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EVENTFORUM BERN

Supply of plasma and use of plasma derived medicinal products in Europe: strategic and ethical aspects

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PLASMA ITALIA

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Disclosure

- I hereby declare that I have neither financial nor non-financial relationships related to any of the products or services described, reviewed, evaluated or compared in this presentation.

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PLASMA IS "GLOBAL"

HANDLING OF PLASMA AND PDMPs IN THE WORLD 2019

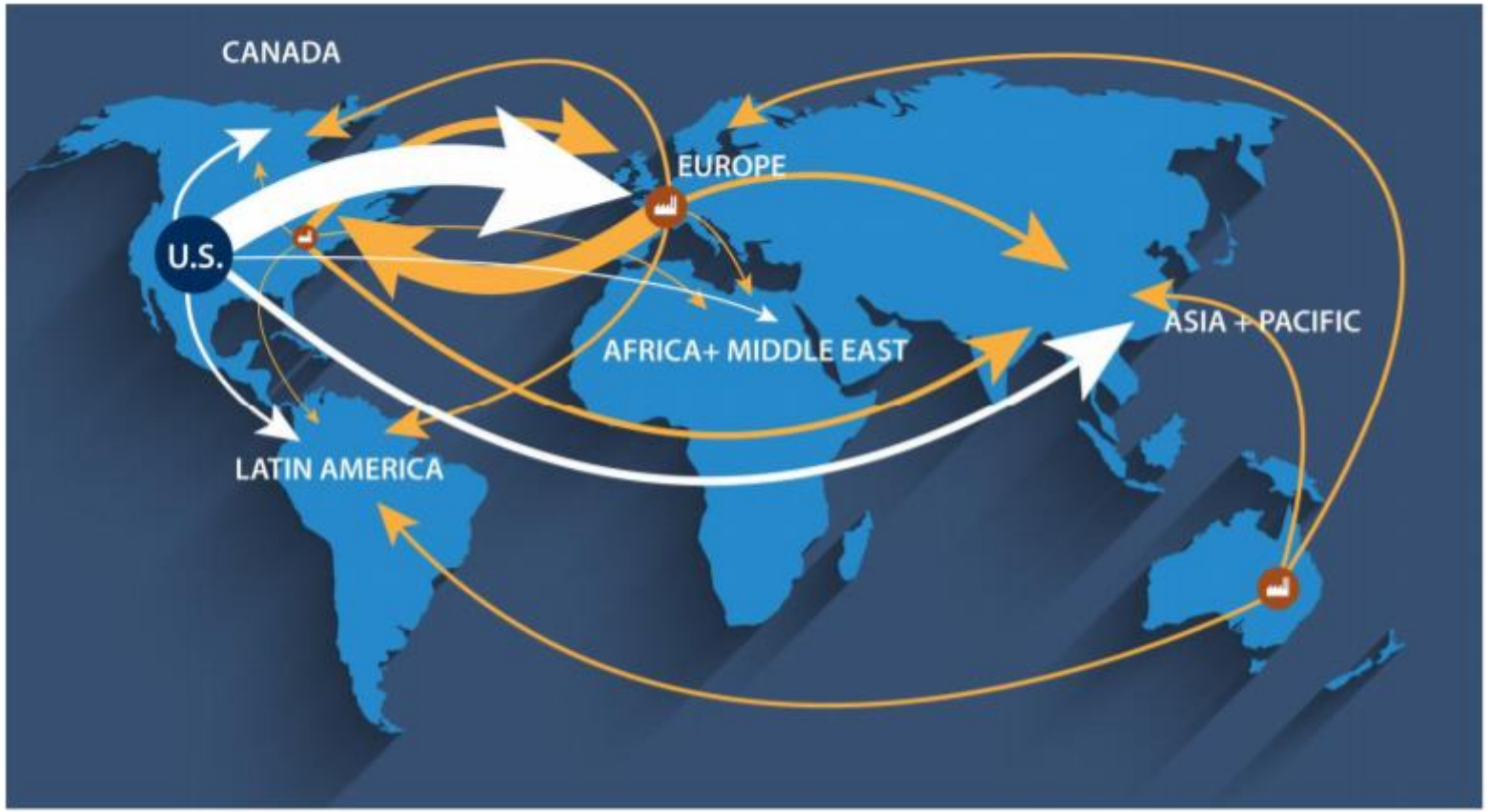
ARROWS:

IN WHITE

HANDLING OF PLASMA

IN YELLOW

HANDLING OF PDMPs



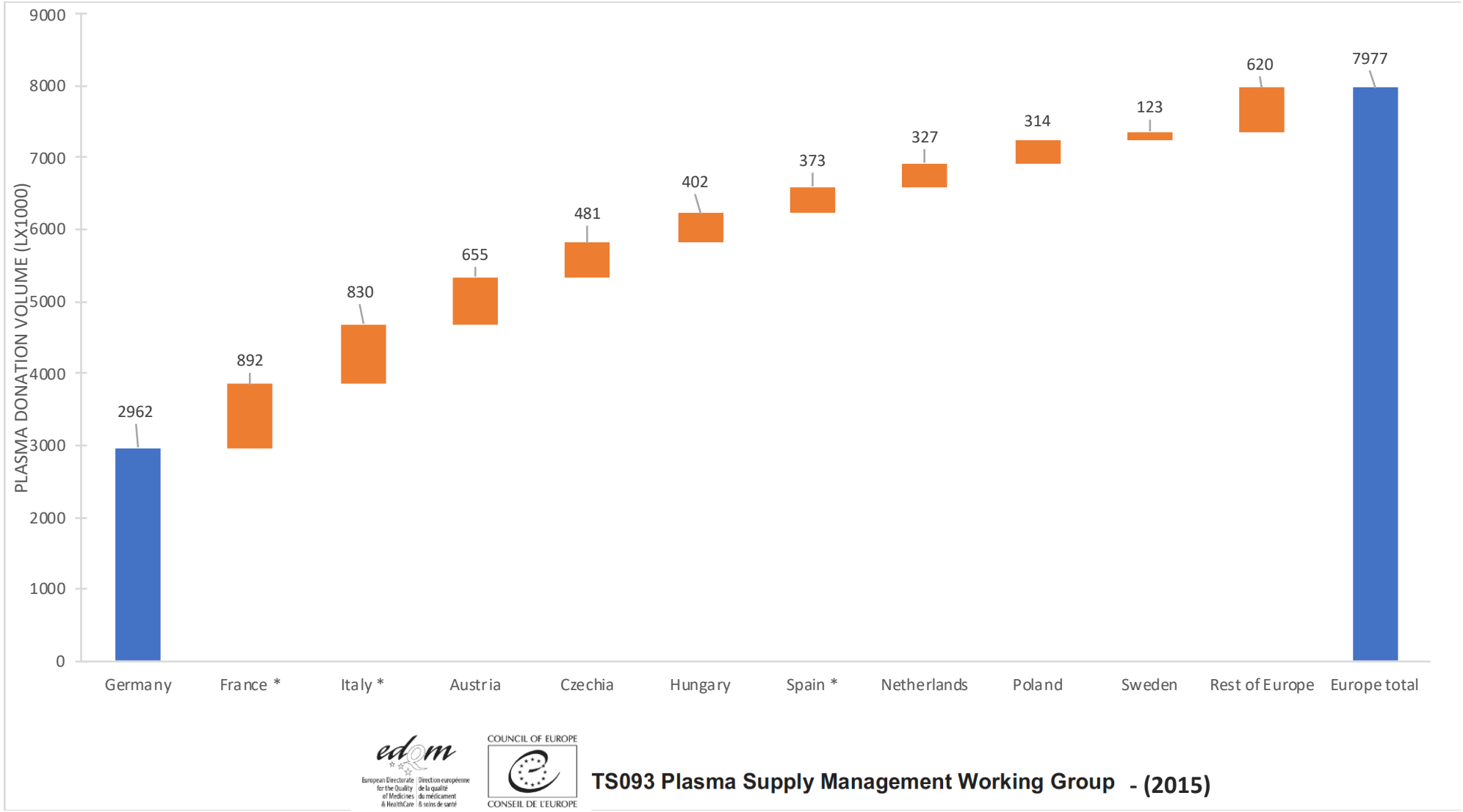
TOTAL PLASMA

FRACTIONATED

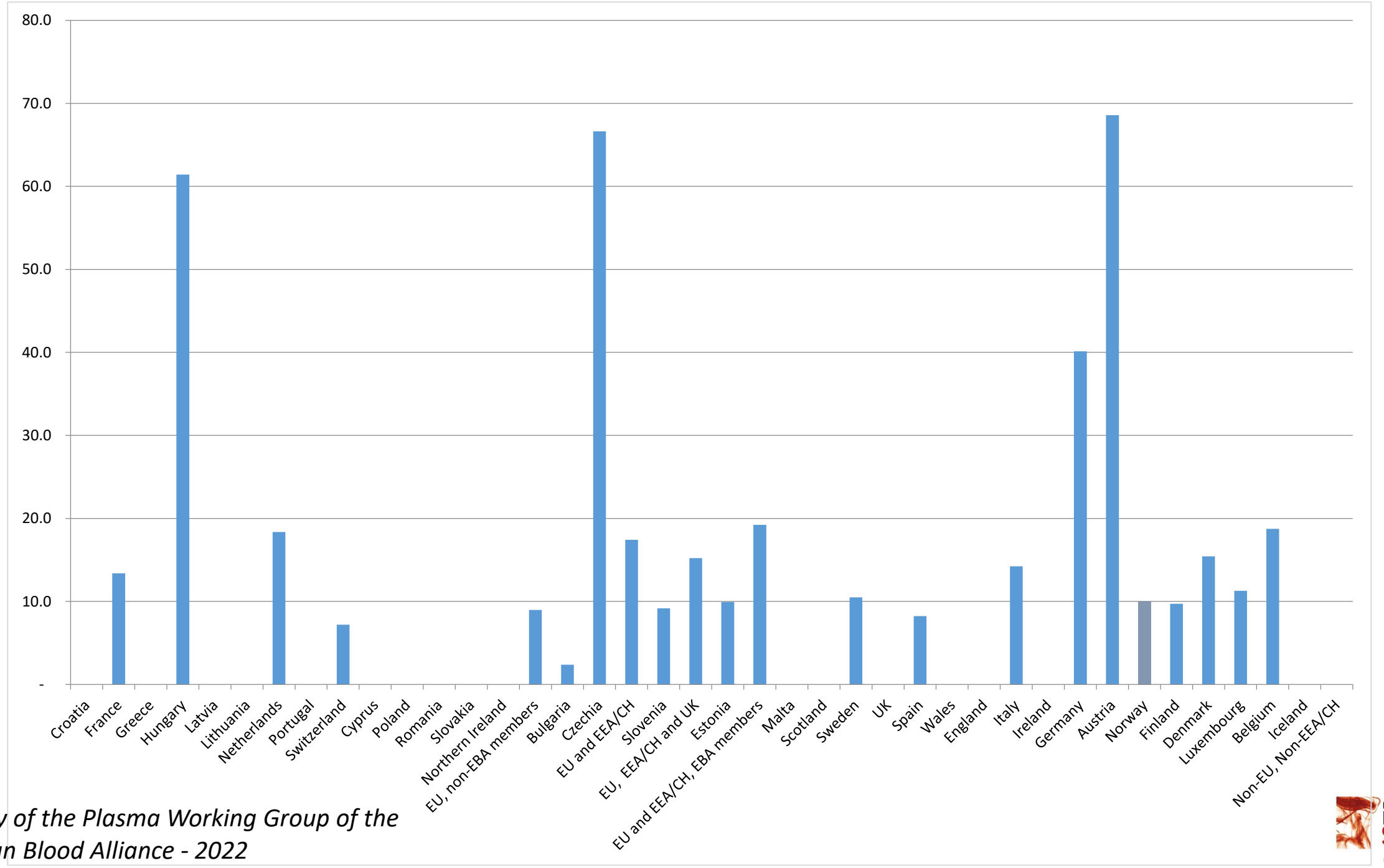
69 M LITERS

Courtesy of: D. Medica on behalf of GAEF – Gruppo Aziende Emoderivati Farmindustria adapted from P.Robert «Dans un Marché Mondialisé, Quel Accès des Patients Français aux Médicaments Dérivés du Plasma »?, November 11, 2020

Plasma for fractionation volume per country in Europe (source and recovered)



TS093 Plasma Supply Management Working Group - (2015)



Courtesy of the Plasma Working Group of the European Blood Alliance - 2022

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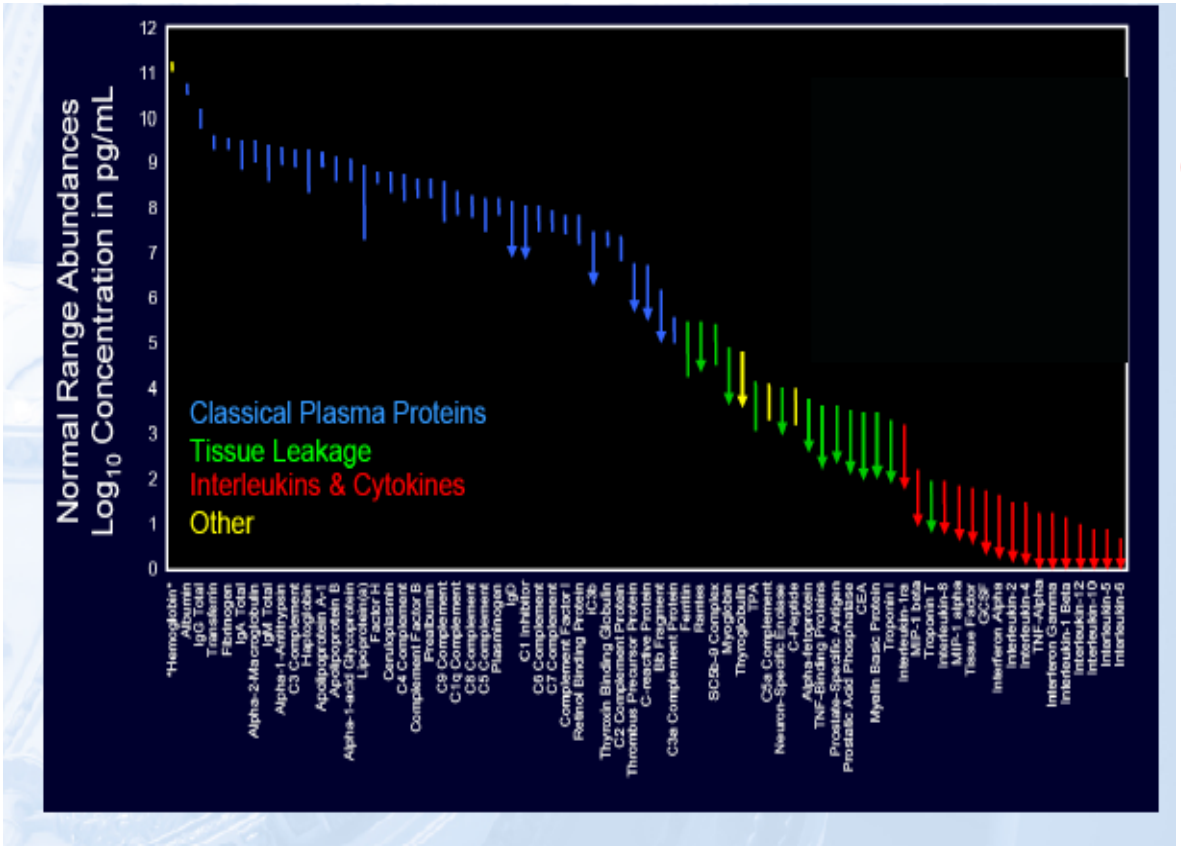
PLASMA IS «STRATEGIC» AND «ESSENTIAL»...

