SPANISH CONSENSUS ON PLASMA SUFFICIENCY AND ITS DERIVATIVE TREATMENTS

AEDIP
ASOCIACIÓN ESPAÑOLA DE DÉFICIT INMUNITARIOS PRIMARIOS

Initiative promoted by the Spanish Association of Primary Immune Deficits (AEDIP). March 2022.

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WHY A CONSENSUS

For thousands of people suffering from rare and chronic diseases, blood-derived medicines are essential to maintain a normal life. In many cases, they are indispensable for survival.

These treatments are special because they have an exclusively biological origin: human blood plasma. Plasma is the blood component that contains the essential defence proteins against infections and coagulation factors, which is why its use in medicine is widespread and increasing as new indications are developed.

There is currently a problem of dependency and, in some cases, limited availability of blood products that are essential for thousands of patients. In Spain, the availability of plasma has diminished in recent years and we import half of the blood derivatives, mainly from the United States. This dependency generates a risk of insufficiency, the consequences of which we already suffered in 2021, due to various factors, including the low collection in 2020 caused by COVID-19 and the progressive increase in the consumption of immunoglobulins.

Reality has shown us that it is urgent to develop viable solutions that foresee and ensure the availability of the necessary medications. People's health cannot remain so exposed to contingencies nor suffer delays in access to treatment.

Currently, the plasma obtained from donations is insufficient to supply the needs, in addition to which the direct donation of plasma (plasmapheresis) is very scarce and there is little information. **It is worrying that many people do not know that they can donate plasma, due to a lack of awareness.**

However, not all problems stem from the current situation: this situation has shown structural challenges in the collection, management and administration of the blood derivatives that must be analysed. An effort is needed in the planning and investment in the infrastructure and resources for donation.

Our ambition with this Consensus, as representatives of patients, scientific societies and experts, is to contribute to this debate and promote a timely analysis of the short, medium and long-term problems and needs which must be resolved through programmed and sustained intervention.

With this Consensus we wish to call on society and the authorities to raise awareness of the scale of the plasma challenge in Spain, within the European and global context, and adopt relevant solutions as soon as possible. Our lives depend on it.

EXECUTIVE SUMMARY

In Spain, it is estimated that the number of people needing plasma-derived treatments exceeds 30,000. People with primary immunodeficiencies, autoimmune diseases or coagulopathies depend on them. Currently, the system for managing plasma-derived treatments does not adequately respond to patients' needs.

The main challenges include: insufficient plasma collection, a low level of sufficiency in the production of treatments – a high dependency on external supplies – and the absence of a common national policy to effectively address the challenges to ensure rapid and equitable access to treatment for patients.

SITUATION	CHALLENGES	RECOMMENDATIONS
AVAILABILITY OF BLOOD DERIVATIVES Plasma-derived medicines are essentially: albumin, immunoglobulins, coagulation factors and alpha-1 antitrypsin concentrate (AAT). The demand is growing. Spain imports most of its plasma-derived medicines, mainly from the USA, our average level of sufficiency being less than 40%.	The level of sufficiency in the manufacture of treatments is low. The high level of dependence on overseas markets puts patients' access to treatment at risk because: 1. it generates vulnerability in any alteration in the supply chain and 2. requires dosing, causing undue delays in treatments.	1. Increase knowledge about plasma and its uses, given the clinical needs of patients and promoting research into new uses. 2. Improve the recognition of plasma within the existing regulations as a strategic and essential resource for the health of very many people. 3. Analyse the situation of plasma and the derived treatments in the light of the principles of sufficiency of essential medicines and guarantee of access to treatment by the patient. 4. Ensure an optimal level of supply of plasma-derived medicines, reducing dependence on overseas sources as much as possible. 5. Promote policies of clinical consensus and optimisation in the use of treatments based on scientific evidence, which make it possible to meet the demand efficiently, especially at times of shortage.
COLLECTING PLASMA The process and distribution of plasma-derived treatments is complex and lengthy, so it is important that sufficient volumes of plasma are always available for fractionation to avoid shortages. Plasma can be obtained from its separation from donated whole blood or directly from plasmapheresis. Plasmapheresis enables a larger amount to be obtained and can be performed more frequently. In Spain, 91% of plasma used in the manufacture of treatments comes from donated whole blood.	Plasma collection is insufficient and scarce in comparison with our neighbouring countries, mainly due to the low level of direct donation (plasmapheresis). Causes: 1. lack of political priority, 2. low knowledge/awareness and lack of facilities to donate, 3. insufficient infrastructure.	1. Promote plasmapheresis to reach donation levels that ensure an optimal response capacity to the needs of the population, by means of institutional policies to raise awareness and encourage donation. 2. Develop a national plan that defines compensation formulas compatible with the principle of voluntary and altruistic donation. 3. Improve information to ensure provision of adequate resources in Transfusion Centres and prioritise the increase in the amount of machinery and personnel available for plasmapheresis. 4. Develop a solid collection infrastructure network with more donation points to meet the specific needs of each area and allow innovative solutions to be devised to bring plasmapheresis closer to potential donors.
MANAGEMENT OF TREATMENT The Spanish system of blood donation is decentralised and hierarchical at functional and territorial levels. The national network is made up from the network of the 17 Autonomous Communities.	There is no national common policy for the planning and management for plasma-derived treatments. The integration mechanisms between the regions are scarce and inefficient. There are disparities in the access to treatment between and within the regions: 1. there is no single information and coordination network to understand the demand for plasma-derived treatments in each region and to establish synergies, 2. the criteria for use of the treatments are not homogeneous.	1. Promote management at national level and strengthen coordination mechanisms that enable treatment needs to be addressed jointly and efficiently, eliminating barriers to cooperation between Autonomous Communities. 2. Promote information systems that make it possible to know the capacities and needs for medication, donation and infrastructure in the various regions.

METHODOLOGY

This Consensus document is part of the initiative promoted by the Spanish Association of Primary Immune Deficits (AEDIP) in defence of the sufficiency of blood products in Spain. It is the result of a joint effort by patient organisations, blood donors and scientific societies, the collaboration of which, through the provision of information and testimonies, has been essential for its drafting. The editing and collection of additional data has been carried out by the public affairs consultancy RPP Group. The coordination and layout of the document was made possible due to the support of Takeda, Grifols and CSL Behring, with the authors maintaining full independence over the content of the document.

