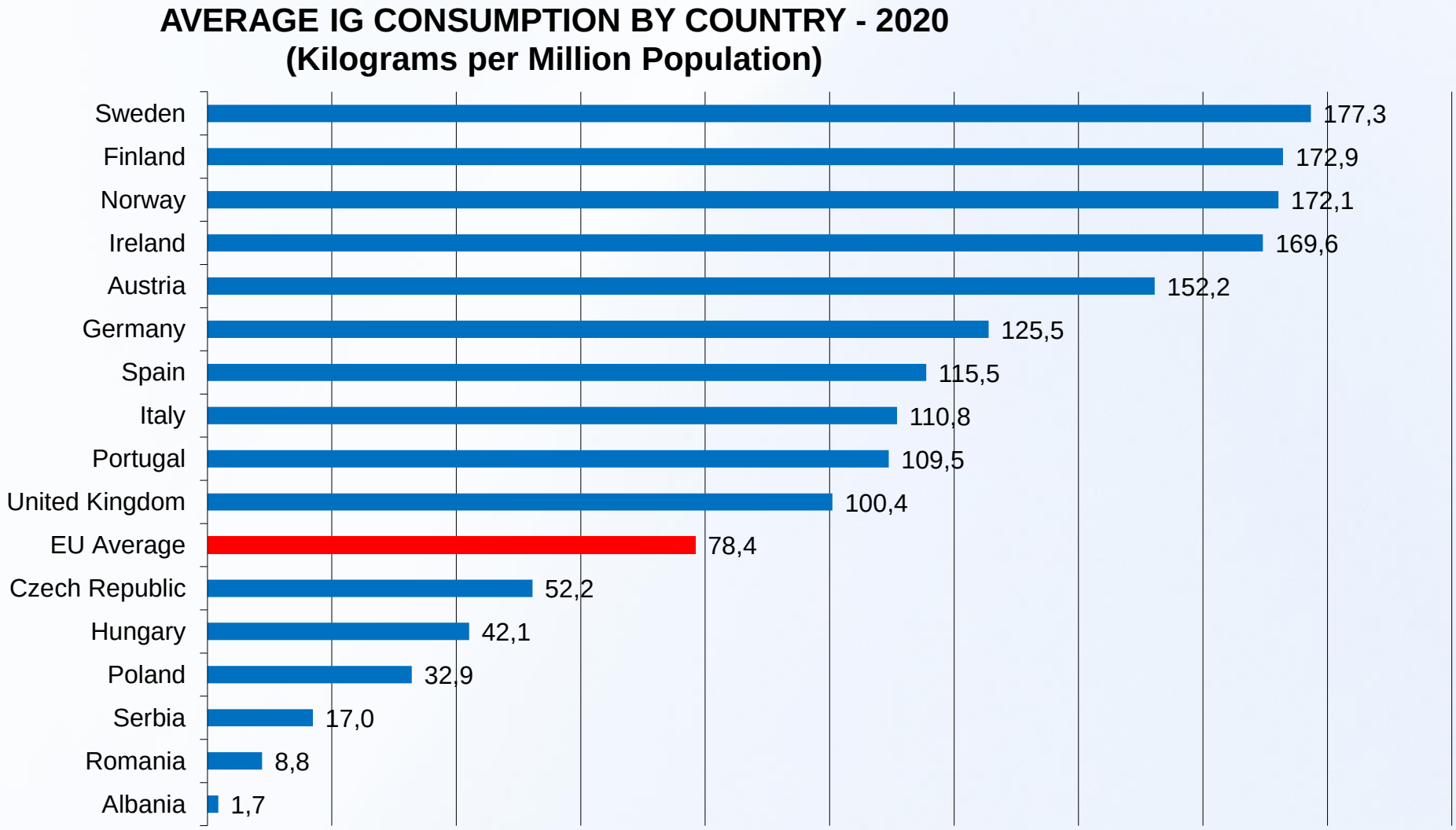
*United States represented over 98% of the North America total

** China represented about 75% of Asia & Pacific total

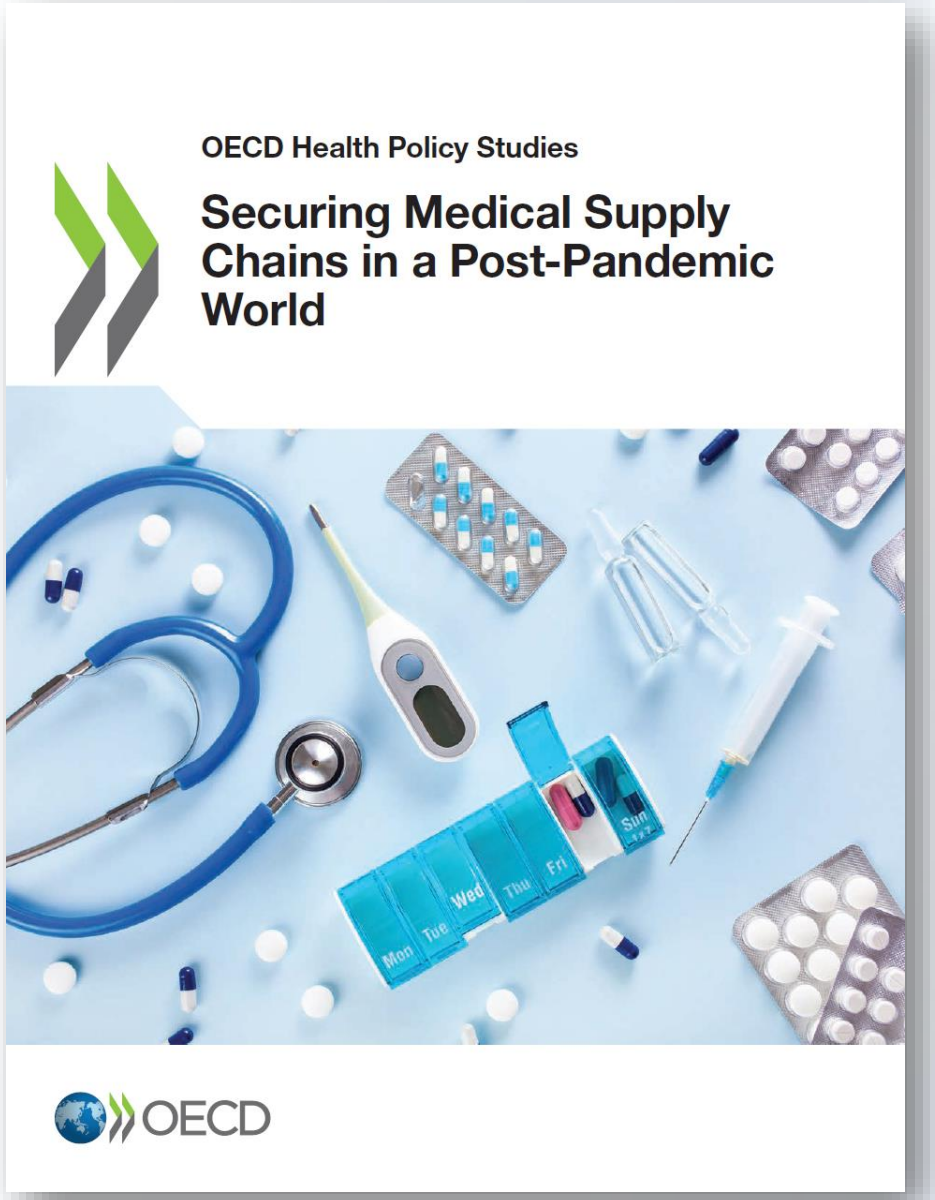
Total Plasma Collection volume 2019: 69 M liters
2020: 59 M liters (-14% vs2019)
2021: 60 M liters (-12% vs. 2019)