More than 1.000 plasma proteins…

Out of which around 250 identified

117 can be detected by a FDA validated test

Around 20 proteins are commercially available to be used in human therapy, effective, well tolerated and safe as to the transmission of infectious diseases



- albumin	(47)	- fibrinogen	(7)
- immunoglobulin (G)	(40)	- thrombin	(3)
- IgM	(1)	- fibrin sealant	(9)
- factor VIII	(26)	- prothrombin complex	(15)
- factor IX	(16)	- activated prothrombin complex	(1)
- factor VII	(2)		
- factor XI	(2)	- antithrombin	(14)
- factor XIII	(1)	- alpha-1 antitrypsin	(5)
- protein C	(2)	- C1-inhibitor	(2)
- activated protein C	(1)	- haptoglobin	(1)
- von Willebrand factor	(3)	- SD-plasma	(3)

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	% Total world population	*Immunoglobulin consumption (%)*	*Albumin consumption (%)*
North America	**5**	**48**	**18**
Europe	**9**	**25**	**16**
Latin America	**8**	**3**	**5**
Middle East & Africa	**21**	**4**	**7**
Asia & Pacific	**56**	**20**	**53**

Adapted from Patrick Robert MRB – Rome, Italy April 28-29, 2022

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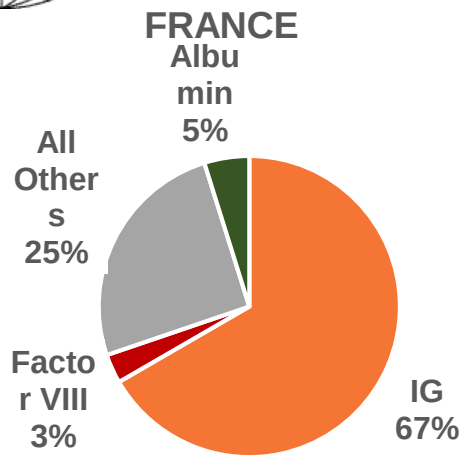
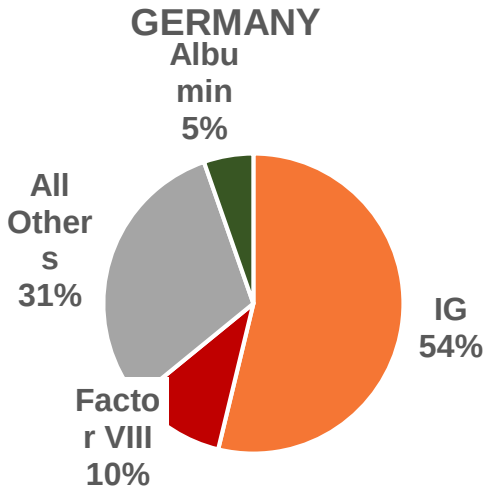
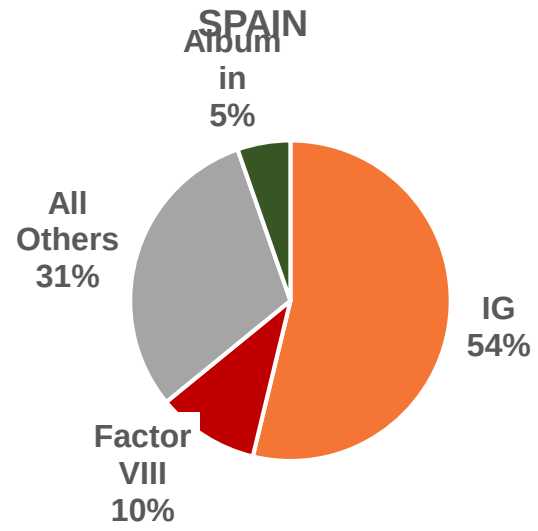
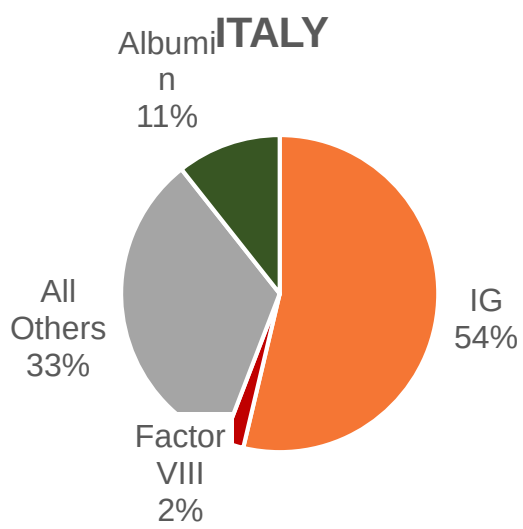
PRODUCT MIX IN SELECTED EUROPEAN COUNTRIES 2020

