# THE DIFFERENTIAL VALUE OF PLASMA-DERIVED MEDICINAL PRODUCTS (PDMPs)

2024

GRIFOLS

Barcelona, May 2024.

# 01/ EXECUTIVE SUMMARY

The purpose of this document is to raise awareness of the unique nature of plasma-derived medicinal products (PDMPs) that contribute to changing lives and to address the challenge of shortages of the crucial raw material, plasma. It aims to highlight the importance for countries within the EU, and worldwide, to have an adequate and efficient infrastructure in place to ensure self-sufficiency and thus the availability of PDMPs to all patients in need.

## WHY ARE PDMPs IMPORTANT?

The importance of PDMPs lies in their irreplaceable role in treating deficiencies of certain essential plasma proteins, which help maintain vital functions of our body. They are medicines that **improve both the life expectancy and quality of life of thousands of people** with rare and potentially life-threatening hereditary diseases, for which there are **no alternative treatments**.

But they also serve to treat health problems that can affect us all. They are used to control bleeding during surgery and traumas, in the treatment of infections, as well as cardiovascular, neurological, and gestational diseases.

# A UNIQUE RAW MATERIAL

PDMPs can only be obtained from human plasma. This singular raw material makes them unique biological medicines, possessing characteristics that differentiate them from other pharmaceutical products:

» The **availability** of the raw material, plasma, **depends on voluntary donations from healthy individuals**.

» **Manufacturing costs** for PDMPs **are higher** than those for chemical synthesis medicines (57% vs 14% respectively).

» Strict **safety and traceability protocols** that entail a longer and more costly manufacturing process than that of other pharmaceutical products. **The production process** of PDMPs **can take up to a year**.

Donor selection and plasma traceability throughout the production process are governed by strict safety protocols, supported by international regulations. Grifols goes a step further in its safety protocols by voluntarily adhering to the Plasma Protein Therapeutics Association (PPTA) standards, considered the best practices in plasma procurement and PDMP production.

**PDMPs are** included in the list of **medicines considered critical** by the European Medicines Agency and the World Health Organization. A medicine is considered critical when it is used to treat serious diseases and cannot be easily substituted by other drugs. Therefore, its **continuous supply becomes a priority**.

# ADDRESSING URGENT CHALLENGES

The production of PDMPs and, by extension, the EU's self-sufficiency in plasma-derived products, depends on the amount of collected plasma. **The problem is the increasingly wide gap between the demand for PDMPs in the EU and the amount of plasma obtained** within its borders. Currently, Europe relies heavily on plasma imports from the U.S.



The demand for PDMPs, and therefore plasma, is skyrocketing due to three main factors:

» Earlier and more accurate **diagnosis** of pathologies treatable with PDMPs. Therefore, patients live longer and with better health.

» Identification of **new applications** for available proteins.

» Constant investment in **research and development** by the PDMP industry to identify new proteins.

# TOWARDS SOLUTIONS

**Plasmapheresis**, developed by Grifols in 1951, is the method by which blood is drawn, the plasma is separated, and the other blood components are returned to the donor through the same vein. This allows for a **greater volume of plasma to be collected**, as well as for **more frequent donations to be made**. To ensure that all patients have access to PDMPs and to achieve a self-sufficient PDMP production model, **plasma donations by plasmapheresis must increase**.

Plasmapheresis takes more than twice as long as a blood donation, making it **a challenge to attract frequent plasma donors**. The United States and some European countries offer donors **compensation** for their time or expenses incurred during plasma donation.

The new **EU SoHO (Substances of Human Origin) Regulation** includes a broad and flexible definition of donor compensation, allowing Member States to decide whether and how to compensate donors, always within the framework of the VUD (Voluntary Unpaid Donation) principle. This new scenario opens a hopeful door for future reforms in pharmaceutical legislation in Spain and EU Member States to adopt the necessary changes to enable a real and sustainable increase in plasma donations.

Additionally, increasing the number of plasma donors and supporting **awareness campaigns** are two key measures to achieve self-sufficiency and ensure a sustainable supply of PDMPs to all patients in need.

# 02/ PLASMA-DERIVED MEDICINAL PRODUCTS

PDMPs, or hemoderivatives, have unique characteristics that differentiate them from all other medicines – both traditional medicines[1] manufactured in a laboratory through chemical synthesis and other biological drugs. They are vital in treating diseases for which alternative therapies do not exist, including many rare* and hereditary illnesses. They are also critically important to health systems in the everyday management of a range of conditions that can affect us all, to treat patients suffering from trauma with significant blood loss or burns, or in controlling hemorrhaging during surgical procedures.



* In the European Union, a rare disease is one that affects no more than 1 person in 2000


Figure:
Therapeutic applications of plasma in everyday medicine (source: PPTA)

PDMP manufacturers also continue to invest in research into novel plasma-derived treatments. For instance, **Grifols is exploring new treatments for prevalent conditions** including cirrhosis of the liver, kidney disease, Alzheimer's disease, and the treatment of cancer patients. The company has also conducted clinical trials assessing the role of convalescent plasma in the treatment of infectious disease, including early-stage COVID-19 and Ebola.

As the name suggests, plasma-derived medicines are developed using proteins obtained from human plasma. This creates a unique connection between donors and the patients who receive these life-changing treatments. A rigorous collection and manufacturing process, including strict safety and traceability protocols, is essential to deliver these medicines safely to the patients who need them.

**Their production depends on the voluntary act by which committed individuals choose to donate their plasma to improve and save other people's lives**

## 2.1/ THE RAW MATERIAL: HUMAN PLASMA

### A UNIQUE AND SCARCE RESOURCE

PDMPs are unique biological medicines. One of the principal aspects that distinguishes PDMPs from other medicines is the scarce raw material from which they are manufactured. Their production depends on the voluntary act by which committed individuals choose to donate their plasma to improve and save other people's lives. Human plasma is a unique resource that cannot be recreated in laboratories.

Each PDMP itself is also unique. Plasma used in the production of PDMPs undergoes a specialized process of fractionation (separation of intermediate parts rich in each of the proteins) and purification that can vary across manufacturers, which may result in product differences. This means that every PDMP is distinct and different brands are not easily interchangeable. In addition, alternatives to hemoderivative treatments currently do not exist beyond a few exceptions.

The pharmacological differences and the manufacturing variations between the different brands of **PDMPs**, together with the diverse patient reactions to these medicines and lack of substitutes, mean that they **are fundamentally unique treatments**.

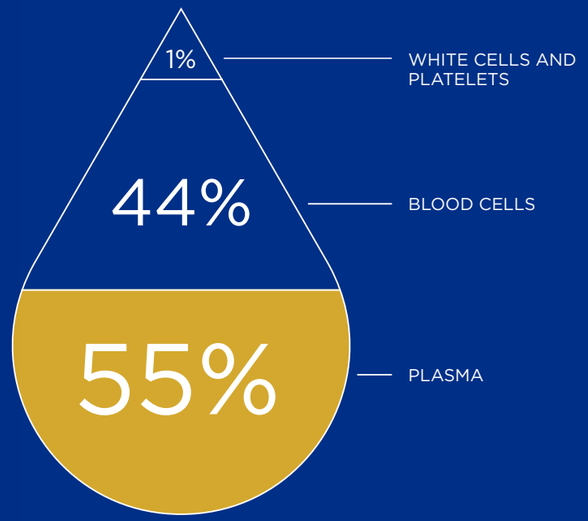
### THE VALUE OF PLASMA

Plasma contains essential proteins that help maintain fundamental functions in the body. If a person lacks sufficient levels of these proteins, such as antibodies or factors that regulate blood clotting, they may suffer chronic and potentially fatal diseases.

**While we know that plasma contains thousands of proteins** within these categories, which are the subject of ongoing research, **only a few are currently used in the production of hemoderivatives**.



## BLOOD CONTAINS

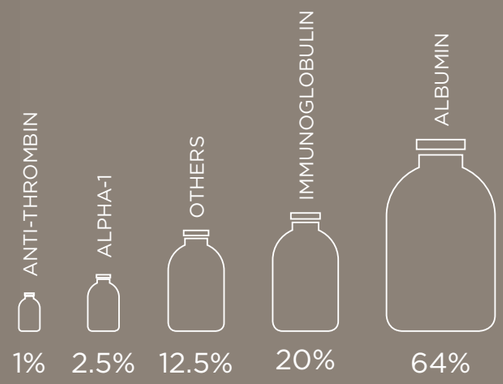



Plasma accounts for 55% of the structure of our blood. The other 45% is made up of red blood cells (44%), white blood cells and platelets (1%).