AUTHORS

Spanish Association of Primary Immune Deficits (AEDIP)

Spanish Federation for Rare Diseases (FEDER)

Spanish Haemophilia Federation (FEDHEMO)

Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency (Alfa-1 Spain)

Asociación GBS|CIDP España Polineuropatías Inmunomediadas (GBS|CIDP España)

Asociación Española de Angioedema Familiar (AEDAF)

Spanish Federation of Blood Donors (FEDSANG)

The Spanish Society for Immunology (SEI)

Spanish Society for Haematology and Haemotherapy (SEHH)

Spanish Society of Blood Transfusion and Cellular Therapy (SETS)

Spanish Society of Allergology and Clinical Immunology (SEAIC)

Spanish Society of Clinical Immunology, Allergology and Paediatric Asthma (SEICAP)

Spanish Patients' Forum (FEP)

Society of Immunology of the Community of Madrid

EDITION

Cristina Fuentes, RPP Group
Alberto Domingo, RPP Group
Kit Greenop, RPP Group

TOWARDS A SUFFICIENCY IN PLASMA-DERIVED TREATMENTS IN SPAIN

1. CONTEXT

1.1. PLASMA-DERIVED TREATMENTS. DEPENDENCE AND OPTIMISATION.

Medicines derived from blood plasma constitute a set of biological therapies essential for the treatment of thousands of people with rare and chronic diseases. Their production depends on a component of human blood which makes them unique, while involving a production process more complex and extensive than the manufacture of other conventional medicines.

Blood	Plasma
55% plasma	7% proteins
44% red blood cells	92% water
	1% other substances

Blood plasma is the liquid component of blood in which red blood cells (erythrocytes), white blood cells (leukocytes) and platelets are suspended. The most abundant protein in plasma is albumin, which helps prevent fluid from leaking out of blood vessels and entering tissues, and also performs transport functions by binding to substances such as hormones and some pharmaceuticals. Plasma contains other proteins, such as immunoglobulins (antibodies), which actively defend the body against viruses, bacteria, fungi and cancer cells. There are also clotting factors, which prevent bleeding.[1]

In the European Union, more than 300,000 people[2] depend on treatments derived from blood plasma, either as an exclusive therapeutic option to survive, or as an essential treatment to ensure an optimal quality of life. Assuming an equal prevalence throughout the EU, we could be talking about 35,000-65,000 patients in Spain, although the lack of official data prevents a more accurate picture of the magnitude of the problem.

People suffering from primary immunodeficiencies, neuromuscular diseases, autoimmune diseases or coagulopathies together make up a broad spectrum of pathologies that require these treatments, usually for life. We are therefore talking about **diseases the origin of which is often genetic, which are life-threatening and have serious associated morbidities,** where treatment has a huge health and social impact.

It is estimated that since the introduction of plasma-derived treatments, the **life expectancy** of people with immunodeficiencies and clotting factor disorders has increased significantly to a normal average, while bleeding and infection rates have been reduced[3]. In addition, these clinical benefits have generated a positive economic impact on the health care system[4].

THE MOST FREQUENT PATHOLOGIES REQUIRING PLASMA-DERIVED TREATMENTS

Primary immunodeficiencies (PIDs) represents a group of more than 6,000 people in Spain, who suffer from changes in the immune system, resulting in a greater predisposition to suffer serious infections. For this reason, they require immunoglobulins to provide them with the necessary defences.

Immunoglobulins are also the standard first line treatment in demyelinating neuropathies, both acute (**Guillain-Barré Syndrome,** GB) and chronic (**chronic inflammatory demyelinating polyneuropathy,** CIDP) and in **multifocal neuropathies** (NMN), as they reduce and slow down the disability process inherent to these pathologies.

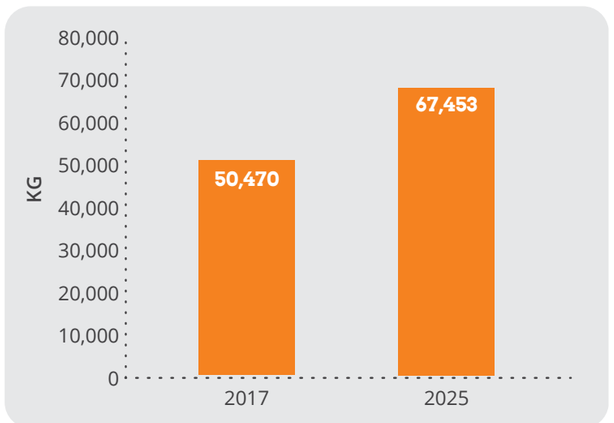
People with **Alpha-1 Antitrypsin Deficiency** (AATD) suffer from a deficiency of this protein, the main known function of which is to protect lung tissue. It is estimated that this disease, which affects 1 in 2,500 people worldwide, affects around 14,500 people in Spain - many of them undiagnosed. The treatment, based on replacement by infusion of alpha-1 antitrypsin protein into the patient's blood, is essential to maintain lung function.

About 3,000 people in Spain have **haemophilia**, an inherited disorder in which the blood does not clot properly, resulting in haemorrhages of varying degrees of severity. People with haemophilia have low levels of clotting factor VIII or clotting factor IX. The factor VIII received by patients who require it may be of recombinant or plasma origin.

Hereditary angioedema[5] is due to an alteration in the gene encoding the C1-activated globulin esterase inhibitor (C1-INH) protein, causing its deficient or abnormal synthesis. Consequently, these patients should be treated with purified C1 Inhibitor in many clinical situations.

In Spain, **the demand for plasma-derived medicines has increased progressively,** both due to the strength of the clinical evidence supporting the routine use of these medicines in immunodeficiencies and as a result of new clinical indications[6], mainly in the use of immunoglobulins. More conditions are being diagnosed as a result of medical advances, so more people need treatment. Immunoglobulins have been shown to be effective in patients with neuromuscular and autoimmune pathologies (such as Guillain-Barré, chronic inflammatory demyelinating polyneuropathy or multifocal neuropathies).[7,8,9] Immunoglobulins are also administered to prevent infections in patients with **secondary immunodeficiencies**, for example, situations resulting from allogeneic, solid organ transplantation or CAR-T therapy.