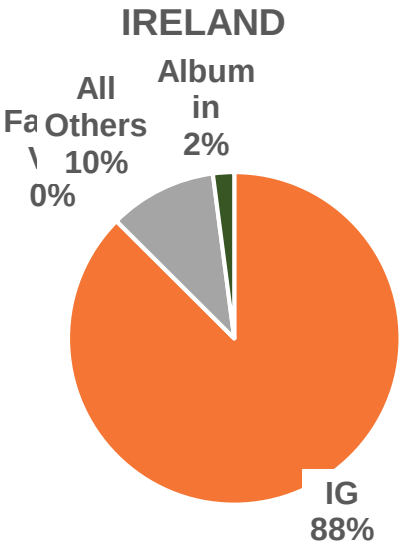


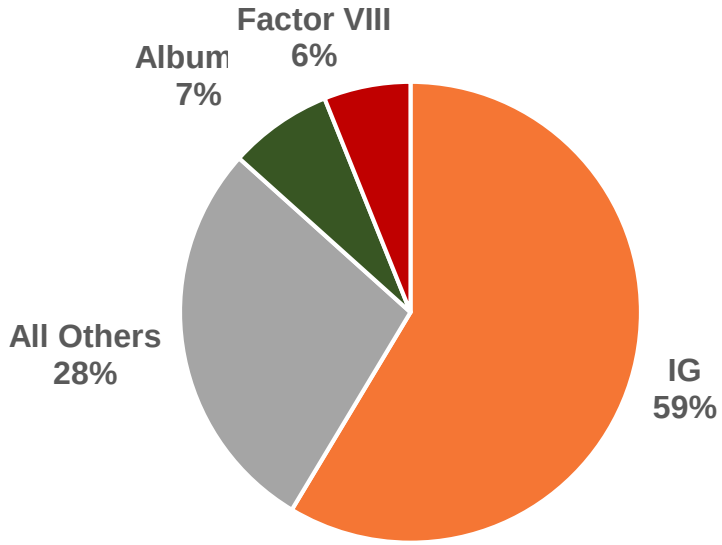


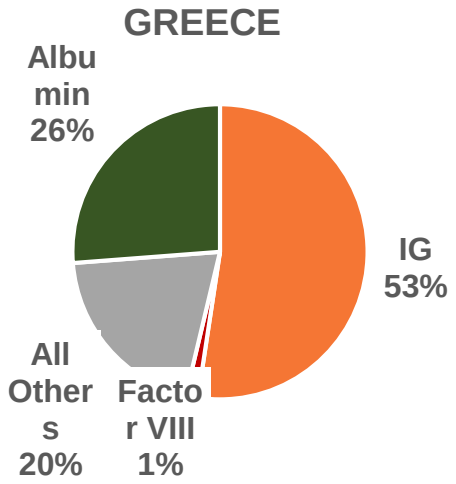




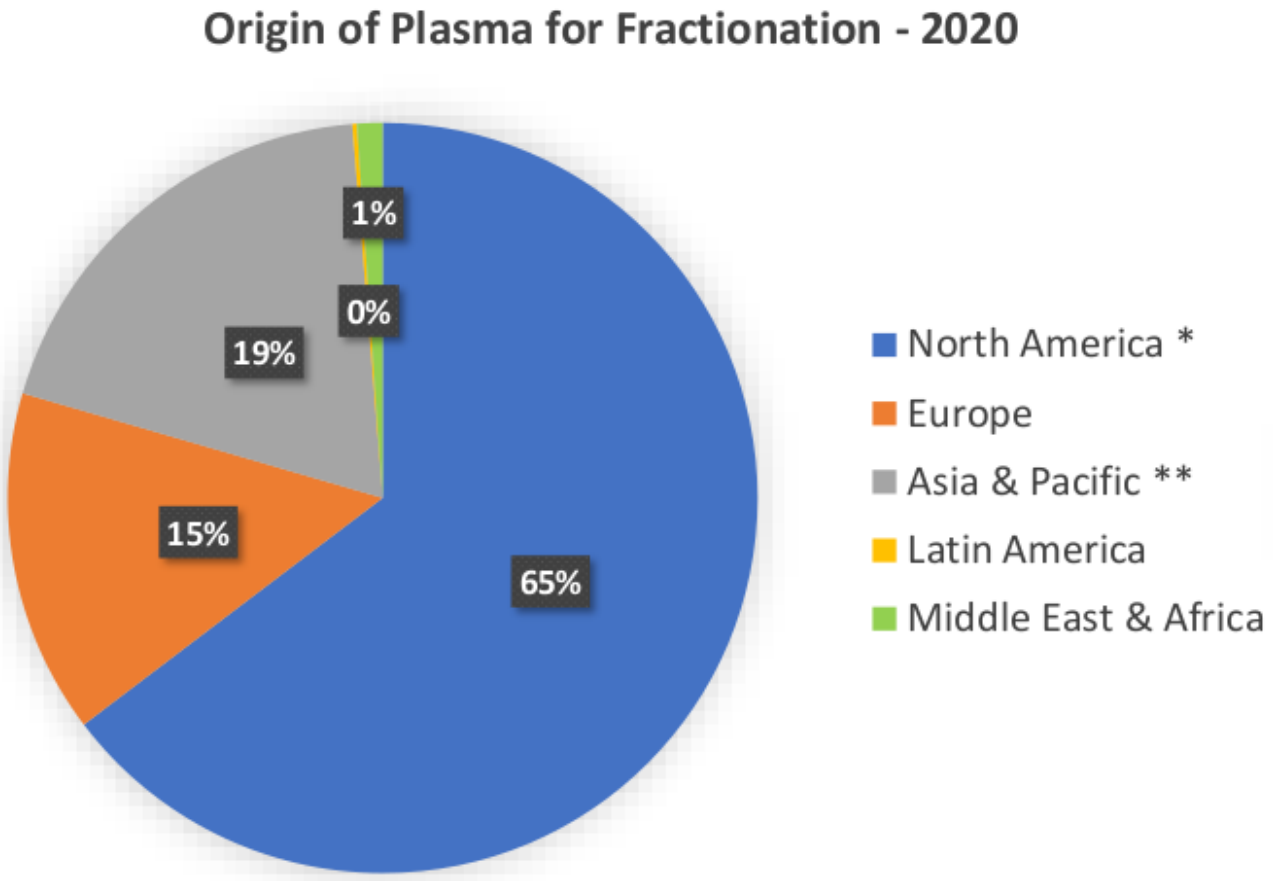
EUROPE

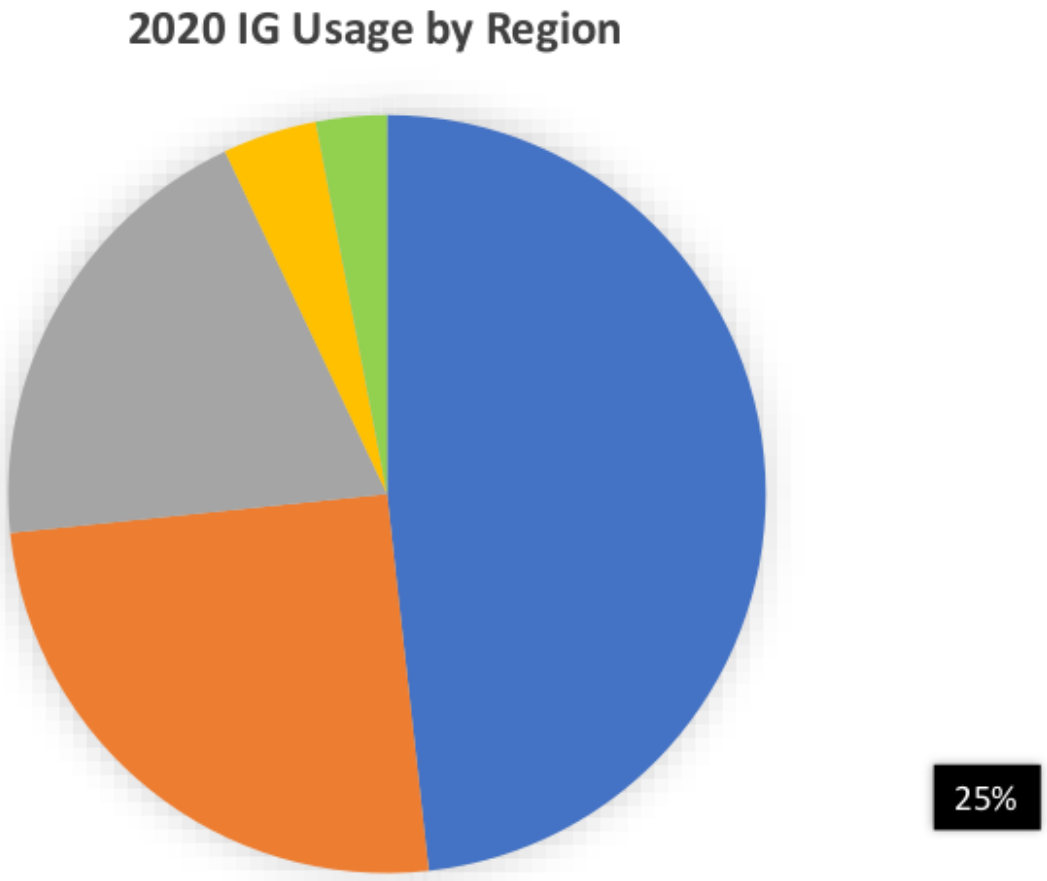






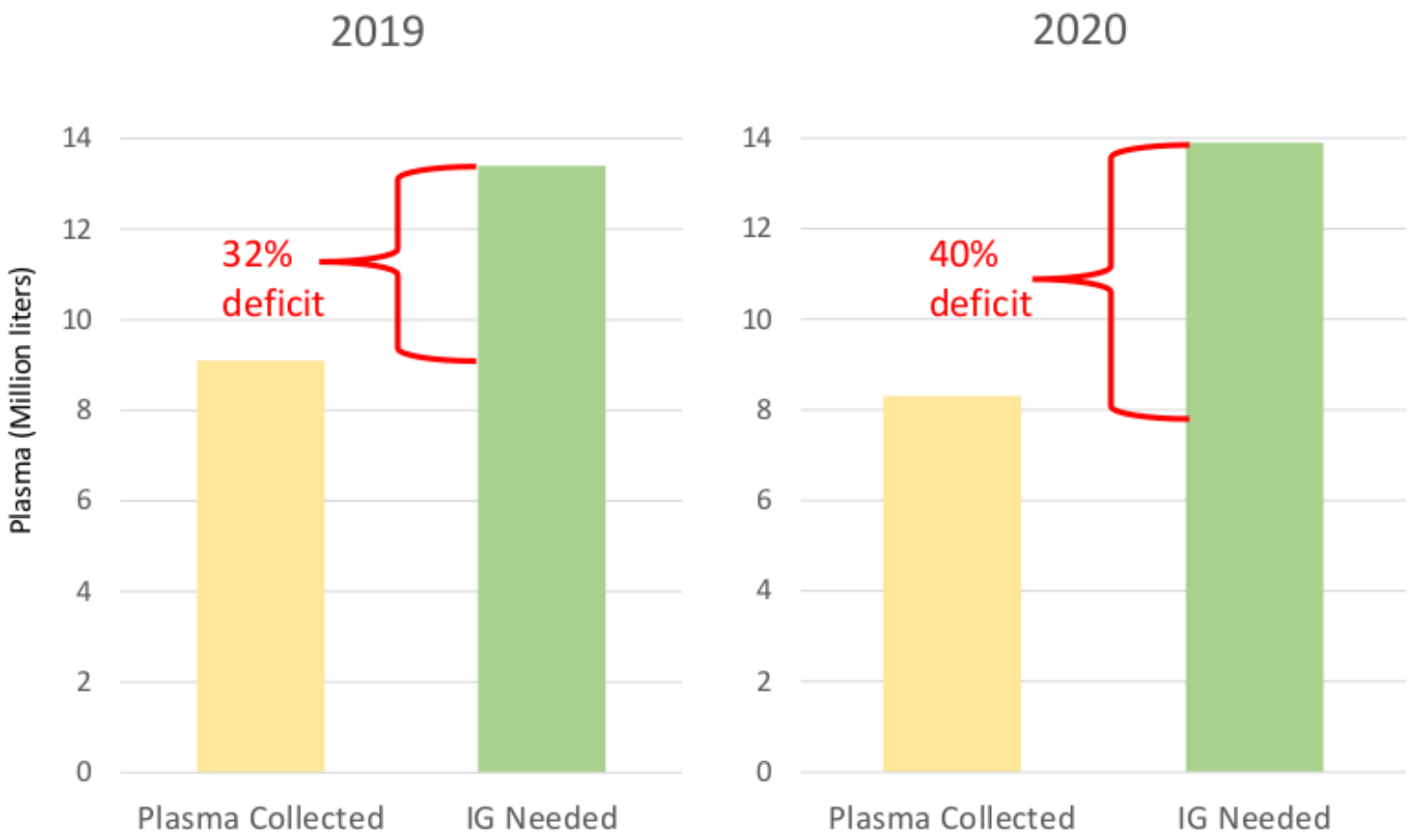
ORIGINE AND USE OF PLASMA FRACTIONATED IN THE WORLD