## PLASMA CONTAINS


Plasma itself consists primarily of water (92%). Proteins, which are crucial for the correct development of our metabolism, make up only 7% of the total volume. Other substances account for approximately 1%.

## MAIN PLASMA PROTEINS




Albumin accounts for 64% of plasma proteins. Immunoglobulins account for 20%, alpha-1 for 2.5%, and other proteins for 12.5%.

Source:
Copenhagen Economics, *The impact of plasma-derived therapies in Europe 2021*

## METHODS OF PLASMA DONATION

There are **two methods** of donation through which plasma can be collected:

» **Whole blood donation:** Blood is collected from a donor and the components are then separated into three distinct products: red blood cells, platelets, and plasma.

» **Plasma donation**: Blood is extracted from the donor and the plasma is separated from the rest of the blood components in a cell separator through a process known as 'plasmapheresis'. The other blood components are then returned to the donor through the same process.

Donation through plasmapheresis requires significantly more time investment from the donor than whole blood donation. **The donation of whole blood can be done in around 30 minutes, while plasmapheresis could require** donors to remain at the donation center for as long as **90 minutes**. For this reason, most EU countries offer compensation for the financial impact of attending a donation center, such as travel expenses, and/or non-financial losses, such as inconvenience (further detail on the role of compensation is covered in section 3.3).

Plasma donation through plasmapheresis is the more efficient method, as **it enables a significantly larger volume of plasma to be collected and with greater frequency.**

» With plasmapheresis it is possible to obtain up to 880ml of plasma per donation, whereas in whole blood donation only around 250ml of plasma is collected.

» Plasmapheresis directly returns to the donor the blood components that take the most time to replenish – **plasma is regenerated quickly and in a matter of days** the human body will have reproduced the proteins that were extracted.

## FREQUENCY OF PLASMA DONATION

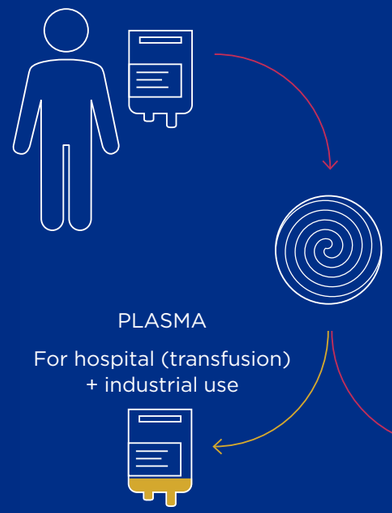
Within the EU, each member state is at liberty to establish how many plasma donations an individual can make per year. For instance, in Germany one can donate up to 60 times per year through plasmapheresis, in Austria, the member state with the most experience in plasmapheresis, 50 times, and in Hungary, 45. However, in the Czech Republic it is only possible to do so up to 26 times. The European Directorate for the Quality of Medicines and Healthcare (EDQMH) establishes a middle ground, recommending no more than 33 plasma donations per year. In the Unites States it is even possible to donate up to twice weekly. By contrast, whole blood donations can only be performed safely once every two months, although the frequency is regulated at country-level by national legislation.



**Donation through plasmapheresis requires significantly more time investment from the donor than whole blood donation**

# METHODS OF DONATION

## PLASMA FROM BLOOD DONATION



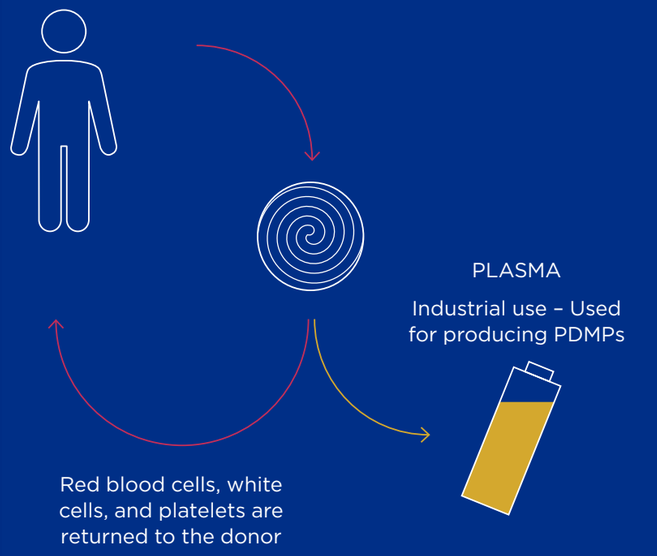

DONATION
FOR TRANSFUSION AND INDUSTRIAL USE

FREQUENCY
3-6
donations per year

DURATION
30 min

VOLUME
250 ml

## THROUGH PLASMAPHERESIS




DONATION
USED TO PRODUCE PDMPs

FREQUENCY
20-104
donations per year, depending on the country

DURATION
90 min

VOLUME
750 ml

**Plasma donations are taken exclusively from a controlled, carefully selected and screened population.** Most PDMP manufacturers in Europe, including Grifols, only accept plasma donations from so-called Qualified Donors, who must comply with a set of criteria established in the PPTA's Voluntary Quality Standards of Excellence, Assurance and Leadership (QSEAL). This is part of the rigorous process for production of PDMPs, which is detailed in the following section.

**The traceability and screening of both the donors and their donated plasma plays an essential role in the safety of PDMPs**

## 2.2/ ENSURING PLASMA SAFETY AND TRACEABILITY IN THE MANUFACTURING OF PDMPs

One of the most important aspects of the production of PDMPs is the strict safety protocols that guarantee **all finished products are free of any potential infectious agents**. The traceability and screening of both the donors and their donated plasma plays an essential role in the safety of PDMPs.

As stated in the European Guideline on Plasma-Derived Medicinal Products[2], "*the quality and safety of these medicines (hemoderivatives) will depend on the control of the starting materials, their origin and the subsequent manufacturing processes, including the analytical methods to detect infectious markers and the elimination and inactivation of viruses.*"

### A COMPLEX AND RIGOROUS COLLECTION AND MANUFACTURING PROCESS

The production process for PDMPs consists of the **fractionation of plasma and the purification of the resulting proteins** that will be used in the manufacturing of medicines.

The extra controls in place for PDMPs, which are not part of the production process for any other medicine, are essential to ensure the highest level of quality and safety. Because of this, **the full process can take as much as a year from the moment plasma is collected** to the point at which the medicines are ready for patients' use.

## INTERNATIONAL STANDARDS FOR THE PRODUCTION OF PDMPS

International standards for the production of PDMPs

In practice, the process to guarantee the safety of PDMPs – aligned with international processing standards – is as follows:

**1/ Donor identification and selection**
Each donor's identity must be confirmed. Donors must also fill in a questionnaire and undertake an interview that allows the healthcare staff working at the donation center to identify and rule out any individuals whose donations may pose a risk to their own health or that of others. For instance, those who have recently undergone surgery or have certain types of infection are temporarily excluded from donating. Individuals who suffer from conditions such as serious heart disease, test positive for HIV, or engage in high-risk behaviors (i.e., drug abuse) are excluded permanently.

**2/ Qualification of suppliers**
Supplier qualification programs are put in place, which ensure internal and external audits are conducted for any contractor involved in the manufacture of PDMPs, including third-party donation centers or blood banks. In addition to the initial donor qualification checks, which are made before a contract is put in place, re-evaluations are regularly performed to ensure the highest standards are being maintained and that the supplying blood banks and donation centers always work in compliance with existing regulations and in line with the additional safety and quality standards upheld by Grifols.

**3/ Screening of communicable pathogens**
To ensure all plasma donations are of high quality, donation centers carry out tests to detect potential infectious agents, such as syphilis, hepatitis B and C, and HIV before the fractionation process begins.

**4/ Inventory-holding and look-back period**
Donated plasma is held in inventory for two months before it enters the manufacturing process. If, during this period, any look-back unit is considered unsuitable for fractionation, it will be withdrawn from the manufacturing process and traced back to the original donor.

**5/ Traceability and control**
Throughout the entire production and commercialization process – from the moment a donor is selected to when the final product is administered to a patient – strict mechanisms are in place to ensure the traceability and control of the raw material (for each and every donation), the product in development and the final medicine at every step. These protocols provide an additional safeguard to ensure the quality and safety of the finished product.