Specifically, **the consumption of immunoglobulins has doubled between 2012-2019** – 11% per year on average, and this demand is expected to continue to grow by 6-10% by 2025 at least[10].



Projected consumption (in kg) of immunoglobulins in Europe 2017-2025. Source: Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe. Plasma Protein Therapeutics Association (PPTA). Original source: MRB reports 2017.

What does the current and potential increase in the need for plasma-derived treatment involve? On the one hand, **increasing its availability** by the necessary amount, either through domestic procurement of plasma and medicines or through their importation; on the other hand, **optimising the use of the available medicines.**

A) THE MANUFACTURE OF PLASMA-DERIVED MEDICINES

The production process of plasma-derived treatments is complex and the average time between donation and administration of the treatment to the patient is long - around 10 months - so it is important that sufficient volumes of plasma are always available for industrial fractionation. However, in our country, plasma collection by plasmapheresis is insufficient and scarce compared to other neighbouring countries.

Plasma-derived treatments are manufactured from **fractionation of plasma obtained from whole blood donations or through direct plasma donations (plasmapheresis).** Transfusion Centres collect, process, test and distribute blood components to hospitals and industry.

The **surplus plasma** that is not used in transfusions is sent to the fractionation industry for the production of plasma-derived medicines.

Comparing the quantities of use versus our own procurement, negative balances are recorded for albumin (59.41% of the demand), immunoglobulins (only 33.6%) and Factor VIII (60.7%). These **(in)sufficiency balances, moreover, have generally decreased over the last 5 years,** with the exception of FVIII.

Plasma derivatives	2015	2016	2017	2018	2019
Albumin collected (gr)	9,075,620	10,509,411	9,833,206	9,815,460	9,572,115
Albumin consumed	12,794,929	14,107,298	14,036,407	15,711,792	16,111,873
Percentage of self-sufficiency	71%	74%	70%	62%	59%
Immunoglobulins collected	1,643,805	1,897,510	1,649,493	1,564,249	1,584,823
Immunoglobulins consumed (gr)	3,040,415	3,369,361	3,756,145	4,443,064	4,718,967
Percentage of self-sufficiency	54%	56%	44%	35%	34%
Factor VIII obtained by fractionation	34,484,391	41,764,000	36,831,500	31,739,489	46,322,251
Factor VIII consumed (UI)	80,813,302	93,129,420	76,872,172	75,507,759	76,263,866
Percentage of self-sufficiency	43%	45%	48%	42%	61%

Source: Own figures based on data from the Ministry of Health[11].

Spain is currently far from the objective of self-sufficiency in blood derivatives based on altruistic donations, one of the pillars of the National Haemotherapy Plan. In the case of immunoglobulins, our level of sufficiency – that is, the capacity to respond to demand with our own production - stands at a meagre 34%.

There exists a **situation of dependence on the outside world** – mainly the United States - for the supply of these essential medicines. This dependence is common to the majority of the countries of the European Union. The European and Spanish inability to secure the supply of plasma-derived medicines can have dramatic consequences for patients.

Some experiences – such as the **stockout** in the supply of C1 Inhibitor concentrate from the United States in 2018 - show how the **high level of vulnerability** of a highly dependent system from overseas can decisively impact access to treatment for many patients for whom plasma and its derivatives are essential. More recently, the context of COVID-19 has also meant a significant drop in donations, thereby affecting the supply chain.

B) OPTIMISATION OF THE USE OF PLASMA-DERIVED MEDICINES

The insufficiency of plasma-derived treatments requires the development of **optimisation plans,** which are justified by the need to prioritise insufficient inventory - of particular relevance in the case of **immunoglobulins**.

Optimising the use of blood derivatives is necessary in the context of insufficiency, and is also essential for three reasons: their incorrect use can be associated with the appearance of adverse effects; the collection of plasma requires an effort to inform and raise awareness among potential donors; and the cost of these products is high and generally borne by the public health system.

In Spain, **there is no institutional consensus on the use of plasma-derived treatments,** with a predominant heterogeneity of hospital and regional protocols. We did find, however, some **attempts at clinical consensus**, such as the "Guía sobre el Uso de Inmunoglobulinas" (Guide on the Use of Immunoglobulins)[12] from 2011 published by Grupo Español de Medicamentos Hemoderivados (Spanish Group of Blood Derivative Medicines, GEMEH) and the Spanish Society of Hospital Pharmacy (SEFH). The **Community of Madrid** has also recently produced a set of "Criteria for the rational use of human immunoglobulins"[13]. Under the premise that an increase in plasma donations is necessary to address a situation of treatment insufficiency, the plan aims to establish a process to rationalise its use, which guarantees the achievement of an adequate balance between supply and demand, in the hope that an increase in the volume of plasma destined for industrial fractionation can be achieved.

1.2. POLITICAL AND LEGISLATIVE FRAMEWORK (EU-SPAIN)

The **European Directives 2002/98/EC and 2004/23/EC**[14] of the European Parliament and the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human blood, tissues and cells - the Blood, Tissues and Cells Directives - provide the European Union with the legislative framework for plasma and plasma-derived treatments.

The European legislation is currently under revision[15]. Some of the relevant demands raised in public consultation: (1) that **the unique and special nature of plasma and its derived medicines** is recognised; (2) that **an adequate level of sufficiency of the treatments be guaranteed, by minimising dependence on external sources**[16] to reduce vulnerabilities in stockout situations or delay in the supply chain.

In Spain, the European regulatory framework inspires the two main rules of the national blood donation system: **Royal Decree 1088/2005**, of 16 September[17], establishing the technical requirements and minimum conditions for hemodonation and transfusion centres and services (RD 2005), and **Royal Decree 1343/2007**[18], of 11 October, establishing the standards and specifications relating to the quality system of the transfusion centres and services (RD 2007). Certain aspects of both regulations have been developed and updated in the light of the European regulation on successive occasions, by means of orders - such as the Order establishing traceability and notification of adverse reactions.

