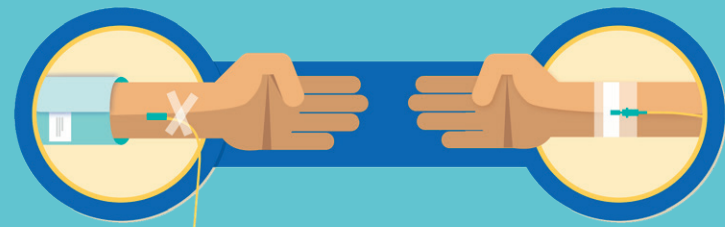


Together toward a broader European plasma donation ecosystem



Strengthening the EU Blood Directive: To meet the needs of patients using plasma-derived medicinal products and plasma donors

The unique aspects of human plasma need to be framed more precisely in the Directive

The revision of the European Union Blood, Tissues and Cells Legislation brings an opportunity to strengthen this legal framework to encourage new approaches that will increase the collection of plasma across Europe, that are needed to manufacture plasma-derived medicinal products.

The EU's original legal framework for blood and blood components was not developed with the needs of increasing plasma collection in mind. A growing clinical need for plasma-derived medicines, and an increasing dependency on plasma from the US requires a policy change in how we collect plasma in Europe.

This briefing discusses the areas where the Directive can be strengthened. The changes proposed here are based on years of experience, detailed knowledge and scientific evidence related to plasma donation, and are informed by emerging donation practices.

The Blood Directive, related European legislation, and national public health regulations need to:

- **Explicitly recognize the unique nature of plasma that is used for manufacturing of plasma-derived medicinal products (PDMPs)**, as it is fundamentally different from whole blood and other labile blood components.
- **Support the EU's policy of 'Open Strategic Autonomy' and address Europe's reliance on plasma from the US**, by encouraging the creation of a stronger European plasma donation ecosystem.

A renewed EU Blood Directive should:

- **Clarify the difference between plasma used for transfusion and plasma used to manufacture plasma-derived medicinal products.** This is the foundation of policies that will encourage increased availability of plasma.
- **Support Member States as they establish dedicated programs for direct plasma collection (plasmapheresis);** and outreach actions that inform communities of the critical importance of plasma-derived medicinal products and the need for plasma donations.
- **Encourage plasma donations by clarifying that a fixed-rate allowance to compensate donors** – for expenses and inconveniences related to donation – is in line with the principle of Voluntary Unpaid Donation, similar to EU Tissues & Cells Directive 2004/23/EC, art. 12.1.
- **Promote the coexistence of public blood and plasma collection centers, together with private plasma collection centers.**

The Plasma Protein Therapeutics Association (PPTA – www.pptaglobal.org), a global industry trade association, represents the private sector manufacturers of plasma-derived and recombinant analog therapies, collectively known as plasma protein therapies, and the collectors of source plasma used for fractionation. Millions of people use these therapies worldwide to treat a variety of diseases and serious medical conditions. PPTA also administers standards and programs that help ensure the quality and safety of plasma protein therapies, donors and patients.



The current state of plasma donation for medicines in the EU

In the coming decade, more European patients will need access to plasma-derived medicinal products.