In addition to complying with all local and international regulations to ensure the quality of its PDMPs, Grifols goes a step further by adhering to additional international safety practices, such as the PPTA's QSEAL Voluntary Standards. These standards stipulate, for instance, that plasma should be collected from "Qualified Donors" who must pass two separate medical screenings and testing for HIV, HBV and HCV on two different occasions to qualify, and then return within six months to retain their qualified status.

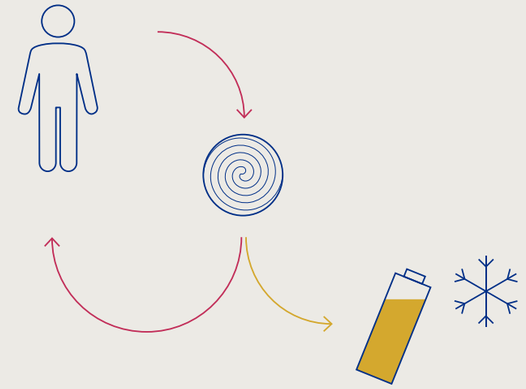
These voluntary standards also encourage the use of advanced genetic detection techniques to identify pathogens in the units of collected plasma before they are sent for fractionation.



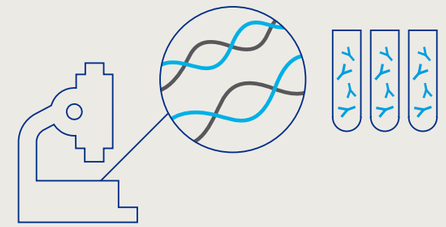
# THE PROCESS TO OBTAIN MEDICINES FROM PLASMA

THE ENTIRE PROCESS CAN TAKE UP TO 12 MONTHS.

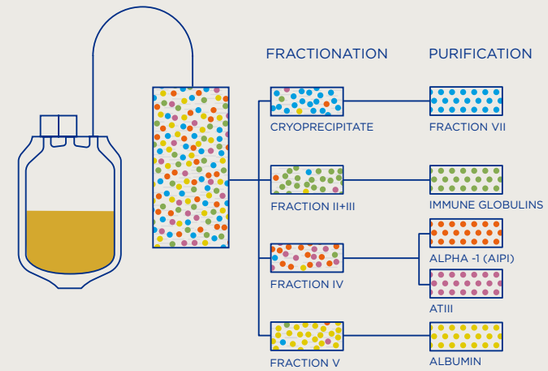
01
COLLECTION



02
TESTING



03
MANUFACTURING




04
MEDICINES

## 2.3/ SUSTAINABILITY OF THE BUSINESS MODEL OF PDMP PRODUCTION

The unique characteristics of PDMPs extend to their production cost structure and business model. **The manufacturing costs for PDMPs are significantly higher than those for other medicines**.

In general, the major costs associated with bringing most other types of medicines to market lies in R&D and commercialization. Due to the nature of PDMPs and the rigorous safety processes required, the largest cost for hemoderivative manufacturers is in raw material acquisition and production. **Manufacturing costs for PDMPs are higher** than those for small chemical synthesis, 57% versus 14% respectively.

See figure 1

### MAXIMIZING VALUE FROM A SCARCE RESOURCE: THE "ECONOMY OF THE LAST LITER"

PDMP manufacturers aim to make use of as many types of fractioned proteins as possible from each liter of plasma collected. This is to **ensure minimal waste of a precious resource**, and to safeguard the sustainability of the production process, given the high costs of sourcing and processing plasma.

The first liter of plasma is the most cost-efficient, as almost all proteins will be used to produce PDMPs to support different patient groups. However, as more liters of plasma are fractioned, the demand for proteins to treat some conditions is met. It therefore becomes less cost-effective to extract them during the manufacturing process. This, in turn, makes each subsequent liter of plasma collected more expensive to process. At a certain point, only immunoglobulin – the protein in greatest global demand – can be used as the demand for the other proteins has been met (see figure 6 below). This is known as **the "economy of the last liter"; the point at which the cost of production exceeds the financial value of the PDMPs produced from it**.

This business model, unlike that of traditional medicines, **cannot benefit from economies of scale in production**.

### GRIFOLS' END-TO-END SERVICE

See figure 2

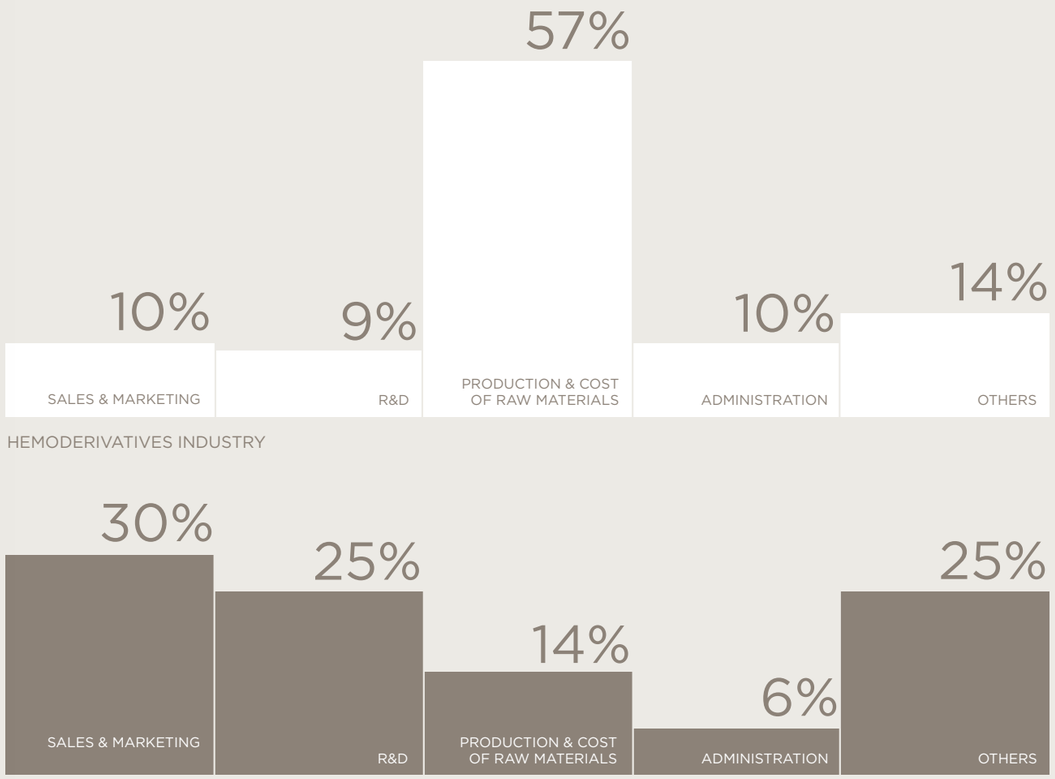
Grifols' vertically integrated business model **ensures quality and control across all stages of the value chain**. This model also ensures continuity of supply and reduces transactional costs, among other benefits.

Grifols offers a comprehensive, high value-added solution that covers the entire supply chain, from plasma logistics to the delivery of the finished product to hospitals, adapting and customizing the different stages to the specific needs of each customer.



FIGURE 1

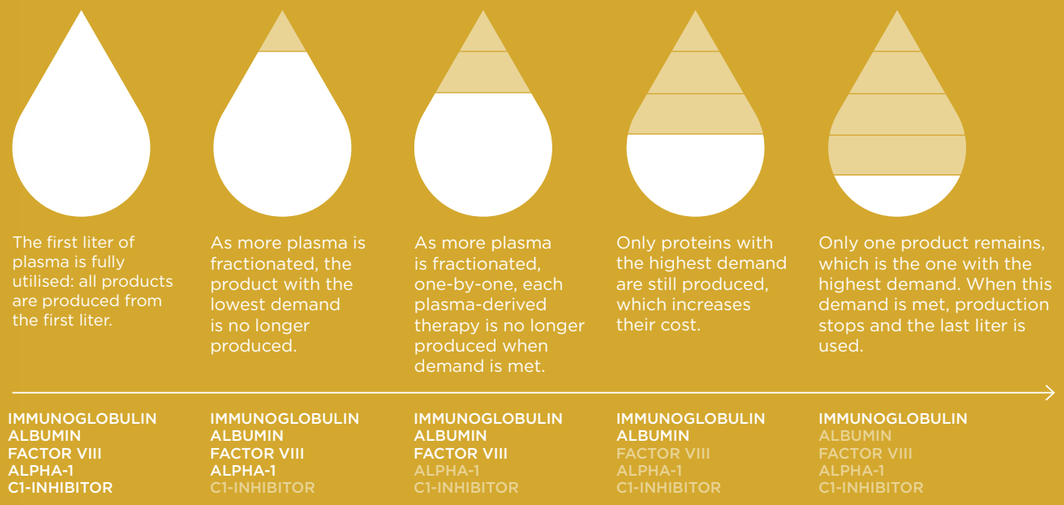
DISTRIBUTION OF PRODUCTION COSTS IN THE HEMODERIVATIVES INDUSTRY AND IN THE SYNTHETIC DRUGS INDUSTRY[3]




Source:
Grabowsk, H., Manning, R. (2018) Key economic and value considerations in the U.S. market for plasma-protein therapies". Bates White Economic Consulting.