SOURCE:
THE MARKETING RESEARCH BUREAU

Europe average consumption of IG (IVIG & SCIG) for the year 2020 – Selected Countries and Europe Average



SOURCE: THE MARKETING RESEARCH BUREAU



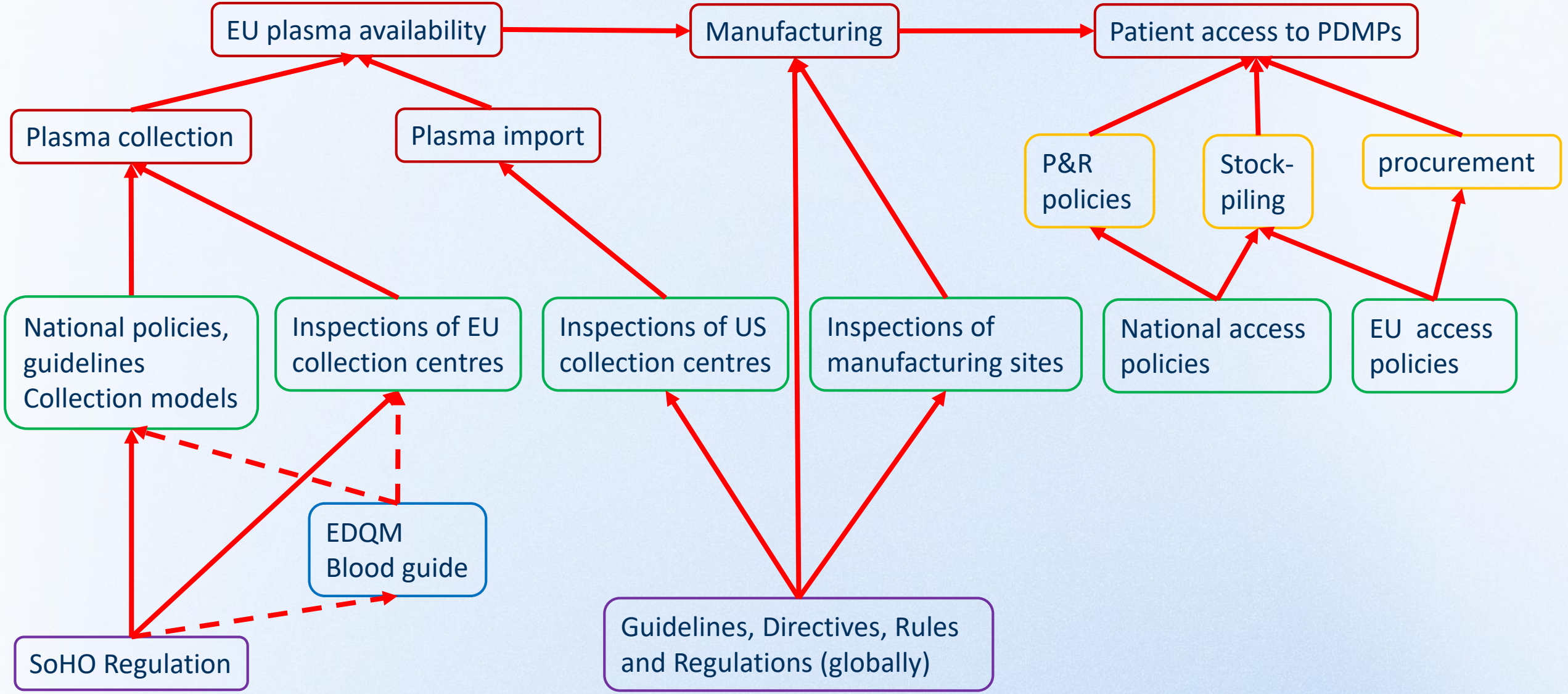
Root causes of supply challenges

- *"The most difficult challenge is in the collection of raw material, i.e. plasma, which can only be sourced from human donors.* ***Finding potential donors is the first and most relevant hurdle to mitigate supply shortages.*** *Beyond eligibility requirements, varying donation frequency and compensation schemes, donations are highly vulnerable to the effects of bad weather, health crises, geopolitical tensions, that can discourage even willing donors."*
- *"Reasons for shortages are likely to be two-fold:* ***increasing numbers of patients eligible to be treated*** *with plasma-derived therapies,* ***and uncertainty in the supply of the raw material*** *(i.e. plasma from human donors)."*
- *"PDMP manufacturing is challenging as it is affected by variations in the volume of donations,* ***complex regulations****, strict safety procedures to ensure purity and eliminate potential viruses and bacterial contamination, as well as lengthy* ***manufacturing processes that can take 7-12 months."***