Since Europe consumes 25% of the worldwide IG supply but collects only 15% of the global plasma for fractionation, there is an imbalance that requires Europe to import IG produced from US plasma.

2019 and 2020 Imbalance of Plasma Collections and Need for IG in Europe



The self-sufficiency of Europe, dropped 8 percentage points from 2019 to 2020.

*Assume average blended yield of 4.5 grams IG per liter of plasma

EU Regulatory environment

- **BLOOD ESTABLISHMENTS**
- **Plasma for fractionation (PfF)**

- EU Blood Legislation
- Mother directive (**2002/98/EC**) and technical directives (2005/62/EC, 2005/61/EC, 2004/33/EC, 2016/1214)
- Guide to the preparation, use, QA of blood components (Appendix to R(95)15) – recommendation)
- GPGs=part of Blood components EDQM Guide (binding)

- **FRACTIONATORS**
- **Plasma-derived Medicinal Products (pdMPs)**

- EU Pharmaceutical legislation (Directive 2001/83/EC)
- GMPs (directive 2003/94/EC)
  - Part I, Part II, Annexes 14, 15
- GDPs
- EU Pharmacopoeia (Ph. Eur. monograph no. 0853 on PfF)

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Blood Guide and European Pharmacopoeia

Blood Legislation

Pharmaceutical Legislation

HUMAN PLASMA FOR FRACTIONATION

Plasma humanum ad separationem

DEFINITION

Liquid part of human blood remaining after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure; it is intended for the manufacture of plasma-derived products.

PRODUCTION

DONORS

Only a carefully selected, healthy donor who, as far as can be ascertained after medical examination, laboratory blood tests and a study of the donor's medical history, is free from detectable agents of infection transmissible by plasma-derived products may be used. Recommendations in this field are made by the Council of Europe [*Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components,* or subsequent revision]; a directive of the European Union also deals with the matter: *Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.*

Monographs F-H

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Good PRACTICE guidelines

- Legal status:
  - EC directive 2016/1214
  - Member States should Implement the GPG by 15 February 2018
    - Dynamic reference
    - No need for regular revisions
  - Transposition and implementation
    - Incorporation of the EU law in the national law
      - Legally binding guidances
- Derived from the detailed principles of GMPs
  - Specificities of the Quality System (QS) directly applicable to Blood Establishments (BEs)

National Legislation in some European Countries

For some countries we know that there are (e.g. Denmark) or there were (e.g. Norway) blood fractionation programmes in place but we do not have access to the regulatory framework

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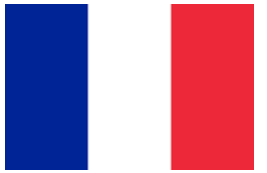
National Legislation in France



Law no.93–5 of 04 January 1993

This law lays down the ethical principles of blood donation and labile blood products: "*Blood transfusion is done in the interest of the recipient and is based on the ethical principles of volunteering and anonymity of the gift, and the absence of profit, under the conditions defined by this book*."

This law prescribed that only **Laboratoire français du Fractionnement et des Biotechnologies (LFB)** can prepare PDMPs from the blood or its components collected by the French blood establishments.

LFB is required to fulfil a public health mission in France under **Law 2009-879 of July 21st, 2009—article 77**, modifying the article L5124-14 of the Code of Public Health as follows: it "*Fractionates in priority the plasma from blood or its components collected by the EFS to meet national needs, particularly those related to the treatment of rare diseases. It distributes, primarily on French territory, the medicines that come from it*."

LFB may also fractionate plasma other than that provided by **Etablissement Français du Sang (EFS)** for its international supply in PDMPs and most of its products are marketed in more than 40 countries. LFB is entitled to perform contract fractionation activities for other countries.

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National Legislation in Spain

The **Royal Decree 1088/2005**, **16th of September**, establishes the technical requirements and minimum conditions for blood donation and transfusion centers and services and compiles and organizes all the national regulations on blood donation and technical requirements, while incorporating the provisions of the Directives 2002/98/CE and 2004/33/CE in the internal legal system.

The aims of the **Royal Decree** are:

- To establish the quality and safety standards for human blood and blood components, In order to guarantee a high level of human health;
- To set the minimum requirements and conditions of the collection, preparation, storage, distribution, supply and therapeutic use of blood and blood components.

In Spain, each of the 17 autonomous regions has its own blood donation program.
In total, there are 24 blood centers and 340 transfusion service centers located in hospitals in Spain. There is also a Red Cross blood donation program in Madrid.
All blood donations in Spain are free of charge. Plasma that is not needed for transfusions, is sent to the global plasma fractionation company Grifols. In return for the plasma provided, the blood centers receive finished blood products.

National Legislation in Germany

- In Germany blood services are provided by four different organisations:
  - ✓ German Red Cross Blood Transfusion Services
  - ✓ State and Communal Blood Transfusion Services
  - ✓ Commercial Blood Centres
  - ✓ Plasmapheresis Centres of the Plasma-Fractionation Industry.

- **The Transfusion Act (Transfusionsgesetz, TFG)** has been in force since **1998**. It regulates the collection of blood and its components and the use of blood products. The goal is to ensure safety during the blood donation and to ensure that the population receives blood products in a safe and secure manner.
  The Transfusion Act promotes the self-sufficiency of blood and plasma on the basis of voluntary and unpaid blood donation.

- The German Medical Association, together with *Paul Ehrlich Institute*, develops **Guidelines for the production and use of blood products (2017-latest version)**. These Guidelines for the collection of blood and the use of blood components set, among other things, the criteria for approval, deferral and exclusion of people donating blood and plasma, and the plasma fractionation requirements.

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National Legislation in Portugal

- **Decree-Law no. 267/2007, 24th of July** - Establishes the legal regime for the quality and safety of blood and blood components, transposing into national law the EU Directives on blood.
- **Law no. 37/2012, 27th of August** - Approval of the "*Statute of the donor*"
- **2015**-Publication of the "*Programa estrategico nacional de fracionamento de plasma umano 2015-2019*": From press release (https://www.tsf.pt/sociedade/saude/primeiros-medicamentos-derivados-de-plasma-portugues-estao-a-chegar-aos-hospitais—10396953.html): completion of the first phase of the plan- 30,000 liters of plasma collected from the IPST network - three medicine obtained , albumin accounts for about 35% , factor VIII to about 25% and human immunoglobulin at about 20% of national demand.
- **Ordinance no. 1649/2017, 21th of February** - Establishes that the activity of blood medicine and transfusion services at national level be monitored centrally by the "*Instituto Português do Sangue and by Transplantação*", IP (IPST, IP).
- **Decree-law no. 86/2017, 27th of July** - Amends the rules and specifications of the quality system of transfusion services, implementing Directive (EU) no. 2016/1214
- **IPST, IP ensures the collection, processing, storage and distribution of blood and its components of approximately 60% of the blood collection in Portugal. The remaining 40% of national blood collection is accomplished by hospital blood establishments, all representing 100% voluntary non-remunerated blood donation**.