FIGURE 2

DEMAND FOR DIFFERENT PROTEINS DERIVED FROM HUMAN PLASMA[4]




Source:
Copenhagen Economics inspired by the Marketing Research Bureau (MRB) and interviews with industry experts.

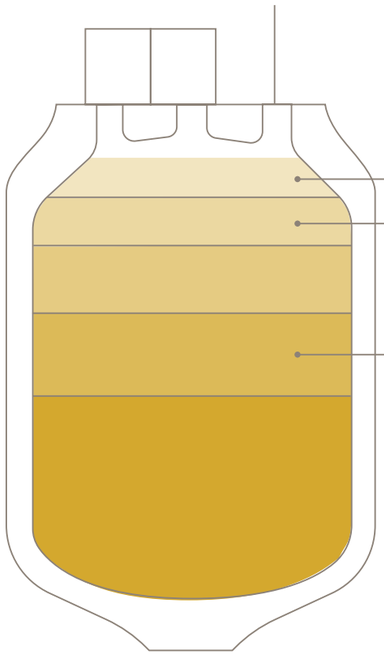
## 2.4/ THE NEED FOR PLASMA PROTEINS

PDMPs are essential in saving and improving patients' lives. **They enhance both life expectancy and overall quality of life** for a broad range of individuals suffering from plasma protein deficiencies, while also **delivering significant cost savings to health systems**.

**PDMPs enhance both life expectancy and overall quality of life while delivering significant cost savings to health systems**

PLASMA PROTEINS ARE USED TO DEVELOP LIFE-CHANGING TREATMENTS

Around 300,000 patients within the EU are currently treated with medicines derived from plasma proteins, e.g.:



CLOTTING FACTORS

For rare and hereditary illnesses like hemophilia and Von Willebrand disease. Life expectancy for people with hemophilia reached 77 years in 2017, versus just 20 years in 1960.

ALPHA-1 ANTITRYPSIN

For genetic emphysema in adults, constituting up to 3% of the ~328 million patients with chronic obstructive pulmonary disease globally.

IMMUNOGLOBULINS

For people with immunodeficiencies. They have a high strategic value and are included in the WHO and the European Medicines Agency list of essential medicines.

Source:
Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network.(2016). Immunologic Research, 64 (3), 736–53.



The proteins derived from plasma that support the development of life changing treatments include:

**The total patient population across all diseases which are treatable by PDMPs is 300,000 within the EU alone**

» **Immunoglobulins**: These proteins have a high strategic value and are included in the World Health Organization (WHO) and the European Medicines Agency (EMA) essential medicines list. They have multiple applications. They prevent infections and have anti-inflammatory and immunomodulating effects in people with immunodeficiencies. They can treat rare neurological disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP). Some immunoglobulins, known as hyperimmune globulins, are unique antibodies produced to combat specific infectious diseases, such as Hepatitis A and B, rabies or tetanus. They can be used both to prevent and treat diseases, helping patients to lead an entirely normal life simply by receiving a regular transfusion.

» The Impact of these proteins on health systems is clearly reflected in the fact that **diagnosing a primary immunodeficiency and treating it with immunoglobulins can deliver health system savings of more than $55,000 a year per patient**, according to the global study "*Primary immunodeficiencies worldwide: an updated overview from Jeffrey Modell Centers Global Network.*"[5]

» **Albumin**: Albumin is used for plasma volume protein replacement therapy, particularly in intensive care settings for patients who have suffered trauma with a substantial loss of blood or severe burns, as well as in cases of cirrhosis of the liver or cardiocirculatory failure.

» **Clotting factors**: Clotting factors – particularly factor VIII and factor IX – are used in the treatment and prevention of diseases that result in abnormal clotting, for example, rare and hereditary illnesses like hemophilia and von Willebrand disease. They are also used in surgical procedures to control hemorrhaging and are included in the WHO and EMA essential medicines list.

» Thanks to the availability of treatments for these clotting-factor deficiencies, **life expectancy for people with hemophilia reached 77 years in 2017[6], versus just 20 years in 1960**. Patients' quality of life – and that of their families – has also greatly improved in recent years.

» **Alpha-1 antitrypsin**: The hereditary disorder that causes a deficit of this protein is the most common cause of genetic emphysema in adults and liver disease in children. It is estimated that up to 3% of the estimated 328 million[7] patients with chronic obstructive pulmonary disease (COPD) suffer from this pathology globally.

In absolute numbers, **the total patient population across all diseases which are treatable by PDMPs amounts to approximately 130,000 in the United States and 300,000 within the EU alone**.

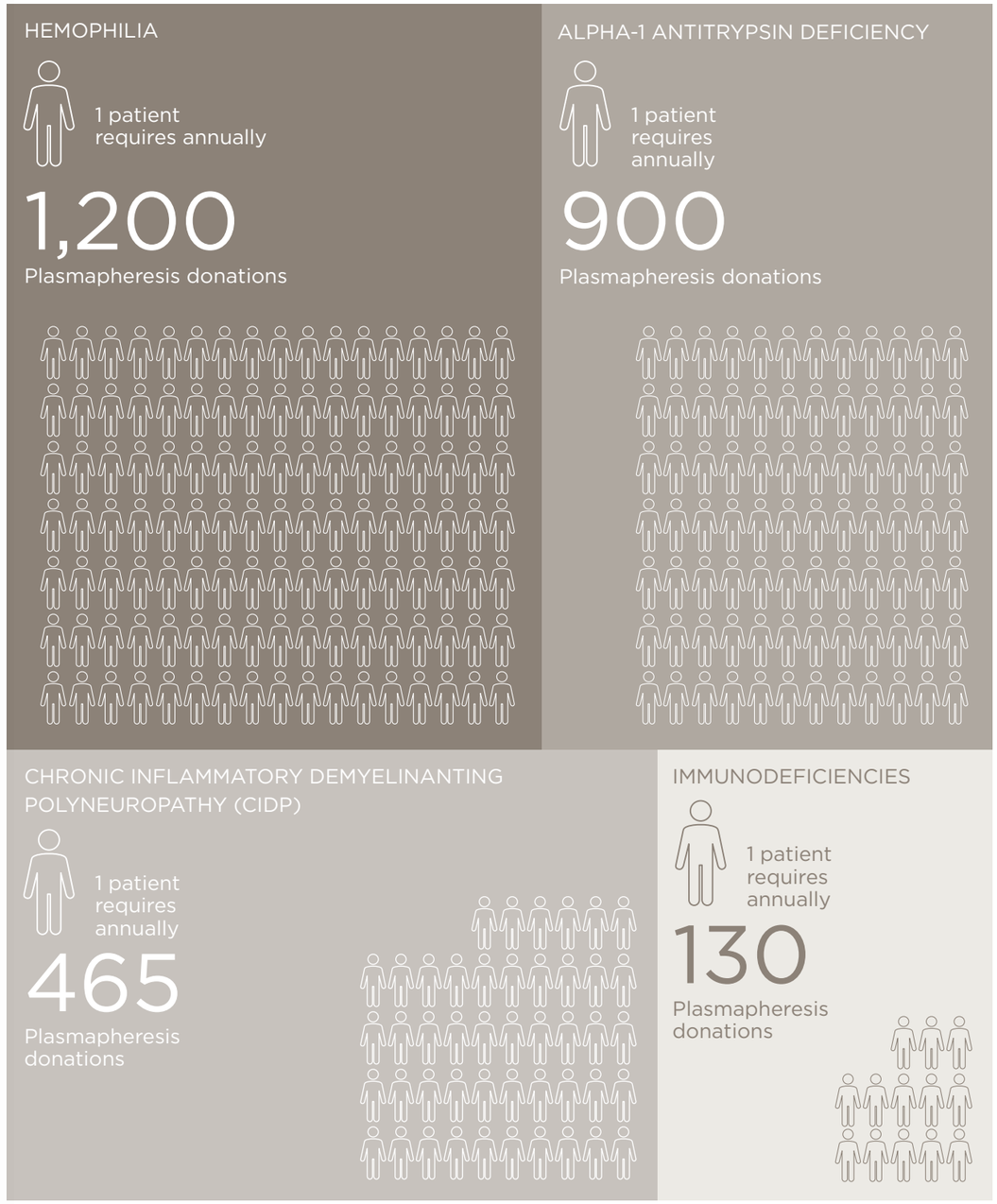
# 03/ GLOBAL CONTEXT OF PDMPs

There is a delicate balance between the volume of plasma donated and the demand for life-saving PDMPs. Countries worldwide are struggling to keep pace with the growing clinical need for PDMPs. The shortage of plasma supply can present critical challenges for local health systems and put patients' lives at risk.