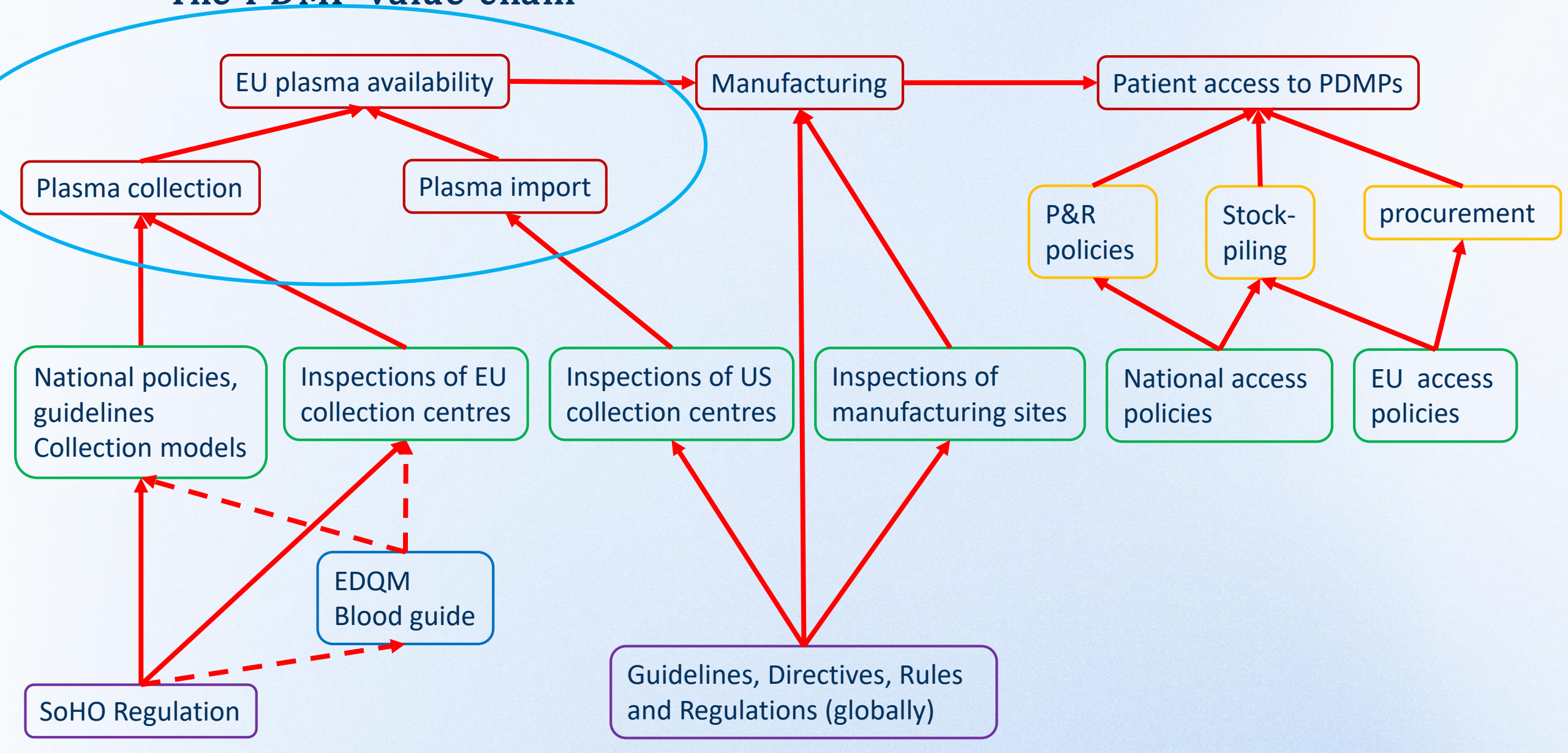
Solutions

- *"Streamlining the regulatory environment for plasma could help to* ***avoid overlapping requirements and double compliance standards****."*
- *"Beyond that, the EU Directive does not* ***differentiate*** *between whole blood and plasma donations, although both products are different in terms of manufacturing and usage. While plasma undergoes a rigorous fractionation and a multi-step purification process with several inactivation steps, the same does not apply to blood donations. Despite that, both products face similar regulatory treatment"*

The PDMP value chain

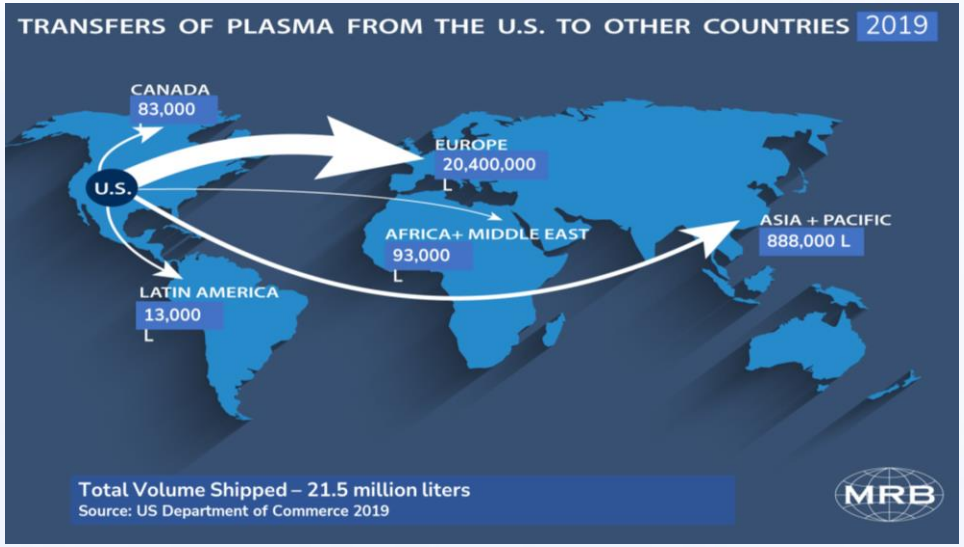


The PDMP value chain



Facts and Figures

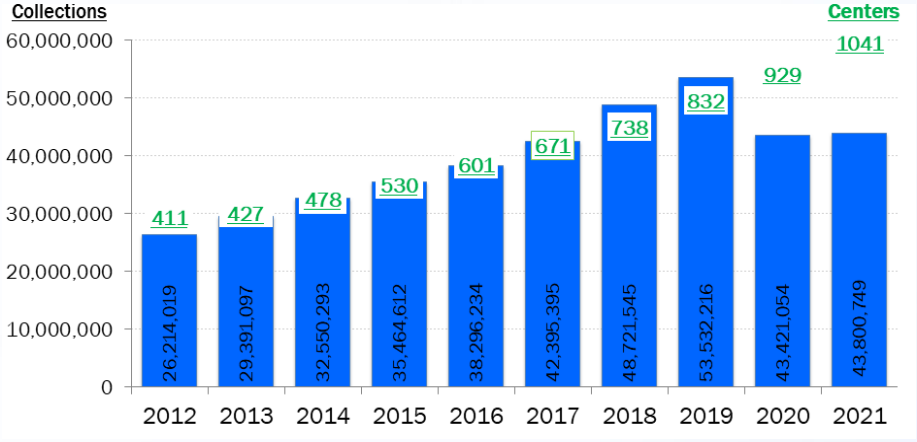
- US collects majority of world's plasma (65%) for PDMP production
- EU relies on US plasma ~40%
- Only four EU countries (Austria, Czechia, Germany and Hungary) contribute to ~55 % of total plasma collected in EU



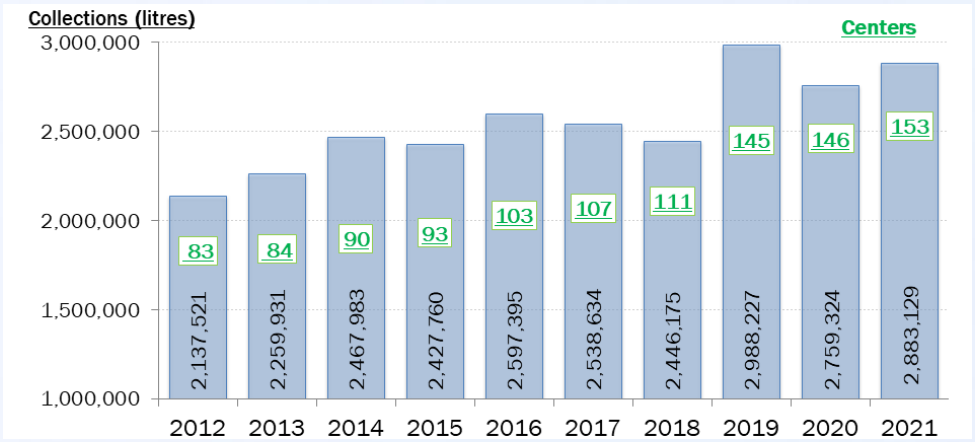
COVID-19 pandemic

- highlighted plasma collection imbalance between EU and US
- increased EU's dependency on US plasma

North America Collections & #Centres (providing data)



EU Collections & #Centres (providing data)