The concept of plasma is included in the legal definition of "Plasma components" of RD 2005, in which it is mentioned that it "may also be used for the manufacture of medicinal products derived from human plasma". The requirements to donate plasma fall under the umbrella of those for blood.

There is a need for greater clarity, in Spanish and European regulations, on the characteristics of plasma-derived medicines, their uses and requirements for donation. This will result in greater knowledge among decision-makers and the population.

RECOMMENDATIONS

1. Increase knowledge about plasma and its uses, given the clinical needs of patients and promoting research into new uses.
2. Improve the recognition of plasma within the existing regulations as a strategic and essential resource for the health of many people.
3. Analyse the situation of plasma and the derived treatments in the light of the principles of sufficiency of essential medicines and guarantee access to treatment by the patient.
4. Ensure an optimal level of supply of plasma-derived medicines, reducing dependence on overseas sources as much as possible.
5. Promote policies of clinical consensus and optimisation in the use of treatments based on scientific evidence, which make it possible to meet the demand efficiently, especially at times of shortage.

2. INCREASED PLASMA COLLECTION

2.1. COLLECTING BLOOD PLASMA: PLASMAPHERESIS

The production of derived medicines to respond to patients' needs is closely linked to the **available blood plasma**. Surplus plasma – that which is not used for direct transfusion – is sent to the fractionation industry for the manufacture of treatments. For this reason, plasma must be considered as a **strategic resource** in order to ensure a sufficiency of medicines.

There are two ways to collect plasma: (1) by separating plasma from a whole blood donation **-recovered plasma-** or (2) by direct donation of plasma through plasmapheresis **-source plasma-.**

	Extraction	Donation	Frequency	Average duration	Volume
PLASMA SOURCE	Donation centre → **Plasma** direct donation of plasma → used to manufacture plasma-derived medicines	**Plasma** plasmapheresis	**1 x fortnightly**	**35 min**	**~600-800ml**
PLASMA SOURCE	Donation centre → Processing centre → **Plasma** for hospital use (transfusion) * manufacture of plasma-derived medicines; **Red blood cells** hospital use	**Blood** blood donation	**4 x a year**	**10 min**	**~250-300ml**

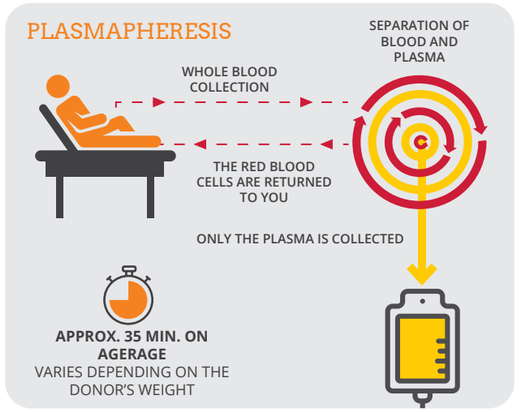
Source: Own figures based on the graph included in PPTA. Plasma donation: New thinking to serve Europe's patients. July 2021.[18]

Direct donation by plasmapheresis is a process by which the donor's plasma (source plasma) is removed from the blood and the remaining cellular components are returned to the donor. The donation of plasma lasts 35 minutes on average and can be performed more frequently than blood donation, between **20 and 60 times a year**, depending on national legislation. The European recommendation is a maximum of 33 donations per year. One plasma donation provides between 600 and 800 ml.

Separated from whole blood through a donation of whole blood. After the donation, the blood is separated into its different components (recovered plasma). The total blood donation lasts about 10 minutes and can be performed up to 4 **times a year**, depending on gender. A donation of 450 ml of whole blood provides about 250-300 ml of plasma.

Plasmapheresis is the procedure of direct plasma donation. It is essential for obtaining plasma-derived medicines because **it allows more plasma volume to be collected** than that obtained in a whole blood donation and **it can be performed more frequently**. The duration of the process is longer than a blood donation.

In plasmapheresis, the blood cells are separated, the plasma is removed, and the remaining blood is returned to the patient. This technique **allows a larger amount of plasma to be extracted than from a donation of whole blood** (600-800 ml as opposed to an average of 280 ml). The process lasts an average of 35 minutes. In addition, since the recovery of the extracted plasma is almost immediate and the donor keeps the red blood cells (which take the longest to regenerate), **it is possible to repeat the donation within 15 days, as opposed to 8 weeks when donating blood.**



Source: Own figures based on the graph included in the PPTA Position Paper: Together toward a broader European plasma donation ecosystem.

Donations for plasmapheresis necessary for one year of treatment for a single patient[18]		
Alpha-1 antitrypsin deficiency	Haemophilia	Immunodeficiency
900	1200	130

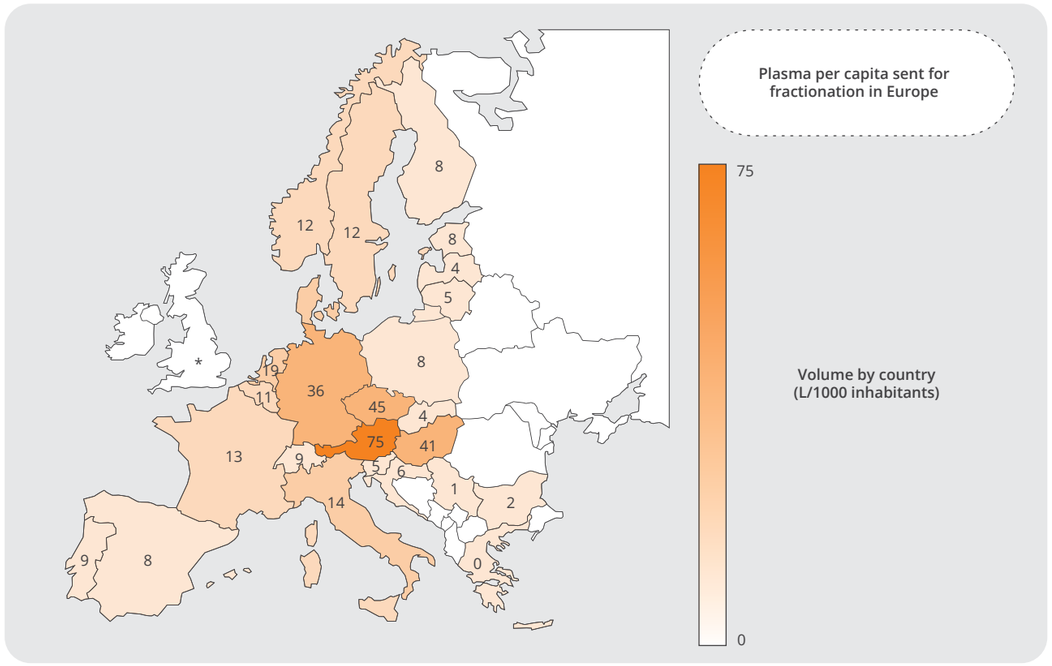
In short, plasmapheresis has **particular characteristics** that must be considered when dealing with the problem of donations: it requires specific equipment and both the frequency of donation and the duration of the process are greater than for ordinary blood donations.

