

THE REVISION OF THE EU BLOOD DIRECTIVE

How to enhance plasma collection by getting more donors via increased regulatory efficiency?

WEDNESDAY 21 APRIL 2021 16:00 - 17:30
HOSTED BY **MEP SIRPA PIETIKÄINEN**

Meeting report

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Executive Summary

The online event entitled “*The revision of the EU Blood Directive: How to enhance plasma collection by getting more donors via increased regulatory efficiency?*”, organized and hosted by Member of the European Parliament (MEP) Sirpa Pietikäinen took place on April 21, 2021.

The speaker panel consisted of the following representatives:

- European regulator (Austria): Dr. Karmin Saadat, GMP Inspector, Institute Surveillance, Austrian Federal Office for Safety in Health Care (AGES)
- European Commission: Dr. Stefaan Van der Spiegel, Head of Sector, Substances of Human Origin - DG SANTE
- Patient organization [International Patient Organisation for Primary Immunodeficiencies (IPOPI)]: Ms. Leire Solis, IPOPI Health Policy and Advocacy Senior Manager
- International Plasma and Fractionation Association (IPFA): Dr. Françoise Rossi, IPFA, Director Scientific and Regulatory Affairs
- Plasma Protein Therapeutics Association (PPTA): Dr. Jens Rehbein, chairman of PPTA Regulatory Affairs Steering Committee, CSL Behring

MEP Sirpa Pietikäinen underlined that the current revision of the EU Blood Directive is a timely opportunity to ensure that the regulatory requirements, including donor eligibility criteria, are science-and evidence based and take into account societal changes and to collect more plasma in Europe and respond to the growing clinical need for plasma and plasma-derived medicinal products (PDMPs).

She reminded that PDMPs are essential to treat a variety of rare, chronic, and potentially life-threatening conditions for around 300.000 patients in Europe and that Europe is reliant on plasma from the United States (U.S) as not sufficient plasma is collected in the European Union (EU).

Dr. Karmin Saadat presented the viewpoint of the Austrian regulatory agency. He described the main technical and regulatory differences between whole blood and blood components for transfusion and plasma for fractionation. He provided an overview of the Austrian legal framework on the matter.

The EU Commission’s representative, Dr. Stefaan Van der Spiegel communicated that the EU Commission is exploring options to address EU plasma supply issues through strengthening supply monitoring and emergency supply measures since most of the world is dependent on the plasma collected in the US. He highlighted the key steps in the revision of the blood, tissues and cells (BTC) legislation, which are an inception impact assessment, a public and targeted consultation and 2 studies to gather evidence: One to inform the impact assessment and one to inform on related data collection. The Commission will reach out to all relevant stakeholders in this process.

As a patient representative, Ms. Leire Solis highlighted the main challenges faced by patients relying on PDMPs. She also emphasized the effect of the COVID-19 pandemic on the collection of plasma and on the development of plasma-based treatments. She pointed out the International Patient Organisation for Primary (IPOPI)’s expectations on the revision of the Directive.

Dr. Françoise Rossi from the International Plasma and Fractionation Association (IPFA) outlined

the need to redefine the acceptance donor criteria for plasma for fractionation, starting material for the manufacturing of PDMPs, for both the protection the donor and the final recipient, highlighting some current deferrals in place for Men having Sex with Men (MSM) and potential donors with tattoos, body piercings or who undergo acupuncture.

As a Plasma Protein Therapeutics Association (PPTA) representative, Dr. Jens Rehbein mentioned areas where the revision of the Blood Directive could have a major impact. He especially highlighted the need for a revision of the donor eligibility criteria, areas where regulatory flexibility could be given, as well as the need for harmonization of regulatory requirements across EU Member States.

The roundtable event included presentations from some of the panelists as well as lively Q&A interactions.

The EU Commission's representative highlighted that all stakeholders must work together to address challenges related to access to PDMPs. The patient groups also raised issues like reimbursement systems, as well as declining plasma donations due to COVID-19.

In light of the key outcomes of the discussion, MEP Pietikäinen concluded that the revision of the EU Blood Directive should:

1. Introduce a clear differentiation between whole blood and the different blood components for transfusion and plasma for manufacturing PDMPs;
2. Include a clear definition of “plasma for manufacturing/for fractionation”, “plasma for transfusion” and “recovered plasma”; and
3. Revise existing eligibility criteria for plasma donors, taking into account the latest technological and scientific progress. These criteria must take into account the ability of the PDMP manufacturing process to remove known and emerging pathogens, and thus, ensuring the highest quality and safety of the final product.