The number of donated plasma units that need to be collected through plasmapheresis to treat a single patient with a plasma protein deficiency is significant, given the scare nature of plasma.

PLASMAPHERESIS PLASMA DONATIONS REQUIRED TO TREAT ONE PATIENT FOR A YEAR



## 3.1/ GROWTH IN GLOBAL DEMAND

**The shortage of plasma supply can present critical challenges for local health systems and put patients' lives at risk**

**There is a growing need for PDMPs worldwide.** The three main factors driving the surge in demand are:

» Earlier and more accurate diagnosis of diseases treatable with PDMPs.

» Innovation to identify new ways to use existing proteins to support a wider range of patients.

» The identification of new proteins that can be used to develop novel medicines.

In addition, improved life expectancy among patients using PDMPs, and even efforts to promote certain hemoderivatives within Europe[8] have a role to play in the growing demand for these medicines.

Immunoglobulin is the plasma-derived protein seeing the greatest growth in demand, followed by albumin and alpha-1. The protein immunoglobulin is in greatest demand in the U.S. where half of the world's supply is used. Around a quarter is used in Europe[9].

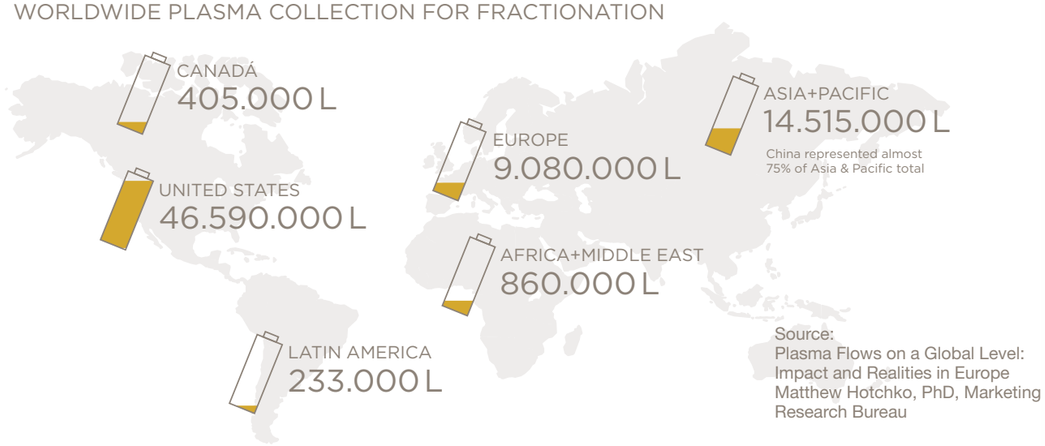
Growth in global demand for this and other plasma proteins highlights **the need to boost the available infrastructure for plasma collection and increase the level of plasma donation at both European and global level.**

### THE NEED FOR GREATER PLASMA SUPPLY

The global growth in demand for PDMPs highlights the **vulnerability of a system** that is dependent on other countries for the supply of plasma.

Around 70 million liters of plasma are collected annually worldwide. **The U.S. covers 65% of the global need**, collecting 46.6 million liters per year, while Europe only collects around 9.1 million liters annually.

WORLDWIDE PLASMA COLLECTION FOR FRACTIONATION




Source:
Plasma Flows on a Global Level: Impact and Realities in Europe
Matthew Hotchko, PhD, Marketing Research Bureau



## 3.2/ THE EU'S DEPENDENCE ON OTHER COUNTRIES

**Europe heavily relies on U.S. plasma imports**

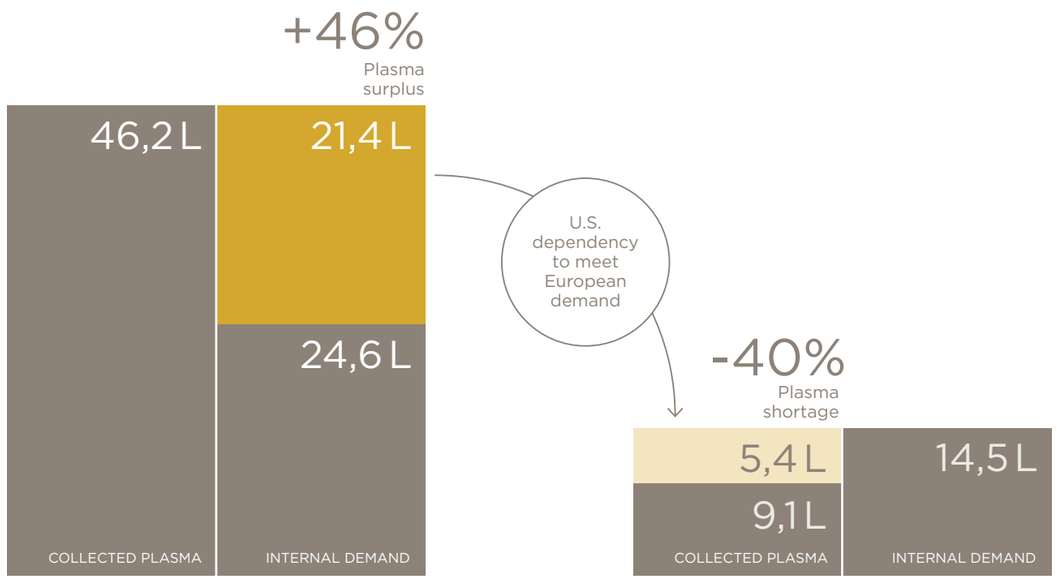
» The demand for immunoglobulins in Europe grew by 6.7% annually during the period 2010-2021[10]. The main drivers for this are the ongoing research into new applications, particularly in neurology, and advances in testing and screening programs.

» According to a study from The Marketing Research Bureau, exceptional growth in demand for albumin is expected in the future; almost eight million liters of plasma will be needed by 2026 to cover the demand for albumin in Europe alone[11].