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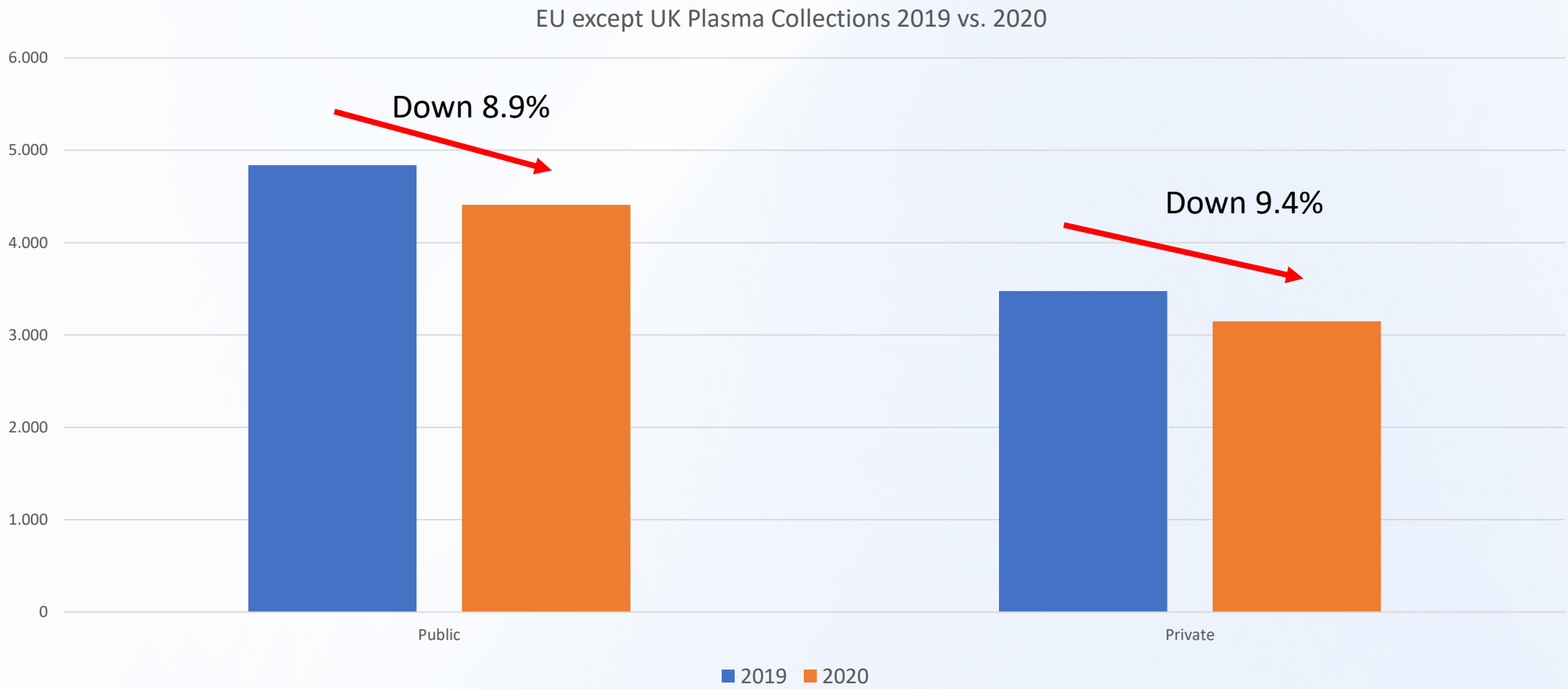
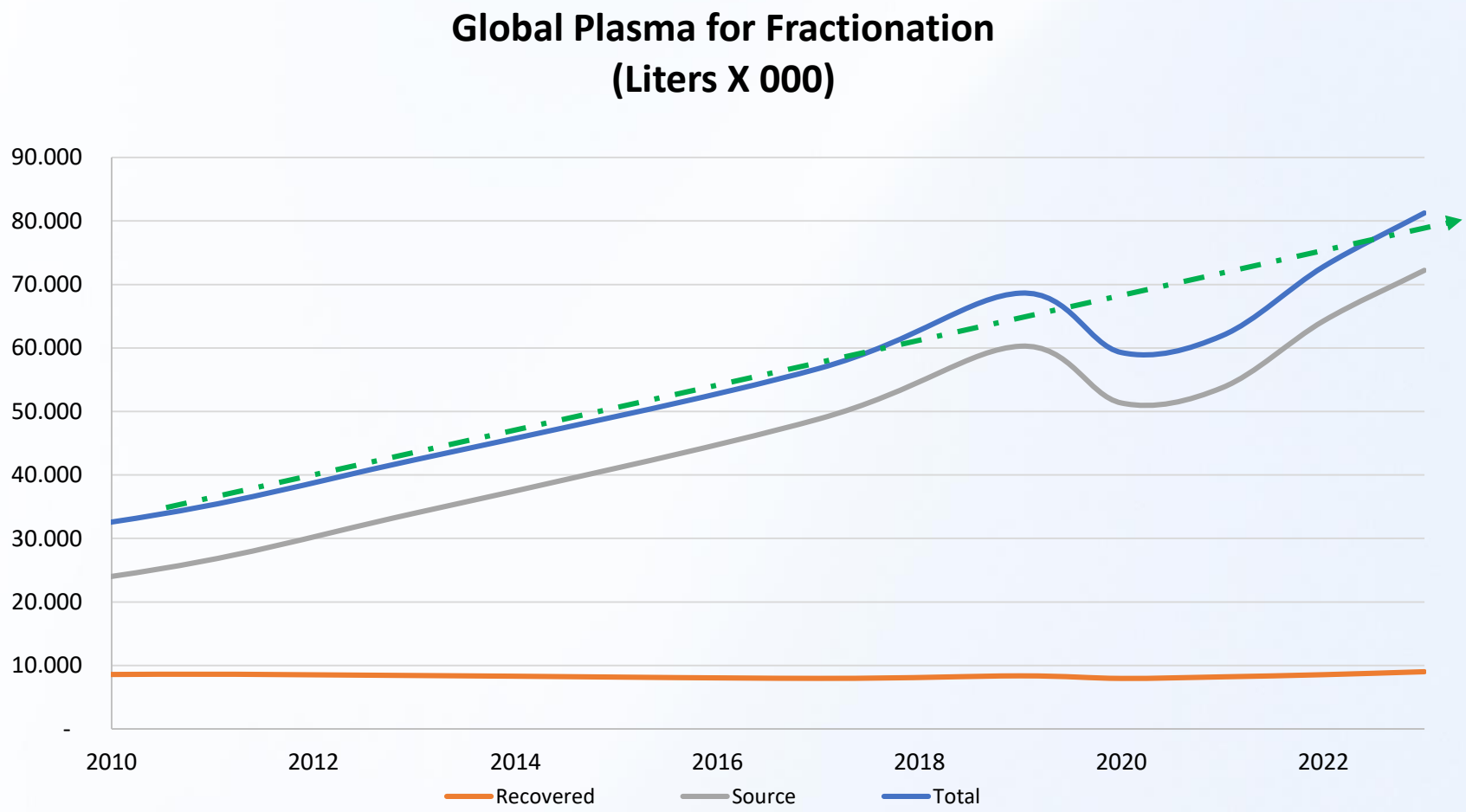
Pandemic resilience

European Union Plasma Collections by Type



Overall EU collections decline was 9.1% in 2020 vs. 2019 due to the pandemic.
Total 2020 EU minus UK volume was 7.6 million liters (excludes private recovered)