A) COLLECTING PLASMA: A EUROPEAN PROBLEM

A close look at the European environment shows that there is a great **dependence on the outside world** for obtaining plasma and its derivatives – generally imported from the United States. The countries of the European Union currently have a deficit of 38 million litres of plasma needed for the manufacture of treatments in demand.

The plasma collected in Europe accounts for only about **65% of the necessary volume** to manufacture the treatments required[19]. This generates a **situation of high vulnerability** to potential supply chain problems, as well as challenges to meet the estimated increase in demand for new indications.

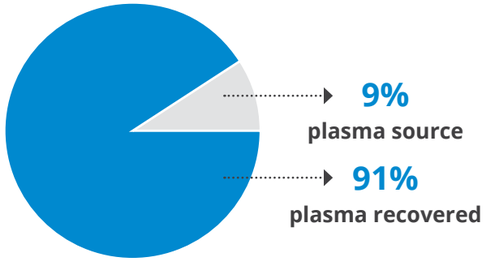
There is an **inequality among the European countries regarding the donation volume** due to a wide disparity in the management models for collecting plasma. In particular, Austria, the Czech Republic, Hungary and Germany have a larger collection, mainly because their systems are based on remuneration for donation. However, even in countries where the principle of voluntary and altruistic donation prevails, there are differences. For example, in Spain the donation volume is 8 L/1000 inhabitants while in France, Italy or the Nordic countries it is between 12 and 14. Consequently, **Spain could improve its plasma collection figures without the need to change the principle of altruism** in its donations.



Source: Own figures based on the map included in the White Paper Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe. Page 47.

B) PLASMA DONATION FIGURES IN SPAIN

In Spain, most plasma is obtained by processing donated whole blood. As a result, most of the plasma sent to the fractionation industry for the manufacture of medicines is recovered from whole blood donations - 91%; only the remaining 9% comes from direct plasma donations, compared to an EU average of 40%.[20]



This places us in a situation of greater vulnerability than that of our neighbouring countries, since **the amount of plasma collected by the separation of whole blood is much less than that obtained from direct plasma donations in each donation,** which **directly affects the number of treatments that can be obtained.**

It should also be noted that blood donations have declined in recent years, partly because of the reduced need for red blood cells due to improved indications and therefore improvement in their use. This **decline in blood donations** inevitably results in lower plasma collection and less treatment production, especially as most fractionated plasma in Spain depends on whole blood donations.

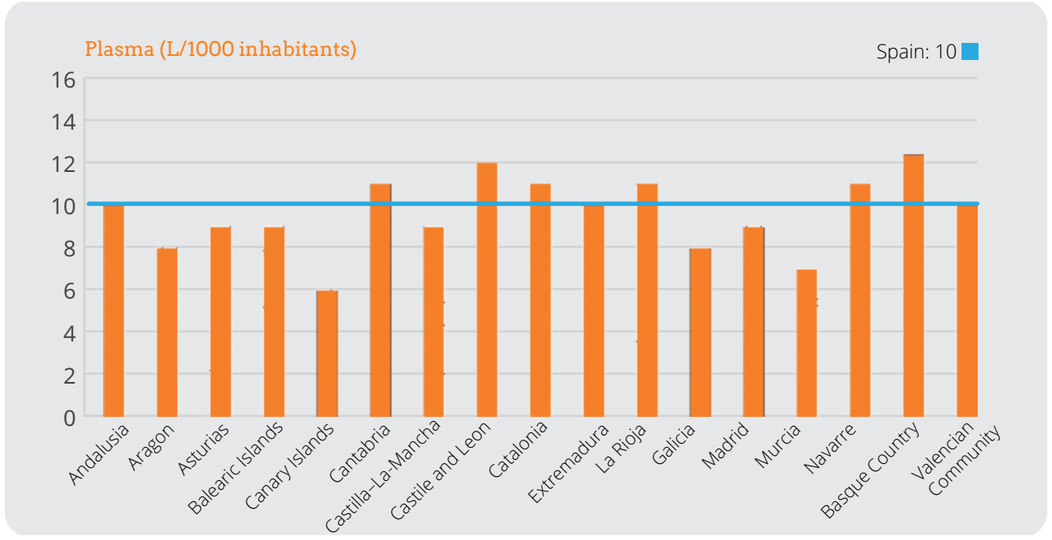
The average number of direct plasma donations – plasmapheresis – in Spain is scarce and well below the European average. This affects the amount of plasma available for fractionation and the volume for treatment production.

Regarding direct plasma donation, our country is far from the EU average: in 2019, 0.7 litres per 1,000 inhabitants in Spain, compared to an EU average of 8 litres, and **up to ten times less plasma per capita than other leading countries in obtaining it,** such as Austria, although its system is based on remuneration.