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National Legislation in Netherlands

- The legal regulations on blood donation in the Netherlands are in the **Act of December 4, 1997**, (**Blood Supply Act**) in regard with the organization of the blood supply. The Ministry of Health appoints a so-called Blood Supply Organization (BSO), which is responsible for the implementation of this law. The tasks of the BSO include: the estimation of the annual medical needs of whole blood, plasma, (semi-finished) blood products, the collection of whole blood and plasma derived from plasmapheresis, the processing of (semi-finished) blood products, the storage, packaging, labeling, transportation and delivery of these products. The law distinguishes between two categories of blood products: the blood components for transfusion and the plasma derivatives. **Sanquin** is the only organization in charge of collecting whole blood and plasma in the Netherlands.
- **Law of January 25, 1996,** applies to **plasma derivatives**, its legal requirements with regard to quality, safety and marketing. According to the Blood Supply Act, Sanquin must first offer plasma derivatives made from national plasma. Only surplus products are allowed to be sold to other countries. Sanquin runs an extensive plasmapheresis program with only **voluntary and unpaid donors**. There are around 350,000 blood donors in the Netherlands, and Sanquin uses their donations to supply 300,000 Dutch patients every year. The Netherlands is self-sufficient for most blood products, but part of the intravenous immunoglobulin is not derived from national plasma.

National Legislation in Belgium

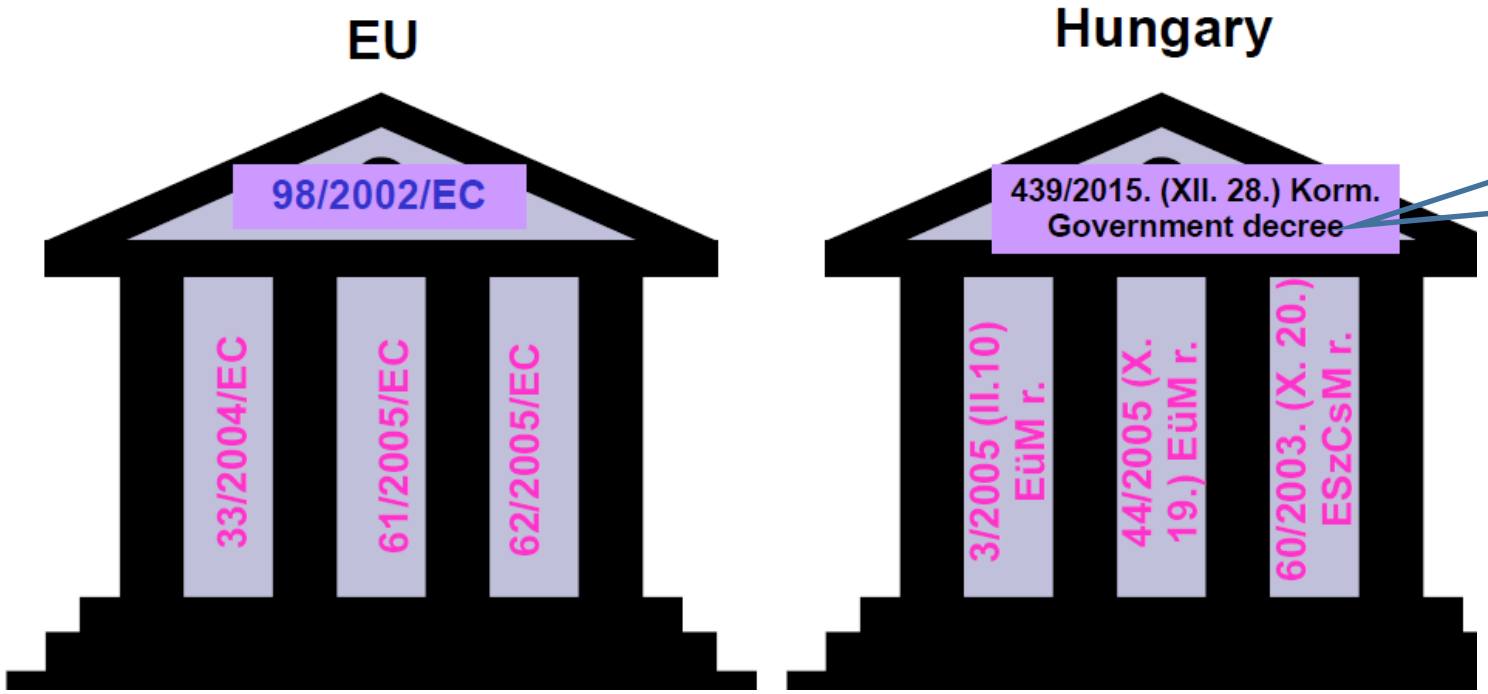
- In Belgium there are four authorized blood establishments, two of those four are French and Flemish sections of the Red Cross who make up together 95% of all plasma collected in Belgium.
- All the Belgian plasma goes to one tender winner. That was CSL Behring from december 2017-November 2021 and again for the second tender from december 2021 – november 2025. Nor other companies are involved in the self sufficiency program.
- Self sufficiency was implemented with the **Law of July 5, 1994 on "Blood and Blood Derivatives of Human Origin". Article 20** of this law establishes that the contractor shall be entrusted ensuring a sufficient supply of stable plasma derivatives manufactured from national plasma and the maintenance of a strategic stock of the relevant products manufactured from such plasma. The level of self sufficiency foreseen in the law is 100% albumin and > 50% IVIG. This can be changed only by a Royal Decree.

National Legislation in Slovenia

- To produce blood-derived medicines, fresh frozen plasma is used that has been prepared from whole blood or through plasmapheresis, donated by **unpaid voluntary donors**, and that has not been used for clinical treatment of patients. The plasma collected in the Republic of Slovenia for the purposes of producing medications is processed at the selected provider abroad pursuant to the procedures laid down in accordance with Directive 2004/18. All medications made from the plasma collected in the Republic of Slovenia are always returned in full to treat patients (with inherited blood clotting disorders, immune deficiencies, etc.) in Slovenia.
- Within the frame of the self-sufficiency program, the Blood Transfusion Centre of Slovenia (ZTM) currently supplies the market with coagulation factor VIII, coagulation factor IX, a combination of coagulation factors IX, II, VII and X, the human normal immunoglobulin for intravenous administration and albumin.
- The Centre for the supply and marketing of medicinal products and medical devices at ZTM has been verified and markets blood-derived and recombinant medicines.
- **Article 6 (71) of the "Zakon o zdravilih" (Law on medicinal products - *Uradni list RS, n. 17/14*)** establishes the priority of the use of medicinal products industrially manufactured from Slovenian plasma.

National Legislation in Hungary

Hungarian regulation on blood supply



Law no. 439/2015. (XII. 28.)
Has declared:

- National self-sufficiency
- Stabile and Labile blood products
- National blood stock
- **Industrial plasma**
- Hospital blood stock

There are five regional blood centers and 23 local blood banks in Hungary. While all blood banks primarily collect whole blood, blood products are only manufactured in the regional centers. The Hungarian National Blood Transfusion Service (HNBTS) coordinates the blood supply and carries out the distribution and transport of blood products. Since 1959, only voluntary donors from low-risk groups have been accepted; there is no financial compensation for the donation.

National Legislation in Poland

- The activity of Polish Blood Transfusion Service (BTS) is regulated by the **Public Blood Transfusion Service Act** passed by the Polish Parliament in 1997 and amended in November 2003 according to the recommendations of the Directive 2002/98/EC. Pursuant to this Act, blood is collected in public Centers exclusively, no private collection Centers are permitted.
- The activity of BTS in Poland is supervised by the Polish Ministry of Health and the Institute of Hematology and Transfusion Medicine (IHTM) exercises supervision over the activity of all Centers. The other competent authority is the Main Pharmaceutical Inspectorate(MPI) which supervises the preparation of plasma for fractionation.