Globally, Source (Apheresis) plasma is providing all the volume growth for fractionation



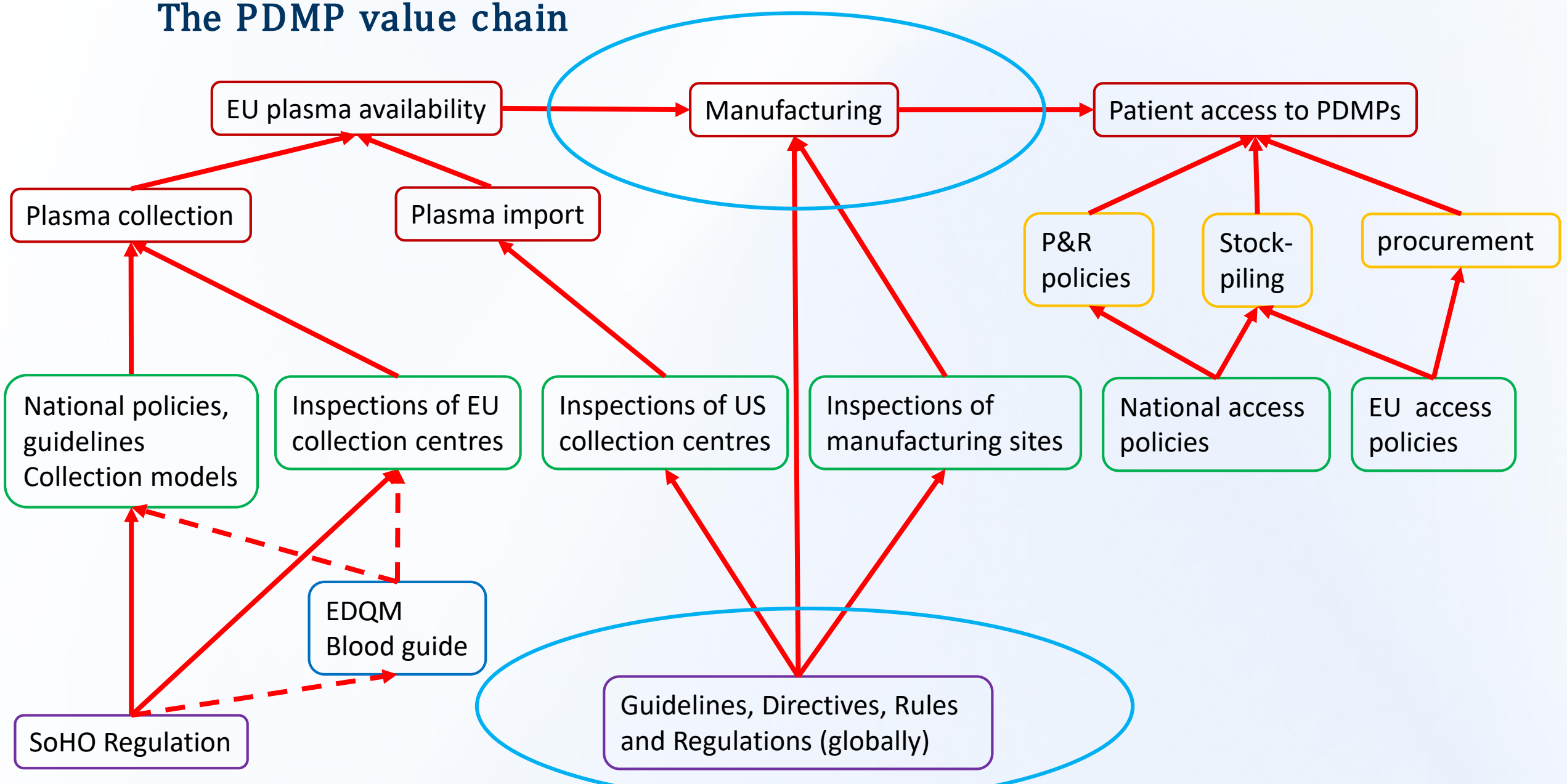
The global volume of plasma for fractionation was >12% higher in 2023 than in 2022. Collections increased slightly above historical growth trendline.

2023 Source plasma grew 12-15% over 2022, driven by the US. European source growth was closer to 2-5% growth. International growth above Western country average.

The volume of Recovered plasma (all public) is returning to some growth after Covid

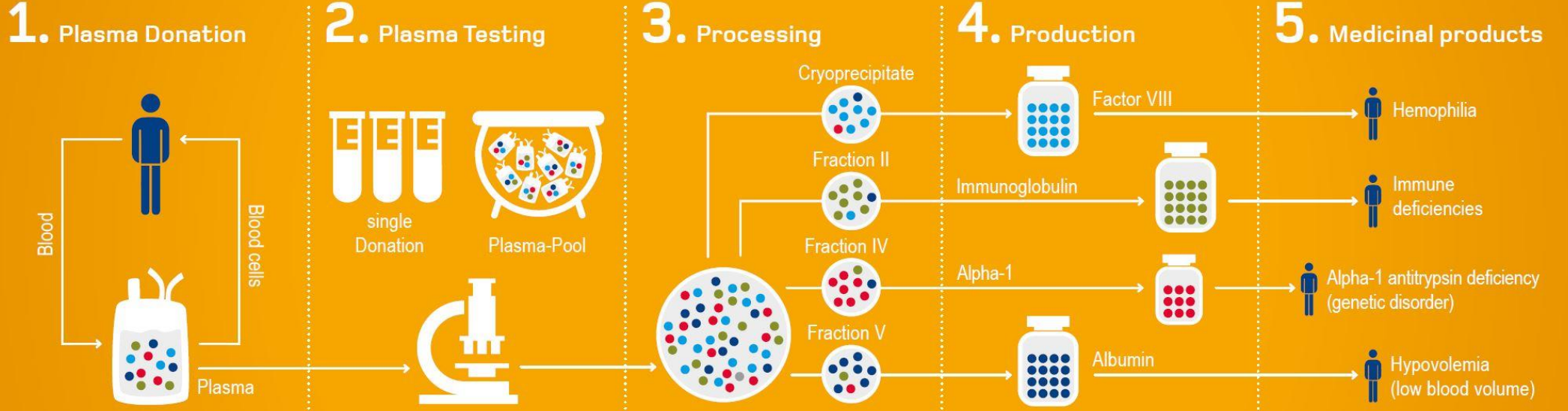
SOURCE: THE MARKETING RESEARCH BUREAU

The PDMP value chain



The Uniqueness of PDMPs and the Complexity + Lenght of the Fractionation Process

Manufacture of plasma derived medicinal products – From the donor to the patient



Plasmapheresis

The pheresis machine draws blood and separates the plasma from the cell components. During the donation process, the donor receives the blood cell back.

Viral safety

Every donation is tested on AIDS, Hepatitis and Parvo–B 19. This testing is performed again on the plasma pool before the fractionation

Base Fractionation

Proteins are precipitated and separated from the plasma. In the order of successive processing steps, they are numbered and called fractions.