The situation in Spain	2015	2016	2017	2018	2019
Total no. of donations (whole blood + apheresis)	1,706,973	1,698,759	1,686,463	1,682,579	1,684,501
Total no. of blood donations	1,651,074	1,639,606	1,615,665	1,605,752	1,602,368
No. of plasma donations (plasmapheresis)	28,045	31,724	42,387	48,134	52,258
Plasma obtained from plasmapheresis (L)	16,790	19,053	25,365	25,500	30,999
L/1000 inhabitants (Spain average)	0.4	0.4	0.55	0.6	0.7
L/1000 inhabitants (average EU)	5.9	6.25	6.3	8	8

Source: Own figures based on data published by the Ministry of Health[21]

In the Autonomous Communities no great disparities are seen in general, the average remaining at 10L/1000 inhabitants. However, the Basque Country and Castile and León lead in plasma donation, obtaining almost twice as much as in the Canary Islands.



As analysed in the following section, there are three elements that explain the low level of plasma donation in Spain in comparison with other countries around us: the **lack of political prioritisation**, the **lack of information and facilities to donate** and the **scarce and rigid infrastructure for plasma donation.**

2.2. INFORMATION, AWARENESS-RAISING AND PROMOTING DONATION

The **special nature of plasmapheresis** demands a **somewhat greater amount of time** from the donor than blood donation; it may involve a **greater number of donations** and cannot be performed just anywhere, as it **requires specific devices** to be carried out, which are difficult to transport. **Motivating donors to go to donor centres is a challenge** that must be viewed from multiple angles, including personal factors - knowledge, perception of safety and time; material and organisational factors; the number of centres and machines for plasmapheresis; sufficient staff; among other things.

A) AWARENESS AND POLITICAL PRIORITY

In Spain **the information regarding what plasma is and the uses of its derived treatments is scarce**, which contributes to the low volume of plasmapheresis compared to other countries around us. While most of the population is aware of the importance of donating blood - as reflected in the success of transfusion centre appeals, despite the continuing overall decline in donations - there is no such general knowledge about plasma.

On the other hand, there is a latent fear among some experts that an appeal for direct plasma donation will result in shortages of whole blood and its components - a phenomenon called "crowding-out". However, retrospective analyses of donation rates in other countries deny this assumption.[22 23 24]

Transfusion Centres, together with **donor and patient organisations**, **play a fundamental role** in the collection of plasma, leading the work of disseminating information and appealing to the population to donate. The Transfusion Centres have specific and professional donation promotion services; donor organisations perform important work through information and awareness campaigns. Their efforts should be supported by the institutions.

Given that these campaigns are limited in time and territory, there have been several proposals for **the authorities to carry out permanent plasmapheresis programmes and mass awareness-raising actions**. In this regard, it is worth taking into account the DOMAINE Donor Guide[25] which, after analysing the challenges of donor recruitment and the main media used, concluded that occasional institutional campaigns on television or other mass media have a greater impact and are more effective in raising donor awareness than other formulas.

"United for plasma": Patient organisations, donors and scientific societies called in a joint Communiqué addressed to the authorities for a sustainable strategy to ensure the sufficiency of plasma-derived treatments[26].

In 2017, the Ministry of Health, recognising the relevance of the issue, managed to contract the development of a programme to promote plasmapheresis[27]. At the end of 2021, it announced the distribution of 2.2 million euros earmarked for actions to promote the implementation of plasmapheresis programmes[28]. Although these actions are a step forward and demonstrate that the authorities perceive the priority for increasing donations to be able to respond to the demand for treatment, the underlying problem persists, since **there is no adequate national planning development** with the will to be sustained over time and with the involvement of all the actors.

It is essential to **articulate a national policy on plasmapheresis and the sufficiency of blood-derived medicines**, with an emphasis on public information through institutional campaigns to promote plasmapheresis.

RECOMMENDATIONS

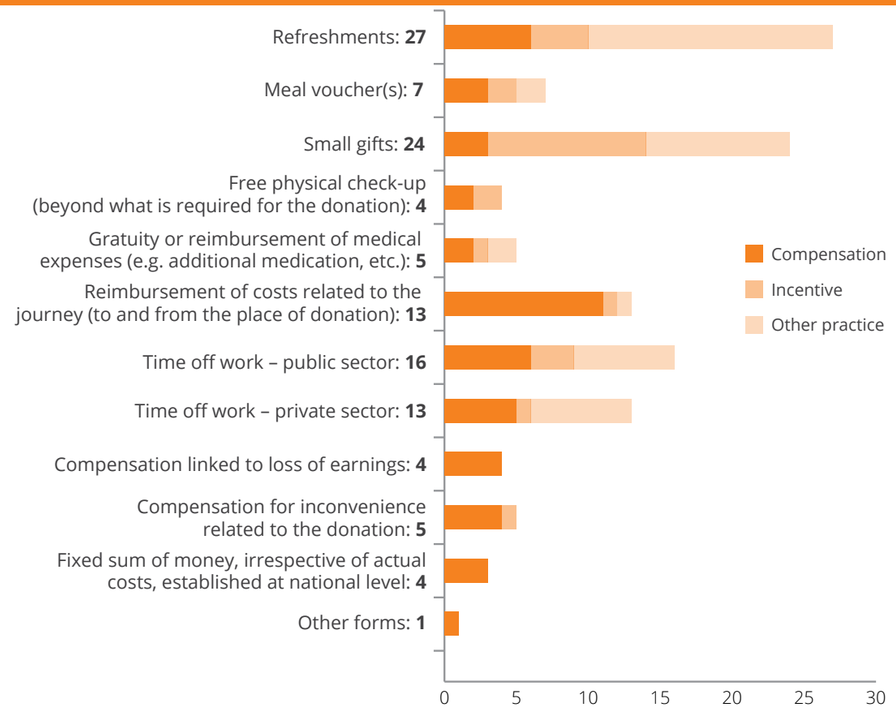
1. Promote plasmapheresis to reach donation levels that ensure an optimal response capacity to the needs of the population, by means of institutional policies to raise awareness and encourage donation.

B) THE INCENTIVE: MULTIPLE SOLUTIONS FOR A CONTROVERSIAL ISSUE

The European countries that collect the highest volume of plasma are those that have efficient incentive systems organised. An analysis[29] by the European Commission showed that **most European countries incentivise donation through various types of compensation** (meal vouchers, snacks, free medical check-ups, time off during working hours, reimbursement of travel costs, small gifts, etc.).