National Legislation - Switzerland

- **812.21**
- **Legge federale sui medicamenti e i dispositivi medici (prodotti terapeutici).**
- 15. dicembre 2000 (versione 1.1.14)

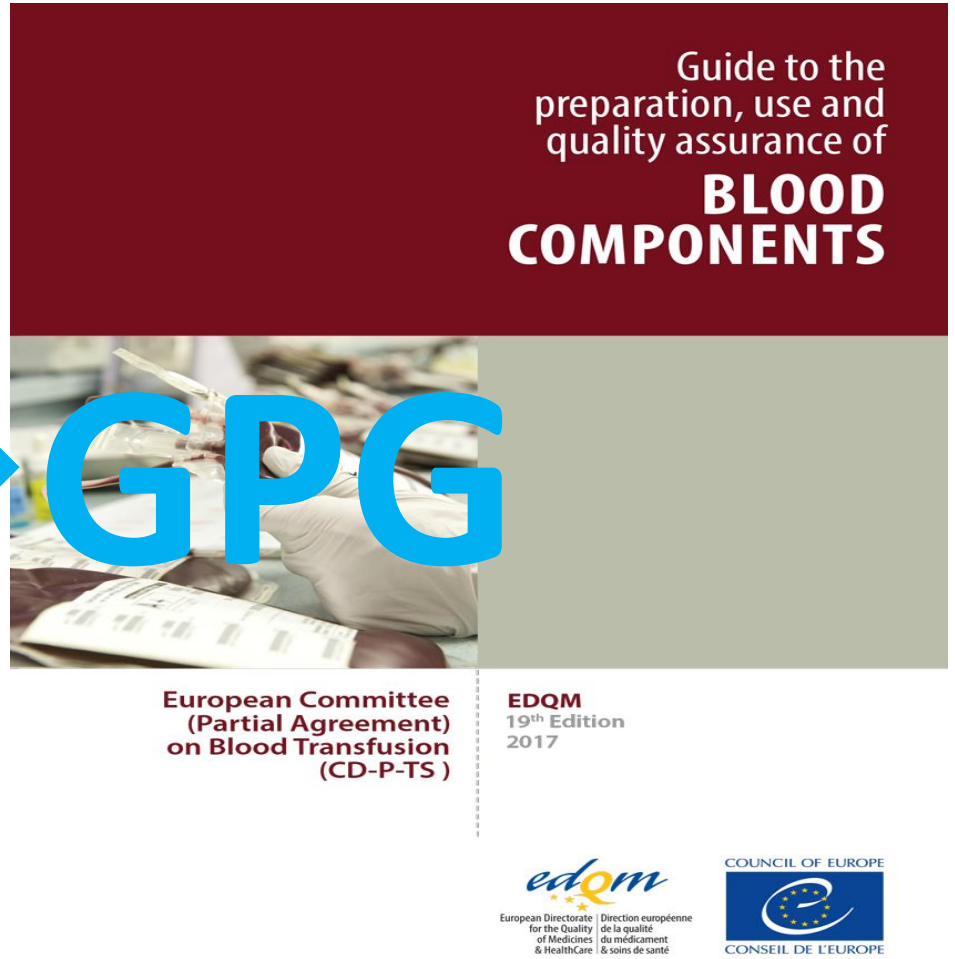
- **812.212.1**
- **Ordinanza sull'autorizzazione nell'ambito dei medicamenti (OAMed) → GMP**
- 17 ottobre 2001 (versione 1.5.16)

- **818.101.32 Ordinanza sui laboratori di microbiologia** 29 aprile 2015 (versione 1.1.16)

- https://www.swissmedic.ch/zulassungen/00153/00205/00212/index.html?lang=fr

- **Prescrizioni Trasfusione Svizzera CRS**
- http://www.blutspende.ch/fr/medecine/ medecine transfusionnelle/prescriptions

→ GPG



Courtesy dr. S. Fontana

National Legislation in Italy (The toll-fractionation system)

- **Law no.219/2005**

- **Self-sufficiency** of blood and blood products, **including plasma-derived medicinal products** (PDMPs) is a national *supra-regional* strategic goal, i.e. independent of the regionalised organization of health-care delivery.
- The plasma collected in Italy comes from voluntary, periodic, responsible, anonymous and non-remunerated donations The Regions, individually or in association, send the plasma collected by their BEs to the authorised company to be industrially transformed into PDMPs.
- The contract with Companies, which operate as service providers, is considered a "toll fractionation process“
- The service provider undertakes to produce the quantity and to guarantee the quality of the PDMPs requested by the client
- The Regions have the right to full ownership of the plasma sent for industrial processing, of all the pharmaceutical specialties derived from it, as well as of the residual raw material.


FUTURE???

The obstacles to strategic independence of plasma for fractionation in Europe

- The EU has as many collection models as its countries.

- Most countries import plasma-derived medicinal products from international sources to meet their national needs, instead of investing in their own infrastructure
- **Legislation**
  - EU Organs
  - National Authorities.

Must cooperate

It is very important to increase plasma donation as plasma shortages jeopardize the manufacturing of PDMPs.
Therefore, the EU Blood Directive should remove the remaining obstacles preventing individuals from donating plasma, by means of:

- Including a clear definition of “plasma for manufacturing”, “plasma for fractionation”, “plasma for transfusion” and “recovered plasma”;
- Revising the existing eligibility criteria for plasma donors, taking into account the latest technological and scientific developments. These criteria should consider the ability of the PDMPs manufacturing process to remove known and emerging pathogens, thus ensuring the highest quality and safety of the final product
- **Supporting the Member States as they establish dedicated programs for direct plasma collection (plasmapheresis), outreach programs to inform communities of the critical importance of plasma-derived medicinal products and the need for plasma donations.**

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“SUPPLY-Strengthening voluntary non-remunerated plasma collection capacity in Europe”.

The **SUPPLY project** - Strengthening voluntary non-remunerated plasma collection capacity in Europe – is a co-funded initiative coordinated by the European Blood Alliance and involving 19 partners (14 EU Member States, including UK) that aims:

- **To formulate recommendations for the development of a proposal of common EU policies (or also legal frameworks) aimed to support national and EU efforts to achieve a higher degree of strategic independence from non-EU sources in the collection of plasma and its fractionation in PDMPs;**
- To provide evidence-based recommendations and implementation tools towards best practices regarding (unpaid) plasma donor recruitment and retention;
- To develop a set of recommendations that will support increased and improved plasma collection programmes by BEs throughout Europe and will ultimately strengthen the resilience of plasma collection during crisis;
- To develop recommendations towards evidence-based plasma donor protection practices;
- To deliver a set of recommendations on the appropriate use of PDMPs at baseline and on its prioritisation in times of crises.

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Conclusions of the Evaluation - 2019

The legislation had increased the safety and quality of blood, tissues and cells across the EU. However, 5 gaps/shortcomings were identified:

1. Patients are not fully protected from avoidable risks

EU safety and quality requirements are incomplete and have failed to remain up to date with frequently changing scientific and epidemiological developments. The outdated provisions are technical in nature

2. Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos

Donor adverse reactions (including serious ones) are not systematically reported and the requirements for testing egg and sperm donors for genetic conditions are limited.

3. Divergent approaches to oversight cause unequal levels of safety and quality and barriers to the exchange of BTC across the EU

Lack of general principles, provisions for verification of effective implementation of inspection, authorisation, vigilance.

4. BTC legislation lags behind innovation

Limited clinical data on safety and efficacy of new ways of processing donations. Difficulties in defining the borderlines for novel BTC with other regulatory frameworks

5. EU vulnerable to interruptions in supply of some BTC

High dependence on plasma import. Lack of supply monitoring for crisis management.

European Commission

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July 14°, 2022….

European Commission

EN English

Public Health

European Commission > Public Health > Blood, tissues, cells and organs > Overview > Proposal for a Regulation on substances of human origin

Proposal for a Regulation on substances of human origin

PAGE CONTENTS

In July 2022, the European Commission adopted the proposal for a Regulation EN on standards of quality and safety for substances of human origin intended for human application. By repealing the Blood Directive (2002/98/EC) EN and the Tissues and cells Directive (2004/23/EC) EN (both evaluated EN in 2019), the proposed Regulation concludes the revision of the legal framework for blood, tissues and cells, which was included in the REFIT Annex (#37 p.15) EN of the Commission's Work Programme for 2021 EN.