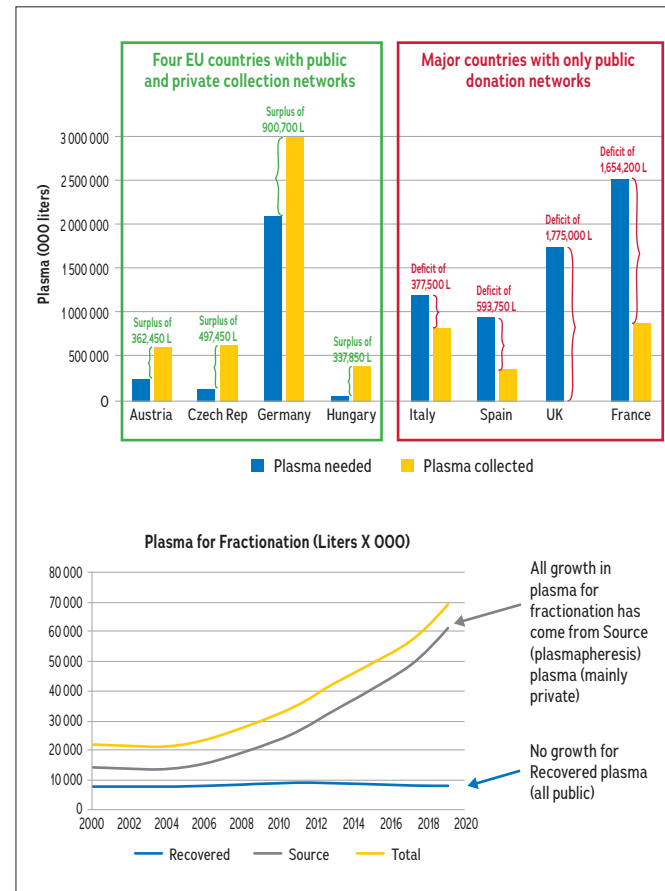
Plasma-derived medicinal products (PDMPs) are unique medicines that can only be made from human plasma donated by committed donors. Over the past 10 years, the use of immunoglobulins – among the most commonly used PDMPs – has almost doubled. For many people's medical conditions, PDMPs are the only possible treatment.*

Medicines made from human-donated plasma are **essential for some 300,000 patients** across the EU who rely on these therapies every day to treat a variety of rare, chronic, and life-threatening conditions.¹ Without these treatments, many patients would have a substantially diminished quality of life, and some may not survive.

The EU's deficit of plasma. The EU currently has a shortfall of 3.8 million liters of the plasma needed to manufacture life-saving plasma-derived medicinal products. Today, some 30% of the plasma used to manufacture PDMPs for EU patients comes from the U.S.²

Countries that have a combined public-private donation model contribute the most to plasma collections in Europe. The EU's public sector has shown little growth in plasma collection over the past decade. In contrast, over the same period, private plasma donation centers have delivered most of the EU's increased plasma donations that are required to meet the growing clinical need for PDMPs.

Public-private plasma systems can coexist. In Europe, 62% of plasma is collected by public and NGO blood collection services, mainly recovered from whole blood donations. The private sector collects 38% of plasma in Europe, but only from four countries (Austria, Czech Republic, Germany, and Hungary), using plasmapheresis. In these four countries, private plasmapheresis donation centers coexist with public services collecting whole blood and plasma. **Here, four times more plasma is collected per 1000 inhabitants compared to other countries.**³



EU-wide figures show that countries with only public programs to recover plasma from their national whole blood donation systems do not collect enough plasma for the needs of their patients. (Source: Market Research Bureau 2018).

The European Commission highlights that plasma donation by plasmapheresis is more efficient, compared to recovering plasma from whole blood donations⁴. The private sector is ready to share its expertise on approaches to operating safe, efficient, state-of-the-art plasmapheresis programs, and to contribute actively to the collection of more plasma for European patients.

Proof of concept: coexistence of public and private plasma donation networks.

There is no evidence to support the perception that the coexistence of public and private plasma donation programs, and the compensation of donors for their expenses and inconvenience, leads to a decline in whole blood donations³. Research shows that whole blood donations have not decreased in countries that apply the public-private model. Some national studies show that the profiles of plasma and blood donors are different. Plasma donors tend to be younger and, like plasma donation centers, city-based; as opposed to whole blood donors who mainly give at mobile blood collection units, more often in rural areas¹⁰.

Voluntary Unpaid Donation.

Today, 25 EU countries provide some form of compensation for plasma donors. It covers expenses incurred and recognizes the inconvenience related to donating, following the principle of Voluntary Unpaid Donation (VUD)⁵. In four EU countries (Austria, Czech Republic, Germany, and Hungary), private centers apply compensation as a fixed-rate allowance^{6**}. This approach is in analogy with the EU Tissue and Cells Directive and is fully compatible with the VUD principle, as recognized in the EU Commission Report on implementation of the VUD Principle⁵, the Council of Europe DH Bioethics Guide⁷, Nuffield Council Guide on Bioethics⁸, and the German Transfusion Law⁹.