Beyond the specific formulas that exist, it is important to note that **there is no common understanding at European level as to which practices are compatible with an unpaid donation**. The same Commission report explains that the same practice towards donors is classified as "compensation" by some Member States, as "incentive" by others, and as "other practice" by a third group. The divergent perceptions seem to be linked to different interpretations of the given definitions of compensation and incentive.

The issue of incentive to donate should not be simplistically reduced to the remuneration of plasma. There are **many ways to compensate the donor for the time and costs incurred** in assisting the health system, without contravening the principle of voluntary and altruistic donation.



Source: extracted from the previously mentioned Commission report.

All this does not prevent **cultural factors** from also being taken into account. A recent study[30] on the determining factors of willingness to donate blood in 20 European Union countries concluded that the perceived safety of blood transfusions and **personal motivations may be more important determinants of willingness to donate than receiving certain incentives.**

It is necessary to develop a donation system that promotes donor education and awareness, while removing obstacles to donation by means of legally permitted compensation formulas and including new ones, compatible with voluntary and altruistic donation.

In our country, the applicable legislation[31] establishes that **"the donation of blood and blood components are voluntary and altruistic acts"**, defining as such those in which "the person donates blood, plasma or cellular components of their own free will and receives no payment for it, whether in cash or in any other form that can be considered a substitute for money." It also expressly recognises that "small gifts such as recognition or reimbursement of direct travel costs are compatible with a voluntary unpaid donation".

As a consequence, **Spanish legislation, essentially altruistic, establishes a broad framework that makes it possible to implement compensation solutions**[32] for the time and costs associated with the donation, such as the granting of time off by public and private employers or the reimbursement of travel expenses incurred. It also does not exclude the granting of certain gifts or rewards as a form of recognition to those who donate, such as meal allowances or restaurant discounts, travel or experiences, gifts, mentions in networks, etc. Another possibility would be the application of a tax incentive to all donors, by means of a comparison against a donor file, in the Personal Income Tax section.

Finally, it is necessary to take into account cultural factors: if in a completely altruistic system, in which the donor does not receive any type of consideration, Spain is self-sufficient in blood donations and a leader in organ donations[33], it is logical to think that **the lack of incentive is not the only reason to explain the scarce plasma donation in our country.**

RECOMMENDATIONS

2. Develop a real national plan that defines compensation formulas compatible with current legislation in the style of other EU countries.

C) THE INFRASTRUCTURE

The European Commission, in its Working Document on the Evaluation of EU legislation on blood, tissues and cells[34], states that "the first **important case of insufficient supply** refers to plasma, where the EU is highly dependent on imports from the United States", and notes that "while, in the EU, the number of private plasma collection centres increased from 37 in 2005 to 103 in 2016, this is far from sufficient to keep pace with the growing demand for the manufacture of plasma-derived medicines".
The emphasis on infrastructure is not trivial: **sufficiency in the number of plasma collection centres** as well as the **adequate provision of these in terms of material (equipment) and personnel,** is a necessary condition to increase plasma availability. Otherwise, the system will not be prepared to handle a greater volume of donations, even if there is awareness and willingness to donate on the part of the population.

Planning policies on the sufficiency of plasma-derived treatments must guarantee the correct provision of infrastructure in the number of centres and the resources allocated to their sustainability. Otherwise, an increase in donations is unaffordable for the system.

Among the countries around us we find **different organisational models**[35]. In some countries, including Spain, the donation system is unique for blood and plasma, with plasmapheresis being possible in the same centres; in others, there are centres exclusively for plasma donation, such as in France, Italy and the Netherlands. In Europe, according to the 2020 figures, there are around 150 plasma collection centres - compared to 900 in the United States[36].

There is also disparity in the **ownership of infrastructure**. The leaders in procurement - Austria, the Czech Republic, Germany and Hungary - rely on mixed systems combining public and private procurement centres. Some analyses correlate the existence of private centres that perform plasmapheresis with a higher plasma volume collection[37] [38]

Beyond the question of ownership of the centres where plasmapheresis is performed - whether they are exclusive plasma collection centres or are part of a single blood donation system, it is clear that **a solid collection network has a direct impact on the volume of plasma collected.** And this solidity is also materialised in other factors that must be considered, such as the **closeness of the potential donor** and the **analysis of the specific needs of each territory.**

In Spain, there are 20 Transfusion Centres, 1 in each region - with the exception of Castilla-La Mancha and Andalusia, which have 3 and 2, respectively - which coordinate the network of donation points at regional level.

The **Transfusion Centres are publicly owned,** and must be authorised by the competent authority of each Autonomous Community[39]. Plasma not used in transfusion is sent to the fractionation industry for the production of plasma-derived medicines - in Spain, we have
one of the 20 fractionation plants in the EU. A single company has been fractionating plasma for more than 20 years, following the programme Aprovechamiento Integral Plasma Hospitalario (AIPH). Plasma of national origin is converted into therapeutic products that are used only in the Spanish healthcare network.

	Transfusion Centres	Transfusion Services	Whole blood donations 2020 (units)	Donation rate (per thousand inhabitants)	Plasma obtained 2020 (L), full donation+apheresis
Andalusia	2	39	277,766	33.06	74,132
Aragon	1	17	42,161	32.04	10,757
Canary Islands	1				
Cantabria	1	4	20,467	35.23	5,084
Castile and León	1	30	103,624	42.76	24,458
Castilla-La Mancha	3	21	73,300	36.05	17,515
Catalonia	1	93	259,714	34.86	61,625
Navarre	1	6	22,952	45.81	5,555
Community of Madrid	1	61	239,458	36.81	60,352
Valencian Community	1	48	164,062	33.28	46,851
Extremadura	1	19	49,353	45.99	9,952
Galicia	1	33	104,640	38.71	23,414
Balearic Islands	1	15	34,984	30.22	10,475
La Rioja	1	3	10,623	34.01	2,673
Basque Country	1	24	81,509	37.6	18,644
Asturias	1	15	37,848	36.75	1,528
Murcia	1	19	46,978	31.88	9,790
Total	21	447			

Source: Own figures based on data from the Ministry of Health.[40]

There is no single information system that allows us to know the demand for plasma-derived treatments in each region in a consistent way - the data available are partial as they come from the hospitals, and are limited in time - and most Transfusion Centres only publish global figures of plasma collection. **There is no single map** that locates the network of units performing plasmapheresis throughout the country. This makes it difficult to analyse from the perspective of regional needs, which is the starting point for the development of synergies in an efficient system.