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- EU's ambition to build a stronger European Health Union, so as to:

  - **better protect the health of our citizens (including patients, donors and offspring)**;
  - equip the EU and its Member States to better prevent and address future pandemics (surveillance, data analysis, risk assessment, early warning and response);
  - **improve the resilience of EU health systems (sufficient supply of SoHOs**).

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Compensation for plasma donors

- No definition of “voluntary non remunerated donation” in the EU legislation: the most relevant reference is the CHARTER OF FUNDAMENTAL RIGHTS OF THE EUROPEAN UNION (2012/C 326/02): art 3 “Right to the integrity of the person”: “prohibition on making the human body and its parts as such a source of financial gain”.
- 25 EU countries provide some form of compensation for plasma donors: It covers expenses incurred and recognizes the inconvenience related to donating, following the principle of Voluntary Unpaid Donation (VUD). In four EU countries (Austria, Czech Republic, Germany, and Hungary), private centers apply compensation as a fixed-rate allowance. This approach is in analogy with the EU Tissue and Cells Directive .

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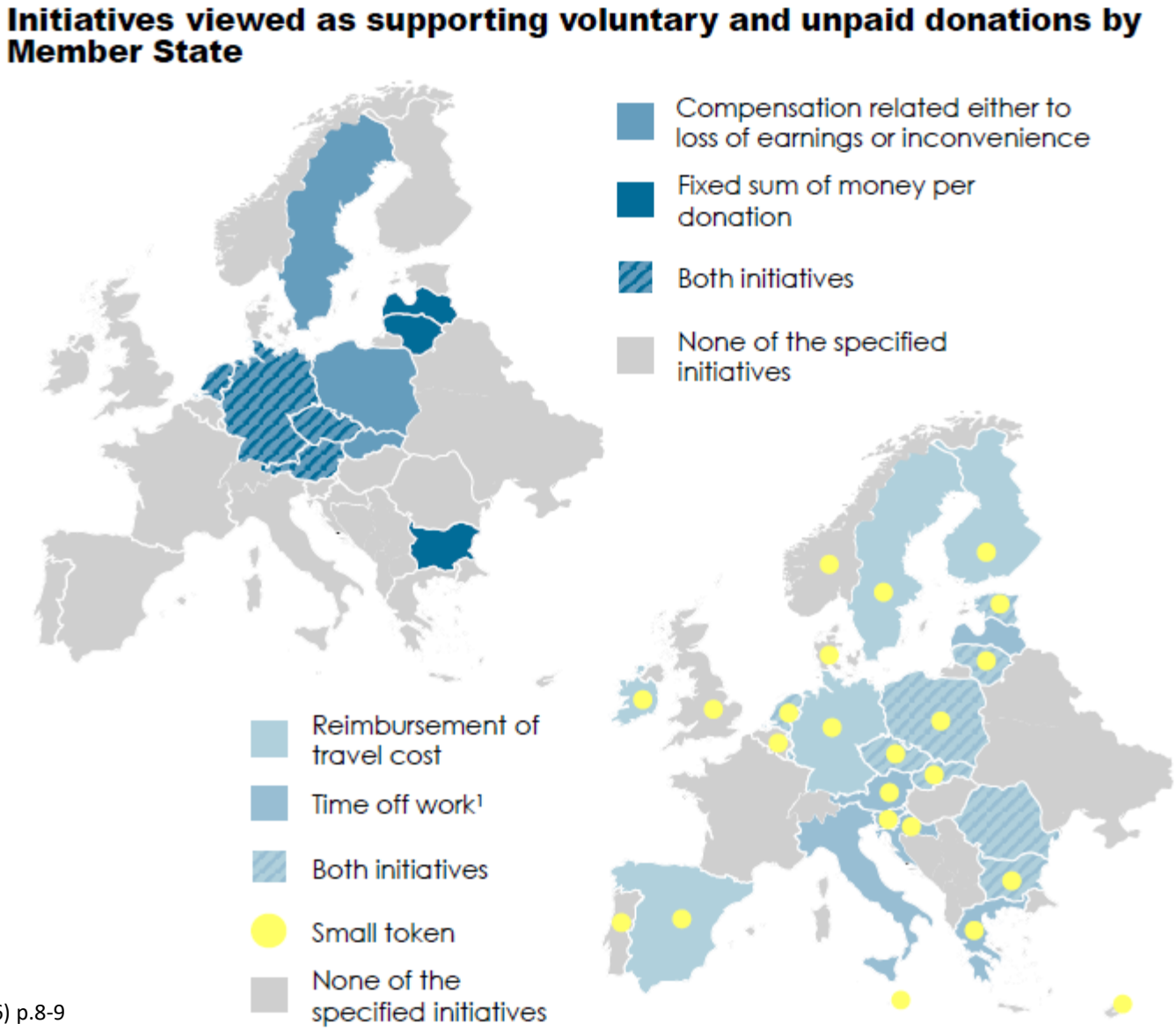
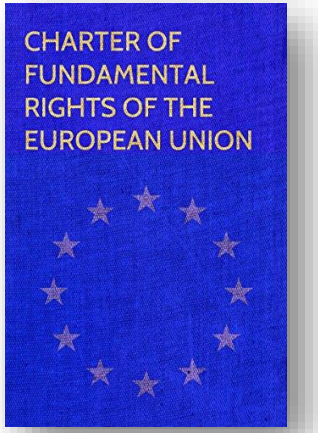
Legislation for incentives to blood/plasma donation



Source: European Commission (2016) p.8-9

The fundamental rights



- This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union and in particular **human dignity**, the **integrity of the person**…
- By ensuring that consent for donation is freely given and donors or their representatives are informed with regards to the intended use of the donated material, … so that the donors and recipients can make well-informed and deliberate choices, that activities are conducted in a transparent manner that prioritises the safety of donors and recipients, and that allocation and equitable access to SoHOs are defined in a transparent manner, on the basis of an objective evaluation of medical needs.
- **Member States remain responsible for decisions of an ethical** and organisational nature ...
- While the EU Charter on Fundamental Rights requires non-commercialisation of the human body which translates into a principle of voluntary unpaid donation in the EU legislation, **it is for the Member States to define the detailed implementation of this principle within the context of each country**.
- When a Member State chooses to allow a particular new practice that can bring ethical questions (such as testing or storage of embryos), the safety and quality of this practice are then regulated by the EU SoHO legislation

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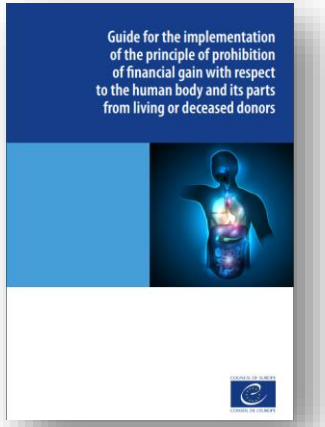
Principles



- As a matter of principle, programmes promoting the donation of SoHOs should be founded on the principle of **voluntary and unpaid donation**, **altruism of the donor** and **solidarity between donor and recipient**.
- Voluntary and unpaid SoHO donation is also a factor which can contribute to high safety standards for SoHOs and therefore to the protection of human health. It is also recognised, including by the Council of Europe Committee on Bioethics, that while financial gain should be avoided, it may also be necessary to ensure that donors are not financially disadvantaged by their donation.
- Thus, compensation to remove any such risk is acceptable but **should never constitute an incentive** that would cause a donor to be dishonest when giving their medical or behavioural history or to donate more frequently than is allowed, posing risks to their own health and to that of prospective recipients
- Such compensation should, therefore, be set by national authorities, at a level **appropriate** in their Member State to reach such objectives.

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European strategic independence in plasma for PDMPs is a must for our patients…..

BUT…...

Recommendation Rec(2002)11

- The irreplaceable fundamental principle in this remains the recruitment and retention of **voluntary non-remunerated donors**

Thank you

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