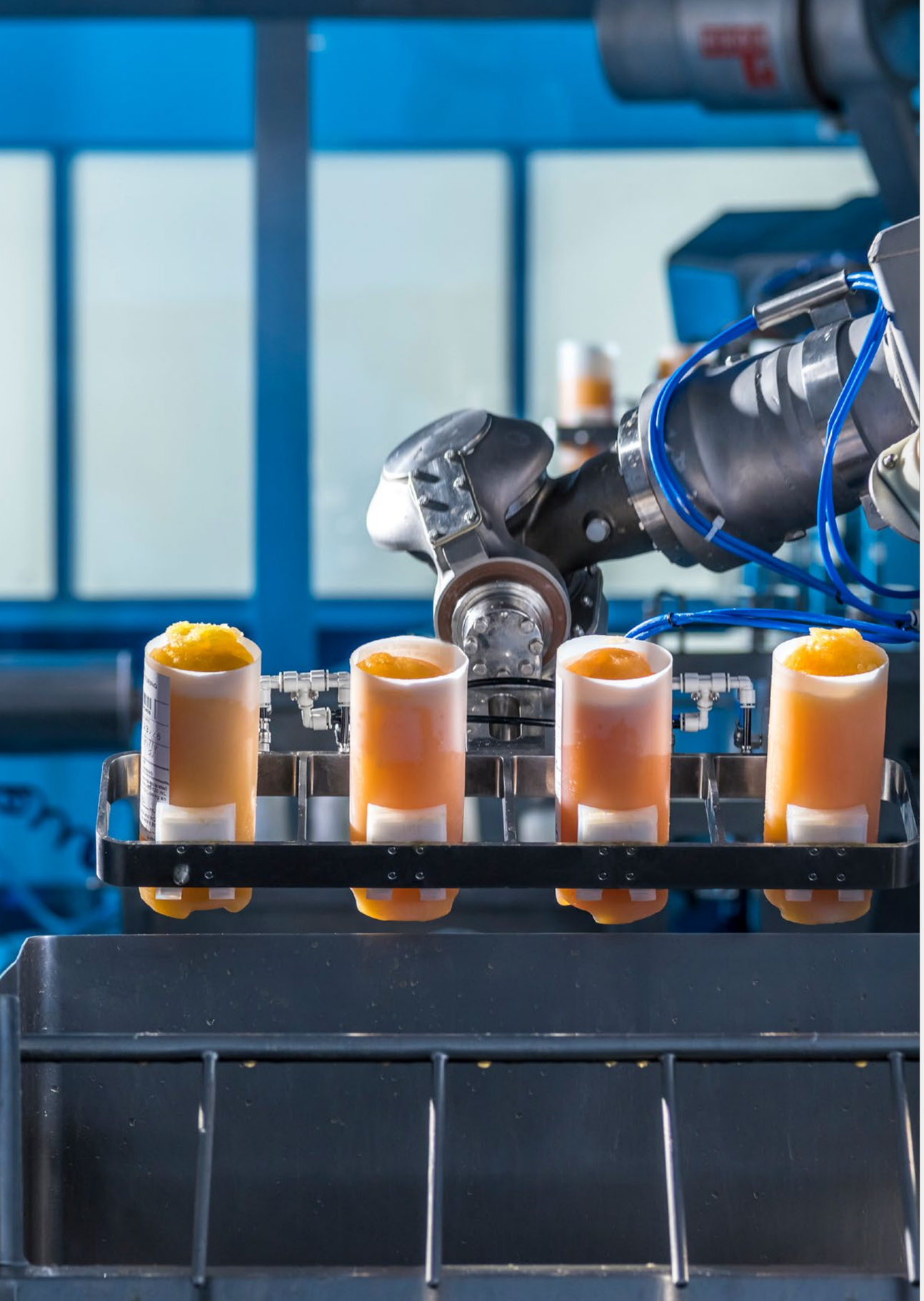
» Earlier diagnosis of several conditions is creating more demand for proteins such as alpha-1, which were previously less widely used.

» Improvement in life expectancy for patients treated with PDMPs.

IMMUNOGLOBULIN (IGG) CONSUMPTION IN LITERS VS. OBTAINED PLASMA BY REGION IN 2019[8]




Source:
MRB (Marketing Research Bureau)
2019



Europe heavily relies on U.S. plasma imports: **50% of the EU's plasma demand is covered by imports**, and almost 40% of this comes from the U.S.[12]

Stepping up the collection of plasma is crucial. Countries worldwide – and especially in Europe, where there is a growing dependence on the U.S. for plasma supply – need to ramp up their efforts to secure greater supply capacity. Some actions that can be taken to increase the plasma collected and thus reduce its dependence are:

- Carry out plasma donation **awareness campaigns**.
- Enhance the use of **plasmapheresis**, as it allows for greater frequency and quantity collected per donation.
- Consider approaches that may support - or hinder - such efforts, such as **donor compensation**.
- Allow the coexistence of **private donation centers**, regulated by health authorities.
- Development of **public-private projects**.

Approximately 300,000 European patients use hemoderivatives on a daily basis to treat a wide range of medical conditions[13]. **Overreliance on other countries for the supply of plasma puts European patients at risk of poorer quality of life**, or even death, if faced with no alternative treatment options.

**The new legislative framework on SoHO points to the need to increase plasma collection in Europe**. Article 62 of the Regulation requires Member States to draw up national SoHO contingency plans to ensure the continuity of supply of critical SoHOs such as plasma.

**Significant disparities currently exist in the amount of plasma collected by individual countries**

## 3.3/ PLASMA COLLECTION MODELS

Fostering a plasma collection system that secures loyal donors is key to guaranteeing a safe, reliable, and sufficient supply of plasma. **Currently, there are significant differences in the amount of plasma collected in different countries**. This is due to the variety of plasma collection and compensation models that co-exist worldwide, and within the EU.

**As plasmapheresis requires more time, securing regular donors remains a key challenge**

### VARIATION IN DONATION SYSTEMS

Plasma is collected through both **public sector and private systems, and in some instances a combination of both**. Non-governmental organizations such as the Red Cross also collect plasma in certain countries.

In general, public-sector systems tend to be more reliant on whole blood donation, as they are less likely to offer compensation and have more difficulty in finding committed plasma donors. **Countries with more private sector donation centers, and that favor collection through plasmapheresis, tend to collect more plasma**. According to the PPTA, in the EU the private and public sectors together collect 8.4 million liters of the plasma required for PDMP manufacturing. Of this, 46% is collected by the private sector in just four countries (Austria, the Czech Republic, Germany, and Hungary) and mainly through plasmapheresis.

The other 54% is collected through public or non-profit organizations and is largely sourced from whole blood donation.[14]

### VARIATION IN THE USE OF DONOR COMPENSATION

Countries that compensate donors tend to collect significantly higher volumes of plasma.

**As plasmapheresis requires more time and resources** from donors than whole blood donation, **securing regular donors remains a key challenge**. For this reason, several countries, including the U.S. and some European countries, offer donors compensation for the time and expenses incurred in donating plasma. The models used for this can include financial compensation for donors' time, expenses and inconvenience via a fixed-rate allowance, or non-financial compensation. In Italy, for example, individuals are given a day off work if they wish to donate plasma.

The different compensation models which co-exist across EU member states add another layer of complexity to an already heterogeneous plasma collection system.



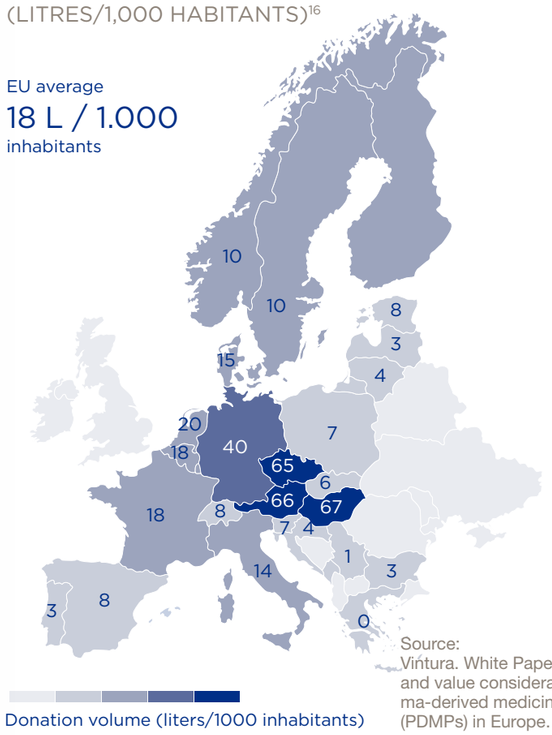
The EU supports the principle of voluntary unpaid donation (VUD), under which it is forbidden to offer financial gains for substances originated in the human body. This does not prohibit countries from offering donors small amounts of compensation, for example to cover their travel expenses to a donation center. However, opposition to this type of financial compensation also exists.

The main concern about providing financial compensation to donors in some member states is that donors may be motivated to donate for financial reasons, even if they are not in good health. However, **the rigorous donor selection requirements and procedures in place ensure the safety of plasma** for medicinal use, and for the health of the donor. This is backed by the European Medicines Agency (EMA)[15], which has found no clinical evidence to prove that compensating donors increases the risk of viral transmission.

It is also worth noting that, even though **the EU does not favor financial compensation, it imports plasma from countries where donors are compensated, such as the U.S**. This calls into question the efficiency and consistency of the EU model, where self-sufficiency is currently at risk.

**The EU does not favor financial compensation, but it imports plasma from countries where donors are compensated, such as the U.S.**

PLASMA OBTAINED PER CAPITA IN 2019 (LITRES/1,000 HABITANTS)[16]




Source: Vintura. White Paper: Key economic and value considerations for plasma-derived medicinal products (PDMPs) in Europe. (PPTA).

# 04/ A NEW EU REGULATORY FRAMEWORK: SoHO, STRENGTHENING DONOR PROTECTION AND SECURING MEDICINES SUPPLY



In July 2022, the European Commission put forward a proposal to revamp the existing rules on blood, tissues and cells, by merging the Blood Directive (2002/98/EC) and the Tissues and Cells Directive (2004/23/EC) into a new Regulation on SoHO[17]. **This new framework aims to** enhance donor protection, ensure the safety of blood, tissues and cells and **secure the supply of medicines to European patients**.