Proposed clarifications & definitions

Recognizing the unique nature of human plasma in the EU Blood Directive

A revised EU Blood Directive can provide a clearer context for plasma. It should include more precise definitions related to the unique aspects of plasma donation and plasma as the starting material for manufacturing PDMPs.

Including the proposed updated concepts and more precise definitions in the Directive texts will recognize the important differences between plasma for manufacturing PDMPs, and labile blood and blood components that are used for transfusion in biological characteristics, processing, and regulations. In addition, recognizing that human plasma is a critical starting material for medicines fits with the EU's own Pharma Strategy. With its goal of *Open Strategic Autonomy* the EU aims to reduce dependency on imported starting materials from non-EU countries.

To encourage more plasma donations, define and differentiate plasma from whole blood and blood components for transfusion

Plasma for manufacturing is a blood component. But it is fundamentally different from blood and blood components that are used for transfusion. This difference needs to be clarified in the definitions used in the revised Blood Directive. Specifically:

- **Distinguish by introducing the following definitions:** plasma for transfusion; plasma for manufacturing and plasma for fractionation; recovered plasma (from donated whole blood); plasmapheresis; and Blood Establishments.
- **Ensure inspections can take place at all times** by including remote inspections, control measures, and an EMA-backed, risk-based approach governing the frequency or intervals of inspections.
- **Ensure mutual recognition of inspections to increase their efficiency** by introducing amendments to trigger the extension of the EU-U.S. Mutual Recognition Agreements and to cover medicinal products derived from human blood or human plasma.
- **Increase donor acceptance** by revising donor deferral criteria, based on the latest scientific evidence.

To collect more plasma, clarify scope and responsibilities, as in other EU Directives

In describing the plasma collection framework, the Blood Directive should clarify its scope and include appropriate definitions as is the case in other EU legislation. Specifically:

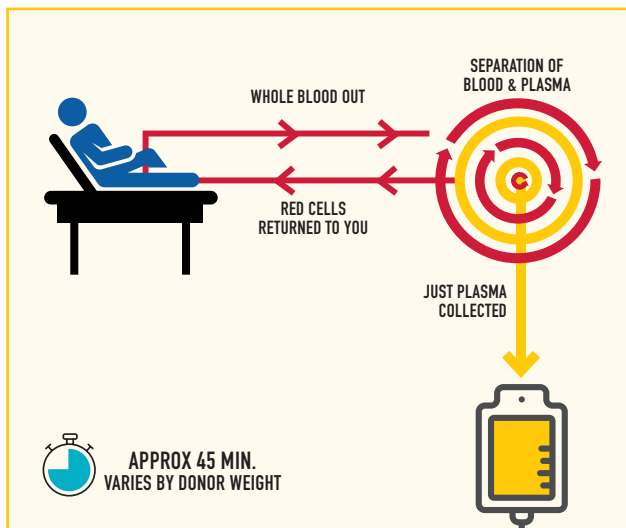
- **Clarify that the EU Blood Directive governs the collection and testing phase of plasma for manufacturing;** while the EU Pharma legislation is applicable to plasma after entering the manufacturing phase. The revised Directive can clarify this scope by cross-referencing to the EU Pharma legislation 2001/83.**
- **Introduce the definition of Health Professional** from Directive 2011/24/EU on applying patients' rights in cross-border healthcare, to clarify that other health professionals (for example registered nurses) in addition to medical doctors can be responsible for examining healthy donors.
- **Specify that compensating plasma donors for their expenses incurred and the inconvenience caused by donating is compatible with the concept of Voluntary Unpaid Donations¹¹** and can be provided as a fixed-rate allowance⁸.

To collect more plasma, set objectives in EU legislation, in line with the EU Pharma Strategy

- **EU Member States should contribute to reaching the EU's objective of Open Strategic Autonomy for human plasma,** a starting material needed to manufacture PDMPs for patients across the EU.
- **Reduce dependency on non-EU countries for the starting material (human plasma),** which is needed to manufacture medicines. Specify that this can be facilitated by applying the model of a combined public-private system to increase plasma donation, in those countries in which public and private sector blood and plasma donation networks coexist.