More plasmapheresis machines and an evaluation of the necessary human resources are needed. At present, the centres would not be able to cope with the volume of a possible increase in donation, so they are also unable to carry out mass appeal campaigns.

There is a need to promote **policies to maximise collection with a more accessible network**, either by **increasing the number of fixed centres or units for performing plasmapheresis**, **expanding the resources of existing donation centres** or promoting ad hoc collection formulas - such as **specific plasmapheresis points at strategic locations** (e.g. near universities). Mobile collections present a greater logistical complexity due to the machinery required for plasmapheresis, but it is possible to develop **mobile means** for the development of campaigns in different population centres.

The **increase in the capacity of existing blood donation centres**, the promotion of **specific plasmapheresis points** or the development of **mobile collections** are viable solutions to make plasma donation more accessible to citizens.

RECOMMENDATIONS

3. Improve information mechanisms to ensure an adequate provision of resources in the Transfusion Centres and prioritise the increase in available machinery and adequate personnel for plasmapheresis.
4. Develop a solid collection infrastructure network with more donation points to meet the specific needs of each region and enable the development of innovative solutions to bring plasmapheresis closer to potential donors.

3. IMPROVE THE MANAGEMENT

3.1. STATE COHESION AND INTER-REGIONAL COORDINATION

The Spanish blood donation system is **decentralised and hierarchical** at functional and regional levels. Although the framework legislation is shared, the Autonomous Communities act is carried out according to regional needs, with **little integration of decisions at national level.** Even within the regions themselves there are **problems of inequality of access** to treatment, especially when the procurement of treatment is the responsibility of the hospitals themselves, which demand plasma derivatives according to their needs.

SPANISH BLOOD DONATION SYSTEM

Transfusion centres and services

National system for transfusion safety

- Scientific Committee for Transfusion Safety, linked to the Directorate-General for Public Health. Composed of seven members: two appointed at the proposal of the scientific societies - one by the Spanish Society of Blood Transfusion and the other by the Spanish Society of Haematology and Haemotherapy.
- National Haemotherapy Commission: coordinating body attached to the Ministry of Health through the Directorate-General for Public Health. Composed of the Director-General of Public Health of the Ministry of Health, the Director of the AEMPS, the Director-General of Pharmacy and Health Products, a representative of the Ministry of Defence, a representative of the health authority with decision-making capacity in the matter for each of the Autonomous Communities, the president of the Scientific Committee for Transfusion Safety, the technical secretary of the Scientific Committee, who will act as secretary of the National Haemotherapy Commission.

Haemovigilance system

The national network consists of the network of the 17 regions, together with the Haemovigilance Unit. The current system is organised on three levels[40]

1. Local level (level 1): this level is composed of transfusion centres and blood banks. The detection and initial analysis of possible adverse events and reactions is the responsibility of the staff of both groups.
2. Regional level (level 2): this level is composed of the Regional Haemovigilance Networks. Within this level, tasks involving the collection of information from transfusion centres and blood banks are carried out, depending on each regional authority in coordination with the Ministry of Health. The person in charge is the Regional Haemovigilance Coordinator.
3. National level (level 3): this is where the Haemovigilance Unit is located, which is responsible for coordinating the 17 regions and liaising with the European Commission. This Unit collects information on the events registered by the regional networks and prepares an annual report.

The **complexity of the manufacturing process** of plasma-derived medicines influences the time from plasma donation (donor) to prescription/administration of the treatment (patient). The time from donor to patient can take up to 7-12 months. With such long time frames **it is essential that sufficient volumes of plasma are always available for fractionation.** For this reason, it is not possible to depend upon a single or an unpredictable source of plasma - for example, a single collection centre, a single country or even a single geographic region. In this sense, the value chain and the plasma collection and manufacturing network must be global in nature, covering plasma availability across different countries and regions.[42]

Under this premise, it is necessary **to move towards a national management model** that enables greater cohesion and coordination between Transfusion Centres, hospitals, patients and donors. Following the model of the successful framework for organ transplantation - which, through the National Transplant Organisation, creates a common platform and enables synergies and organ allocation in a hierarchical manner - a similar system for blood and blood components with a body capable of optimising the system according to local needs would make it possible to manage a national pool of plasma and optimise its collection and use.

RECOMMENDATIONS

1. Promote national management and strengthen coordination mechanisms that allow treatment needs to be confronted jointly and efficiently, eliminating barriers to cooperation between Autonomous Communities.

2. Encourage centralised information systems that make it possible to know the donation and infrastructure capacities and needs of the different regions.

CONCLUSIONS

The insufficiency of plasma-derived medicines is a pressing problem for thousands of **people with rare and chronic diseases** whose life and well-being depend on them. It is also a present problem with the prospect of being maintained over time, given the progressive increase in demand in the coming years as a result of research and new clinical indications.

Spain does not currently have adequate planning to respond to these current and future needs, which includes an ambitious plasma collection plan that promotes plasmapheresis and promotes the important work of the Transfusion Centres and donor associations.

Ignorance and lack of awareness, among both the authorities and society, must be challenged. And we must work towards a coordinated and sustainable model for the sufficiency of plasma-derived treatments, reducing the risk of excessive dependence on external sources.

In short, it is essential to **to work towards a National Strategy for plasma and derived treatments,** with the participation of all the agents involved (patient associations, clinical experts, scientific societies and donor organisations). This strategy must contemplate far-reaching solutions that make our country a reference point in the collection, management and use of plasma, capable of guaranteeing the sufficiency of medicines and rapid and equitable access to them for the people who need them.

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