Having evaluated the previous legislation, the Commission found that EU citizens face the risk of interruption of supply of these critical substances, including plasma.

**The EU has taken significant steps towards achieving plasma self-sufficiency** by updating its regulatory framework on SoHO, which includes blood, tissues, and cells.

The new SoHO Regulation is embedded in the EU's ambition to build a stronger European Health Union. The new Regulation, alongside a revamped pharmaceutical legislation proposal on medicinal products for human use, aims to boost the overall resilience of European health systems across the bloc. It aims **to address medicines shortages** and **reduce dependence on other countries in strategically critical sectors such as plasma**,[18] by **strengthening European pharmaceutical supply** chains and enhancing strategic autonomy in the European drug manufacturing sector.

In December 2023, the European Parliament and the Council of the EU reached an agreement on the SoHO Regulation, which was approved by the European Parliament in April and by the European Council in May 2024. **This Regulation represents an opportunity**, welcomed by Grifols and the PDMP industry, **to strengthen donor protection and increase plasma collection.**

**This Regulation represents an opportunity to strengthen donor protection and increase plasma collection**

## 4.1/ MAXIMIZING THE OPPORTUNITY THROUGH REGULATORY REFORM: SOHO AND THE PRINCIPLE OF VOLUNTARY UNPAID DONATION

The EU is well aware of the over-reliance on plasma from third-party countries and urges Member States to i**ncrease plasma collection, their donor base and the use of plasmapheresis**.

The new rules under the SoHO Regulation provides an efficient framework for EU Member States to increase plasma collection capacity and meet patient needs It also defines plasma as a blood component and a critical SoHO.

The SoHO Regulation emphasizes **donor and patient safety**, a focus shared with the blood products industry's commitment to quality. It will also enable manufacturers to contribute to the resilience of healthcare systems across the EU – including for pandemic preparedness – and to **reduce dependency on other markets for the procurement of critical SoHO**.



Donor compensation has been one of the most contentious issues in the negotiations among the European co-legislators. The approved text states that **Member States can allow compensation through fixed allowances or non-financial forms based on transparent criteria and in accordance with the principle of voluntary and unpaid donation (VUD)**. A definition of donor compensation that provides all Member States with the flexibility to implement collection systems that meet their own supply needs, and that ensure an adequate supply of SoHO within the EU as a whole.

While many European countries provide some form of non-financial compensation, such as days off work, tax reductions or vouchers, only four EU countries currently provide financial compensation through fixed allowances. These four countries are both self-sufficient and collect almost half of all donated plasma in the EU.

Member States' national authorities are entitled to determine if, how and to what value donors are compensated, in order to boost plasma collection in their country. **Compensation is a tool available to all those involved in the collection of plasma and can therefore play a key role in ensuring self-sufficiency within the EU**. National authorities will also establish frequency of plasma donations.

Member States must have a **SoHO National Authority** to monitor the availability and demand for these products and shall draw up a National SoHO contingency plan to ensure the sufficiency of critical SoHO.

The Regulation also provides for the establishment of the **SoHO Coordination Board** (SCB) to monitor its implementation and enhance intra-community coordination.

The PDMP industry supports Member States' efforts to guarantee an adequate supply of plasma, and to ensure that the over 300,000 patients in the EU who rely on these essential medicines can access the treatments they need.

**Grifols, as a European headquartered, global company, is committed to supporting Europe's vision of strategic autonomy.**

**Compensation is a tool available to all those involved in the collection of plasma and can therefore play a key role in ensuring self-sufficiency within the EU**

# 05/ GRIFOLS' LEADERSHIP



## 5.1/ GLOBAL LEADER IN THE PDMP SECTOR

Grifols is a **global healthcare company**, founded in Barcelona in 1909 by hematologist Josep Antoni Grifols Roig. Today, it is a global leader in the production and development of plasma derivatives and other innovative treatments for chronic, rare and prevalent diseases.

The company is also a **recognized leader in transfusion medicine**, offering a comprehensive portfolio of solutions designed to enhance safety from donation through to transfusion.

GRIFOLS BUSINESS UNITS

**BIOPHARMA**
Plasma-derived medicines and other innovative solutions based on plasma knowledge

**DIAGNOSTIC**
Diagnostic solutions for blood screening and typing as well as clinical diagnostics.

**BIO SUPPLIES**
Biological materials for health sciences research and third-party manufacturing.

**HEALTHCARE SOLUTIONS**
Specialty pharmaceuticals and hospital management solutions.

Grifols' leadership in the PDMP sector is underpinned by **its vertical integration model that works across the entire production cycle**, from the acquisition of plasma through a network of donation centers in the U.S. and Europe, right through to the finished product. This includes the capacity to transport and manufacture the collected plasma, and to conduct screenings and analyses.

Grifols' mission, to improve people's health and well-being, has patients, donors and society at the heart of everything it does.

**Grifols' leadership in the PDMP sector is underpinned by its vertical integration model that works across the entire production cycle**

## PUBLIC-PRIVATE PARTNERSHIPS

**Grifols is working to help countries achieve plasma self-sufficiency and facilitate access to plasma-derived medicines worldwide**. The company believes access to medicines and healthcare should be universal.

This is exemplified by public-private partnerships in Canada and Egypt, where Grifols is supporting their work to reach self-sufficiency in PDMP supply.

» **Canada:** in 2022, Grifols entered into a pioneering long-term agreement with Canadian Blood Services (CBS), Canada's national blood authority, to significantly increase the country's self-sufficiency in immunoglobulin medicines. Grifols is building a national, vertically integrated supply chain that will include plasma collected in new donor centers due to open over the next few years. This expands on recent acquisitions Grifols made in the country, including the first Canadian plasma center in Winnipeg in 2022, and manufacturing facilities in Montreal in 2020.

» **Egypt:** in November 2020, Grifols struck a first-of-its-kind deal in a pioneering alliance with the Egyptian government. The agreement led to the creation of a new public-private enterprise, Grifols Egypt for Plasma Derivatives, which intends to guarantee the treatment of the most vulnerable patients. Through the National Service Projects Organization (NSPO), Grifols is supporting the Egyptian government in developing a fully integrated plasma-supply infrastructure aiming to reach self-sufficiency in PDMPs in the country, and across the MENA region.

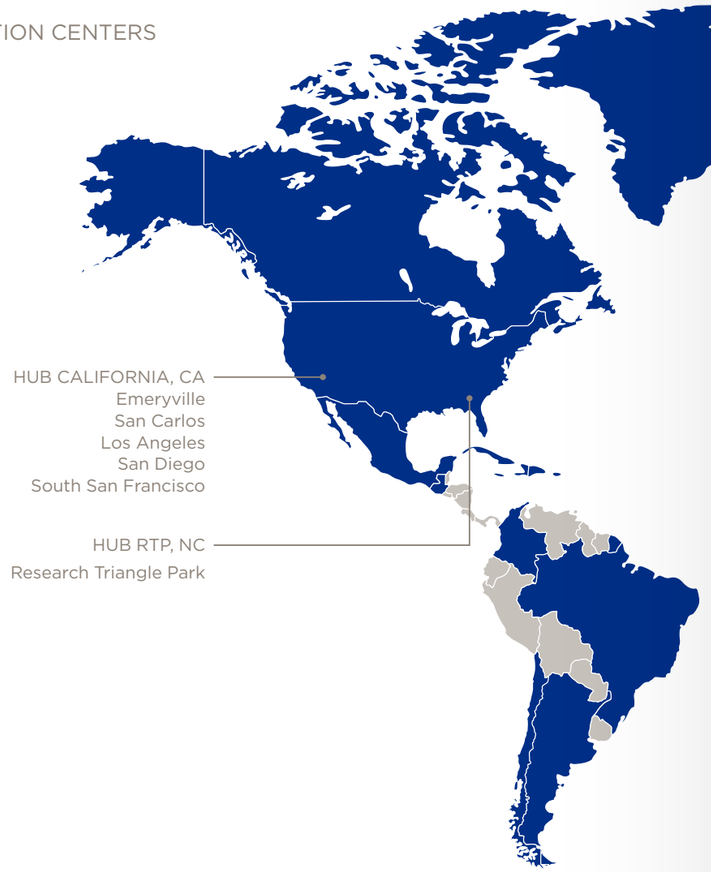
## GRIFOLS' GLOBAL NETWORK OF INNOVATION CENTERS