Plasmapheresis



Plasmapheresis uses specialized equipment that separates plasma from the donor's blood, and returns the blood cells to the donor.

Proposed clarifications & definitions

Plasma in the revised European Blood Directive

Detailed comments

Clarify principles of self-sufficiency

Current references to self-sufficiency in EU legislation should relate to blood and blood components that are intended for direct transfusion, but not for plasma and plasma-derived medicines.

This lack of a clear differentiation creates misunderstandings in addressing the growing clinical need for the plasma needed to manufacture plasma-derived medicinal products (PDMPs) – such as human immunoglobulin and others.

All labile blood components have a short shelf-life and cannot easily be transported from one country to another. Plasma for medicines is different. It is part of a global supply chain as it requires significant manufacturing capabilities to fractionate plasma-derived medicines. Therefore, it can be frozen to ensure stability of therapeutic proteins and transported.

In the legislation, the concept of self-sufficiency should be specific to human blood or blood components intended for transfusion. For those products, Member States may target national or regional self-sufficiency. However, plasma needed for manufacturing plasma-derived medicinal products needs to be considered part of the EU's policies of Open Strategic Autonomy. The EU's pharma and trade strategies require it to decrease dependency on non-EU countries for starting materials. Here Member States should support the EU's goal of decreasing dependence on plasma imported from non-EU countries, as it is a critical starting material for many medicinal products. The European Commission's evaluation of the BTC legislation of 2019 already highlighted that its dependency on plasma from the U.S. is a vulnerability for Europe's access to PDMPs.

Specify 'healthcare professionals' in plasma donation centers

In EU legislation, the responsibility for donor examination lies with a qualified 'health professional'. Several EU countries have transposed this qualification into national law as a medical doctor. Consequently, regulations in many European countries require the presence of a physician at all times in plasma donation centers. In some cases, it is becoming increasingly difficult to fill these positions, resulting in shorter center opening hours, or hindering new centers from opening.

A revised EU Blood Directive should use an existing definition of health professionals, which includes doctors but also specifies: a nurse responsible for general care, a dental practitioner, a midwife or a pharmacist who are trained to perform tasks related to donor care and the use of medical devices for plasma collection; with a physician on call for questions or emergencies.

PPTA proposes that the Blood Directive uses the definition used in Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. Here article 3 (f) clarifies for EU Member States that health professionals may refer to members of the healthcare profession other than medical doctors¹².

Harmonize the notion of inspections to alleviate the administrative burden on inspectors and entities being inspected.

A disparate range of inspection approaches is currently applied across the EU, largely due to variable resources in different Member States. Better resource allocation and efficient oversight mechanisms are needed to harmonize inspections and bring in risk-based approaches. This lack of harmonization has been particularly visible during remote inspections and facilities audits during COVID-19, where the sanitary

measures in place created barriers to (new) centers to be inspected, adding complexity and uncertainty for national authorities and the industry.

A risk-based approach encourages the sharing of information among national authorities, and the use of remote and physical inspections. This approach is in line with the EMA's risk-based approaches for inspecting blood establishments in third countries. The Agency's ongoing work in this area, and analogous with the guidance on pharmacovigilance audits (Good Pharmacovigilance Practices – GVP Module IV), should be considered in the revision of the Blood Directive.

Clarity on Voluntary Unpaid Donations for donating plasma

In their policies and regulations, all Member States comply with the principle of Voluntary Unpaid Donation for blood and blood components, including plasma - as detailed by the European Commission⁵. Following this principle, donors can be reimbursed for the costs they have incurred and can be compensated for non-financial losses such as the inconvenience related to the donation. EU countries have different approaches that are aligned with Voluntary Unpaid Donation. Some apply fixed-rate allowances, others reimburse specific expenses or compensate with time off from work, tax reductions, vouchers or by other means.