Purification and Filling

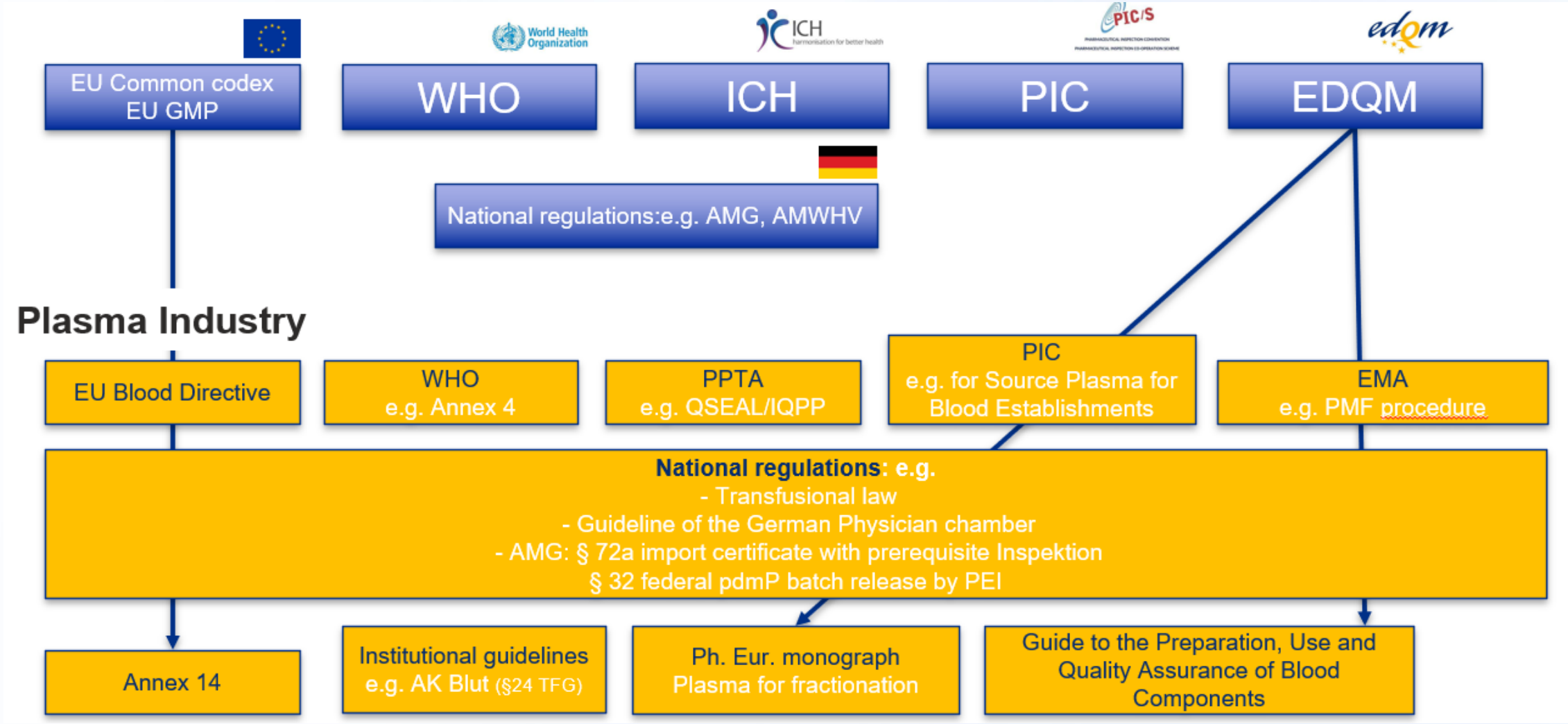
Viral removal, reduction, pathogen elimination and inactivation with various treatments. Purified proteins are filled and packed.

Indications

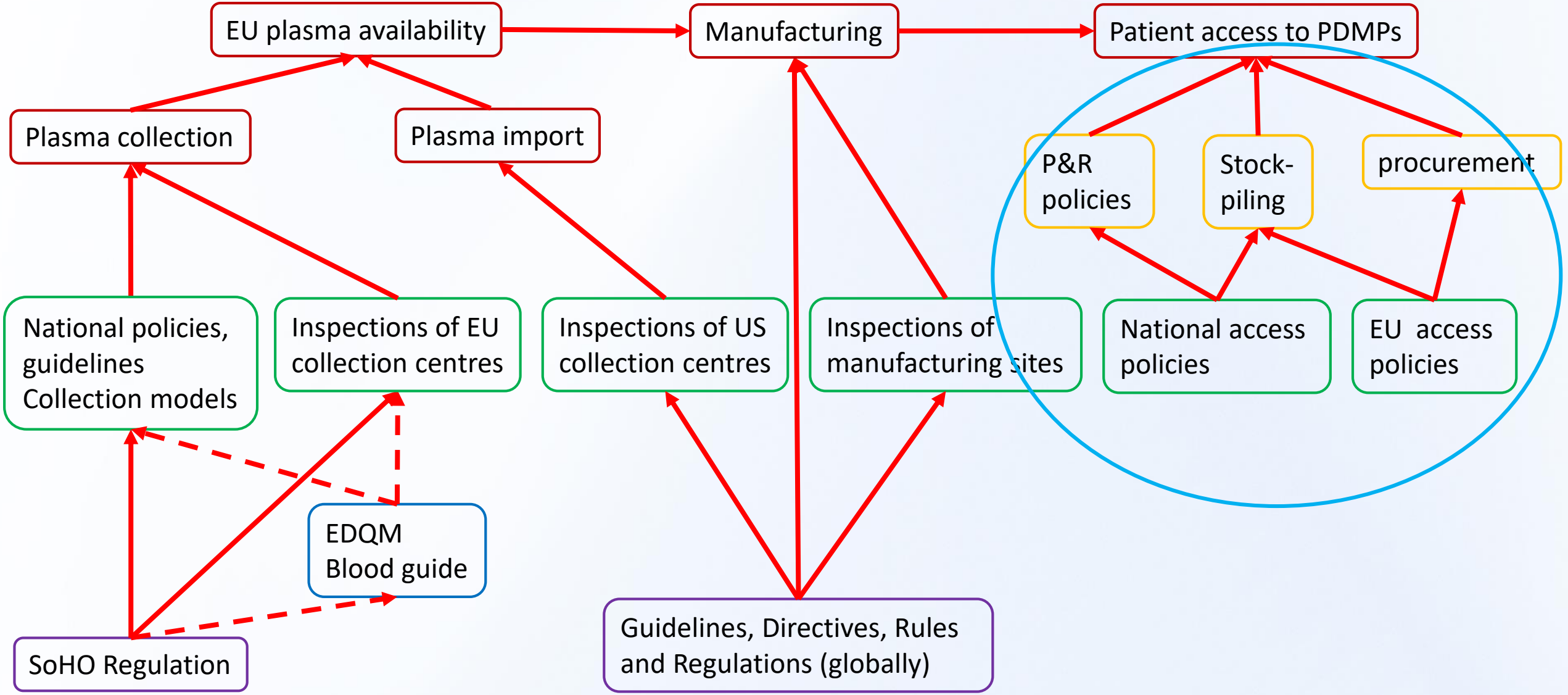
Medicinal products made from plasma are used to treat various genetic, chronic and acute life-threatening diseases.

30 years traceability from donor to patient.