**14**
R&D+i centers

**+1,200**
Researchers

**1,682 M€**
Investment in the last 5 years

**2,705**
Patents




Grifols Affiliates  * Biotest



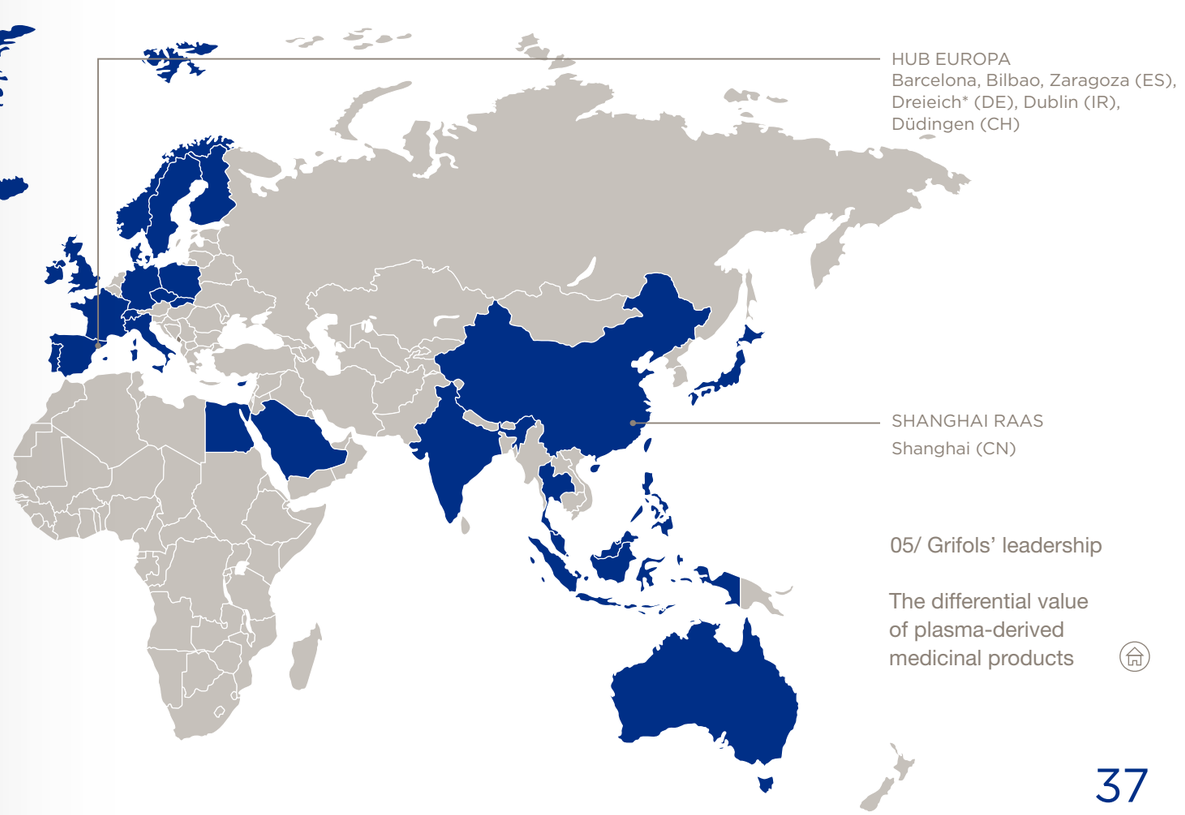
## 5.2/ COMMITMENT TO INNOVATION

Since its foundation, Grifols has been dedicated to **enhancing the health and well-being of people around the world**. It has a track record of supporting scientific advances by sharing its discoveries with the scientific and patient community, mirroring the altruistic ethos of the founding family. Grifols created the first private blood bank in Spain, developing practices and standards that have evolved to become global benchmarks.

In 1951, **Josep Antoni Grifols Lucas developed the plasmapheresis technique**, a method through which blood is withdrawn from the body, the plasma is separated out and collected, and the other blood components are returned back into the bloodstream. Plasmapheresis allows for more frequent donations because plasma regenerates quickly and the human body reproduces the extracted proteins in a matter of days.

The development of this technique, which is still used today, was a global milestone that shaped the future of the company, the industry and, most importantly, patients' quality of life. This trend has continued over the decades as the company has grown and expanded.

Grifols remains committed to **strengthening its innovation pipeline**, including identifying further therapeutic opportunities in immunology, hepatology, pulmonology, hematology, neurology, infectious diseases, and intensive care. Over the last five years, Grifols has invested €1.682 billion in innovation.



The company complements internal research with external collaborations and investments in new platforms and start-ups to continue innovating for society.

### INNOVATING FOR PATIENTS

Patients are the purpose of the company, the core of its mission. **Grifols' commitment to patients inspires it to maintain the highest standards of quality and safety** for the medicines it produces and to innovate in the development of new therapies.

The company strives to exceed the standards required by government agencies, with additional levels of control and safety built into all its processes.

It innovates with the patient in mind. Recent noteworthy advancements include:

» Yimmugo®, a new version of an immunoglobulin G preparation, which was approved in 2022 to help patients with immunodeficiency.

» The development of a biological fibrinogen adhesive sealant for the treatment of severe bleeding in patients with congenital or acquired fibrinogen deficiency.

» Analyzing the effects of human albumin in the early stages of Alzheimer's disease and in cardiovascular and renal functions, when administered frequently to patients with advanced liver cirrhosis and ascites.

» Trimodulin, a new protein with potential indication in the treatment of severe community-acquired pneumonia (CAP).

## 5.3/ SOCIOECONOMIC IMPACT AND SUSTAINABILITY

### SOCIOECONOMIC IMPACT

Grifols is an inclusive company with a committed and diverse workforce. It has direct presence in 30 countries and regions, and sales in more than 110. The company has more than 23,000 employees worldwide, working across:

» 14 research, development and innovation (R&D+i) centers in Europe, the U.S. and China.

» 16 manufacturing plants located in Spain, the U.S., Germany, Ireland, Switzerland, Canada and Australia.

» More than 390 plasma donation centers.



A global family with more than 90 nationalities, in which women make up 58% of the staff.

**Creating shared value, Grifols contributes to sustainable development and improvement of social welfare**. Based on a cost-benefit analysis of the social, environmental, and economic values created by a company, Grifols has assessed the social return on investment (SROI), as of 2023[19]:

» The social value created by Grifols for donors, patients and local communities was EUR 32,427 million.

» Total SROI: 1.87. For every €1 Grifols invests, it generates €0.87 in social return.

### SUSTAINABILITY

**Grifols is committed to the sustainable development of our society and our planet**, ensuring sustainable consumption and production in line with the Sustainable Development Goals defined in the United Nations 2030 Agenda. This long-term commitment, which reflects the company's values, is its response to the needs of patients, donors, local communities and society as a whole. They also strive to protect the environment and fight climate change. The company has set environmental targets to **accelerate the transition to a low-carbon economy and achieve net-zero emissions by 2050**.

Grifols works with local and international organizations to generate a positive social impact through social, environmental, educational and sports activities in the communities where it is present.

Its three foundations, the Víctor Grífols i Lucas Foundation, the Probitas Foundation, and the J.A. Grifols Foundation, complement Grifols' social outreach initiatives by **promoting ethical rigor and care for the most vulnerable people**.

Grifols donor centers help strengthen the cities and towns where they are located by creating job opportunities, stimulating the local economy and offering a variety of outreach activities. All these centers also participate in community engagement events and contribute through charitable donations and volunteer programs.

# 06/ CONCLUSION

It is essential that countries ramp up their efforts to enhance plasma collection as the global demand for PDMPs continues to rise. Key to this is an increase in donations **through plasmapheresis**, which supports collection of greater volumes of plasma and more frequent donation.

To achieve this, we must ensure that the right mechanisms, support and regulatory framework are in place to:

Encourage and grow a cohort of loyal and **regular plasma donors** at country-level. The **broad and open definition of SoHO donor compensation**, allows Member States to choose whether and how to compensate donors within the framework of the VUD principle.

Ensure **adequate and efficient infrastructure** is in place to support plasma donation through plasmapheresis.

Support country-level **awareness raising campaigns** that emphasize the importance of plasma donation to produce life-changing PDMPs.

Explore **public-private collaborations**. Grifols is working with governments to achieve self-sufficiency in the supply of PDMPs. Examples of these efforts are being implemented in countries such as Canada and Egypt.

As a global leader in the PDMP sector, strongly rooted in Europe, Grifols is committed to continue working with government and third-party stakeholders to guarantee an adequate and sustainable supply of these life-saving treatments for the wide range of patients who need them.

# 07/
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