PPTA proposes that the Blood Directive should specify that "an allowance that is limited to making good the expenses and inconveniences related to each specific type of donation" is compliant with Voluntary Unpaid Donations or Voluntary Non-Remunerated Donations. This approach is considered ethically acceptable by bioethical bodies such as the Council of Europe Committee on Bioethics (DH-BIO)⁸ and the Nuffield Council on Bioethics⁹.

References

- 7 Committee on Bioethics (DH-BIO) - Guide for the implementation of the Principle of Prohibition of Financial Gain with respect to the human body and its parts, as such, from living or deceased donors (article 23, 24) <https://rm.coe.int/guide-for-the-implementation-of-the-principle-of-prohibition-of-financ/16807af9a3>
 - 8 Nuffield Council on Bioethics - Human bodies: donation for medicine and research. https://www.nuffieldbioethics.org/wp-content/uploads/HumanBodies_report_developments_web.pdf
 - 9 German Transfusion Law, article 10 – https://www.gesetze-im-internet.de/tfg/_10.html
 - 10 KCE Reports 120A – Hoe zelfvoorziening in stabiele plasmaderivaten voor België verzekeren?
<https://kce.fgov.be/sites/default/files/atoms/files/d20091027357.pdf>
<https://kce.fgov.be/sites/default/files/atoms/files/d20091027357.pdf>
chapter 2.1.1: Key points
 - 11 This is also confirmed in: the EU Tissue and Cells Directive (Article 12); European Commission staff working document on the implementation of the principle of Voluntary and Unpaid Donation for human blood and blood components; Council of Europe DH Bioethics Committee - Guide for implementing the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors (article 23, 24); German Transfusion Law.
 - 12 *This definition is used in other EU legislation (European Parliament Directive 2011/24/EU and Council Directive of 9 March 2011 on the application of patients' rights in cross-border healthcare, here article 3 (f) clarifies for EU Member States that health professionals can be others in addition to medical doctors.*
- ***This approach echoes that of the Tissues and Cells Directive (Directive 2004/23/EC), which specifies that products manufactured are covered by other Directives. EU Pharma legislation already foresees a reference article (article 109a – Directive 2001/83/EC) to the EU Blood Directive, which still lags behind usage in the Western countries.*

References

- 1 More patients across the EU are diagnosed every year with life-threatening plasma protein related disorders, such as immune-deficiencies, immune-mediated peripheral neuropathies, Hereditary Angioedema, Alpha 1-antitrypsin Deficiencies, Hemophilia and other bleeding disorders. In many cases, PDMPs are the only treatment option for these rare diseases. New indications, improved diagnostic techniques, greater use in emerging markets, and increased use in cancer treatment-induced secondary immunodeficiency are further contributing to the growing clinical need for PDMPs.
 - 2 The Market Research Bureau (MRB) – 2019. Including UK, the EU reliance on US plasma was 38%. After Brexit: the EU reliance for EU plasma is still 30% and growing every year; after Brexit, the UK became 100% reliant on US plasma and decided to start collecting plasma in the UK.
 - 3 Vintura White Paper: *Key economic and value considerations for plasma-derived medicinal products (PDMPs) in Europe*. <https://bit.ly/VINTURA>
 - 4 Statement from the European Commission: *Coronavirus: European Commission strengthens support for treatment through convalescent plasma*. https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1435 (accessed September 2021)
 - 5 Commission staff working document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. <https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:52016SC0130>
 - 6 It is the responsibility of each Member State to define the details and conditions for compensation. The concept of 'fixed-rate' compensation is defined in the DH BIO Interpretation Guide of the Principle of Prohibition of Financial Gain <https://rm.coe.int/guide-for-the-implementation-of-the-principle-of-prohibition-of-financ/16807af9a3>
- * *This represents a yearly increase of some 8%, with usage almost doubling in 2019 to 60 tons, compared to 32 tons in 2009 (Market Research Bureau data, 2019). This increase is driven: by innovations in medical research; improved and early diagnosis; the extended patients' lifespans due to timely treatments; and efforts to increase immunoglobulin usage in the Eastern EU countries, which still lags behind usage in the Western countries.*
- ** *In all countries where donors are compensated, including countries that apply a fixed-rate compensation, Member States define the conditions.*