Guidelines, Directives, Rules and Regulations - Pharma and Plasma Industry Example: Germany

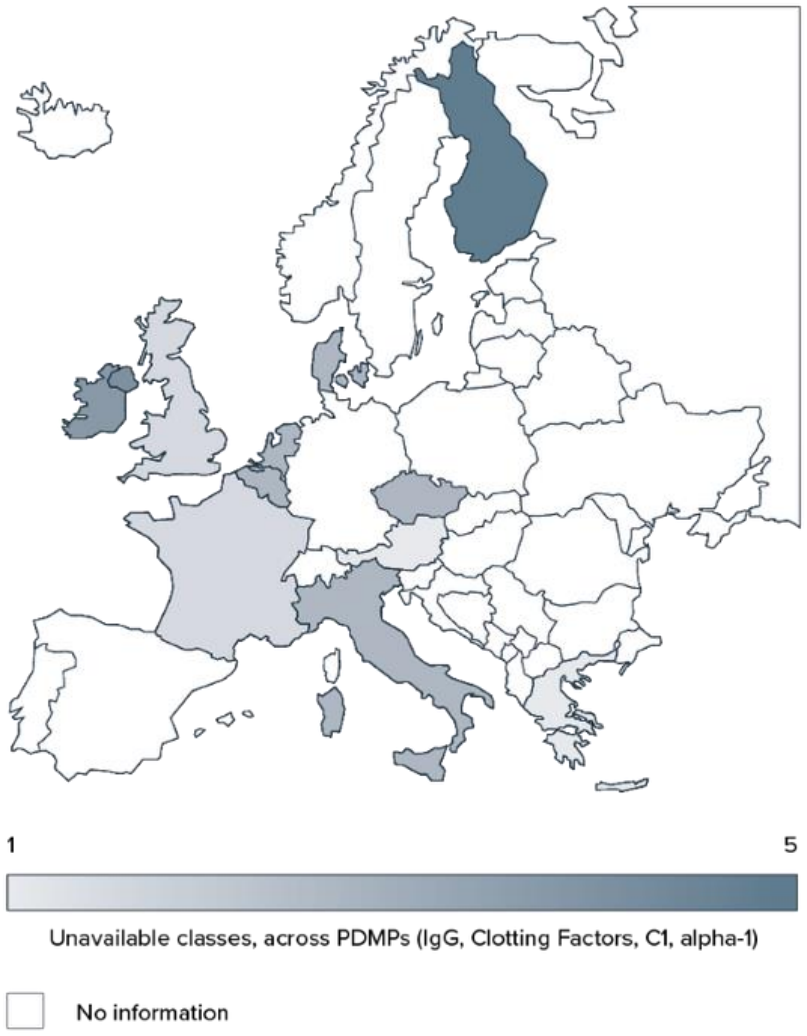


The PDMP value chain

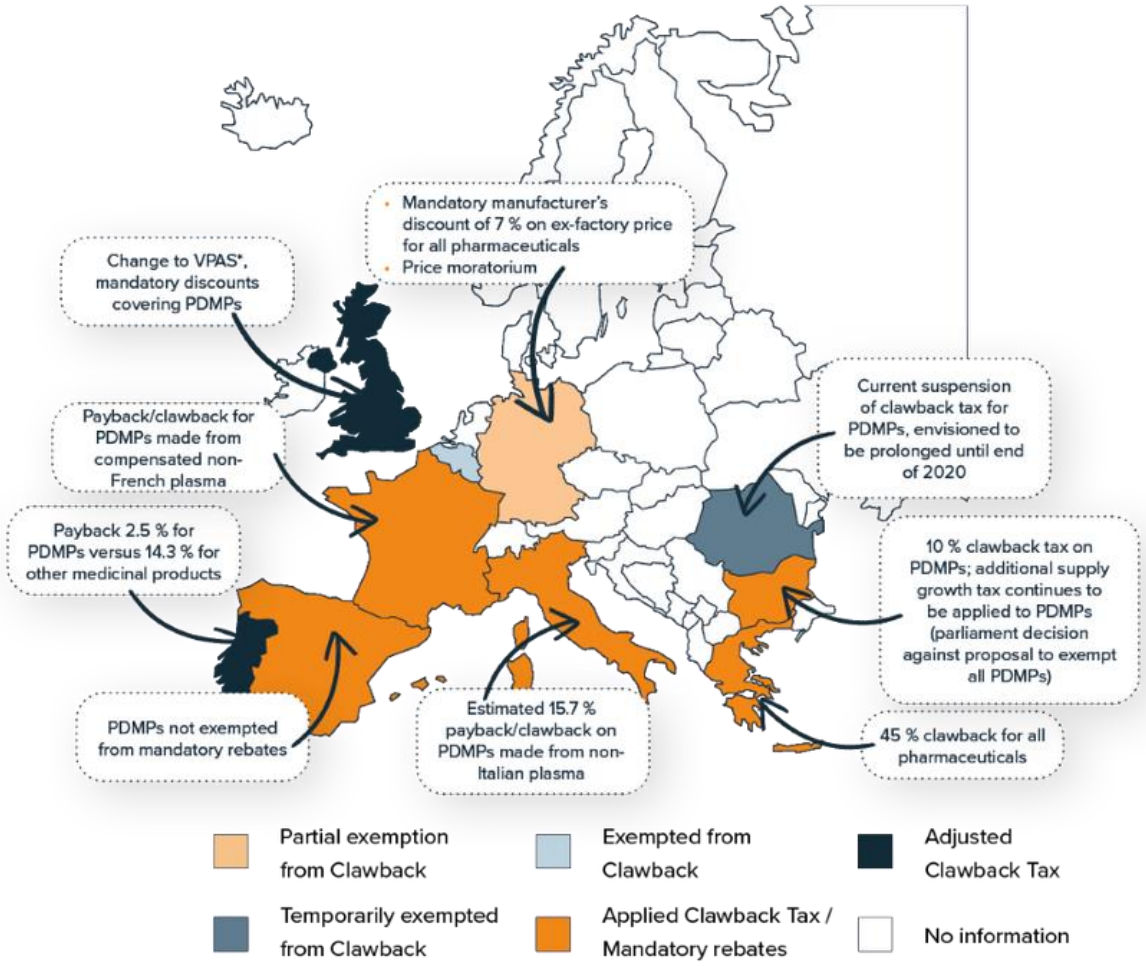


Formal Patient Access: Reimbursement coverage and cost-containment measures impact availability of treatments to patients

REIMBURSEMENT COVERAGE & CHALLENGES



ECONOMIC & COST CONTAINMENT MEASURES



Therapeutic Patient Access: Tenders often necessitate “automatic” switch between brands for economic reasons, due to non-exchangeability this affects patient’s tolerability

NON-EXCHANGEABILITY & PATIENT PROFILES

PRODUCT CONSIDERATION		PATIENT RISK PROFILE
STABILISERS: SUGARS & DERIVATIVES	• Sucrose	• Renal pathology
	• Glucose/dextrose	• Diabetes
	• Maltrose	• Interference with certain glucose monitoring systems in diabetic patients*
	• Sorbitol	• Contraindicated in hereditary fructose intolerance
STABILISERS: AMINO ACIDS	• L-Proline	• History of hypersensitivity • Related metabolic disorders (hereditary hyperprolinemia)
IMMUNOGLOBULIN A		• Presence of anti-IgA antibody in persons with selective IgA deficiency (IgA<0.05 g/L) • History of hypersensitivity
SODIUM		• Infants • Individuals with hypertension, cardiovascular disease, kidney disease, endocrine system, adrenal gland disorders
HIGH OSMOLARITY		• Infants • Individuals with hypertension, cardiovascular disease, kidney disease, previous thrombosis and hypercoagulable state, pathologies with increased blood viscosity, central nervous system disorders, migraine or persistent headaches, hypovolemic state
FLUID VOLUME		• Infants • Individuals with conditions requiring fluid restrictions: cardiovascular disease (congestive heart failure), kidney, endocrine system, and adrenal gland disorders, conditions causing the release of stress hormones, treatment with corticosteroids, hyponatremia

NECESSITY FOR MULTI-BRAND AVAILABILITY

MEDICAL JUSTIFICATION AND/OR PATIENT NEEDS	IVIG*	SCIG/FSCIG**
INSUFFICIENT EFFICACY (OCCURRING INFECTIONS)	• Shorten interval between treatments • Increase the dose • Change product	• Shorten interval between treatments • Increase the dose • Consider IVIG
WEAR-OFF EFFECT	• Shorten interval between treatments • **Consider SCIG/fSCIG**	• Shorten interval between treatments • **Change product**
COMORBIDITIES	• **Change product** • Change infusion conditions • **Switch to SCIG/fSCIG**	• **Change product** • **Switch to IVIG**
POOR TOLERABILITY	• **Change product** • Consider premedication • Consider post medication • Lower infusion rate • **Switch to SCIG/fSCIG**	• **Change product** • Consider premedication • **Switch to IVIG**
LOCAL REACTIONS (SCIG)	• Uncommon	• **Change product** • Consider topical medication • **Switch to IVIG**
POOR VENOUS ACCESS	• **Switch to SCIG/fSCIG**	• N/A
POOR COMPLIANCE	• Change site of care	• Change site of care • **Switch to IVIG**
INCONVENIENCE	• Change site of care • **Consider or switch to SCIG/fSCIG**	• Change site of care • **Switch to IVIG**

Stockpiling can create severe distortions of trade within the internal market.

- national stockpiling can impact availability of medicines in other Member States (European Commission - Addressing medicine shortages in the EU, COM(2023) 672 final/2)
- A two-month stockpile requirement for Immunoglobulins for France is equivalent to more than the total annual supply for Belgium or Sweden.
- **A four months stockpile would exceed the total annual volume of IG use in Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Slovenia, Croatia and Greece combined**

(The Marketing Research Bureau (2017) – annual volumes IG supplied to France: 10,87 tonnes)

European White Paper on Key Economic and Value Considerations of Plasma Derived Medicinal Products in Europe

Green Paper: IgGs Appropriate Use

RECOMMENDATIONS

VINTURA

Patient Access challenges across Europe are severe and often differentiated by country; further exacerbated by insufficient plasma availability

FORMAL PATIENT ACCESS CHALLENGES

- **Reimbursement coverage** of PDMPs is uneven, leading to unacceptable access inequalities among European patient population
  - Coverage for IgGs is generally good for PIDs but low for SIDs
  - Factor X, Factor XIII and Protein C, are often entirely omitted from reimbursement lists
- **Eligibility criteria** even for reimbursed classes is often insufficient with treatment criteria unnecessarily limiting
- **Economic and Cost Containment measures** such as external reference pricing (ERP model), and/or clawback or payback taxes threaten the already fragile balance of the PDMP industry structure, ultimately limiting Formal Patient Access

THERAPEUTIC PATIENT ACCESS CHALLENGES

- **Procurement practices** such as centralized tenders are effective in controlling budgets but if based on price alone may limit access to the optimal treatment/ brand
  - Limitation of HCPs' therapeutic decision power
  - When a procurement system contravenes the clinical guidelines and therapeutic need, this system may require adjustments to better serve the patients.
- **Non-exchangeability** means that different brands within the same PDMP class have different tolerability profiles
  - Switching between brands for economic reasons rather than clinical need can have adverse effects on patients

PLASMA AVAILABILITY

- **Plasma collection** policies and collection volumes directly impact the amount of PDMPs produced. With availability of source plasma is extremely uneven: just four countries contribute more than 55 % of the total amount of plasma collected in Europe for manufacturing.
- **Therapeutic Need** for PDMPs is high and expected to increase. Plasma volume collected in Europe fulfils only around 63 % of the European PDMP clinical need; the rest is imported from the United States
- **Monetary Compensation** for donors' time and inconvenience is proven to be singularly effective but is only available in the four countries collecting the most plasma per capita (AT, CZ, DE, HU)
- **Coexistence** of private and public collection not only does not affect whole blood collection but effects greater plasma collection volumes

European IgG Advisory issued 7 powerful Recommendations on how to address the issues and fully realise the value of IgGs

- **Prof. Isabella Quinti *(Immuno, IT)***
- **Prof. Nizar Mahlaoui *(Immuno, FR)***
- **Prof. Karina Jahnz-Rozyk *(Immuno, PL)***
- **Prof. Jacob Van Laar *(Rheuma-Immuno, NL)***
- **Prof. P. Martin Van Hagen *(Immuno, NL)***
- **Prof. Silvia Sanchez-Ramon *(Immuno, ES)***
- **Prof. Mark Stettner *(Neuro, DE)***
- **Prof. Guido Cavaletti *(Neuro, IT)***
- **Prof. Richard Knight *(Neuro, UK)***
- **Prof. David Hunt *(Neuro, UK)***
- **Prof. Alexander Enk *(Derm, DE)***

1. **AVAILABILITY**: awareness through education, modern human plasma collection initiatives and infrastructure development in support of increasing plasma donation across Europe to address increasing medical need
    - Boost to plasma donations achieved by acceptance of demonstrably most effective means (e.g. private-public plasmapheresis coexistence and compensation)
2. **MEDICAL NEED**: acknowledgement of IgGs growing medical need to ensure access for all patients who could benefit in line with the appropriate use framework
    - Ensure equitable access in all indications where appropriate use criteria apply
3. **POLICY**: re-assessment and/or revision of policies on clinical, real world and HEOR data acceptability in regulatory and HTA processes at country level
    - Revision of regulatory requirements to authorise current IgG use (both in-label and off-label prescribing) in line with the proposed appropriate use criteria, and supported by different available data/evidence
4. **PATIENT VOICE**: ensuring patients, through patient support and patient advocacy groups, are invited to share their opinions and experiences, and are empowered to shape the future of the therapeutic IgG landscape in Europe
5. **COLLABORATION**: pan-European collaboration to exchange best clinical practices and data and foster joint initiatives, studies, and registries, both at single indication level as well as cross-indication
6. **RESEARCH & EVIDENCE**: intensify efforts to generate and/or analyse clinical and real-world evidence data in indications that remain data poor or fragmented (e.g. range of immune-mediated diseases), and agree on data generation formats and contents acceptable for further regulatory decisions in rare and ultra-rare diseases
7. **RESILIENCE**: explore key conditions and actions necessary to ensure resilience of European healthcare systems, both in terms of plasma collection volumes and sustainability and IgGs availability, patient access and appropriate use

PLASMA PROTEIN
THERAPEUTICS
ASSOCIATION

THANK YOU!