1. Welcome & Introduction



Sirpa Pietikäinen MEP thanked all participants for joining the online roundtable on the revision of the EU Blood Directive, communicating that the revision of the directive is an opportunity to discuss how to enhance plasma collection via increased regulatory efficiency.

During her introductory speech, MEP Sirpa Pietikäinen reminded that plasma-derived medicinal products (PDMPs) are made from plasma donated by healthy donors. These medicines are essential for around 300,000 European patients who rely on them to treat a variety of rare, chronic, and potentially life-threatening conditions, such as primary immunodeficiencies.

She observed that the European Commission is currently revising the EU Blood, Tissues and Cells legislation to take into account the most recent technological and scientific developments and societal changes. This will allow to address the current issues, including the need for more plasma collection in Europe. This is therefore an opportunity to ensure that relevant regulatory requirements, including donor eligibility criteria, are adequately revised.

She also highlighted that Europe is relying on US plasma imports and is currently not collecting enough plasma to respond to the growing clinical need for PDMPs.

MEP Pietikäinen gave the floor to regulators, patient representative, policy-makers and the industry, expecting concrete suggestions that could be reflected in the upcoming legislation.

2. Panel discussion - How to increase plasma collection by getting more donors via increased regulatory efficiency

2.1. European regulator's perspective (Austria)

Dr. Karmin Saadat (Inspector, Institute Surveillance, Austrian Federal Office for Safety in Health Care AGES) presented the different process and uses of whole blood for transfusion and plasma for fractionation.

He stated that various viral inactivation steps are employed during the plasma manufacturing process: several methods are used to ensure that any pathogens are removed, which is not the case for whole blood and explained that whole blood establishments also provide plasma for fractionation but to significant lower levels than source plasma establishments (plasma collection centers).

He presented the Austrian legal framework in the context of the EU Blood Directive as well as referencing overarching EU relevant legislation and guidelines.

He provided an overview of the legal framework in Austria with regards to both whole blood and source plasma in terms of compensation, testing requirements, donation frequency and amount of plasma that can be donated by a healthy donor, clarifying that so far no "crowding-out" effect (negative impact of plasma donation centre(s) in vicinity of whole blood collection centres) has been observed by the competent authority in Austria. The Austrian competent authority will keep monitoring the development with regards to potential crowding out.

	Whole Blood 	Source Plasma 
Remuneration €	Not allowed.	Only compensation. No profit.
Testing requirements	ABO/HIV/HBV/HCV/ATYAT PHA (& HIV/HCV PCR)	HIV/HBV/HCV (Antibodies only) IgG, total protein, WBC, MCV, RBC
Hb g / 100ml	M: 13,5 F: 12,5	12
Donation frequency	1x / 8 weeks	2x / week, 50x / year
Donation amount	M: 3000ml F: 2000/2500ml p.a.	Depending on weight of donor

Dr. Karmin Saadat also stressed the relevance of 'Distant Assessments' for the compliance of plasma collection and PDMP manufacturing sites with the EU Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) principles performed by the Competent Authorities. The Distant Assessment was implemented by the European Medicines Agency (EMA) in the context of the COVID-19 pandemic as a 'regulatory flexibility' measure to allow surveillance of GMP compliance of facilities at times where no physical inspections were possible. The Distant Assessment has proven to be a suitable means to assure compliance of collectors and certain manufacturers during this time frame. Its use will remain a possibility for similar situations in the future, but for now on-site inspections will remain the method of choice for inspections, if possible.

2.2. European Commission's perspective

Dr. Stefaan Van der Spiegel from DG SANTE reminded that the contamination of blood products with HIV and hepatitis and other health concerns about blood contamination led to the adoption of the Blood Directive in 2002 and the Tissues & Cells Directive in 2004 to set high standard of safety and quality for blood and blood components for medicinal use. This legal framework defines the safety and quality standards of substances of human origin, from donation until processing and human application. Plasma collection falls under this legal framework, (2002/98/EC) however it's further manufacturing into plasma derived medicinal products falls under the medicinal products legislation (2001/83/EC).

The revision of the Blood, Tissues and Cells (BTC) legislation aims to address the shortcomings identified in the 2019 Commission's evaluation. The provisions related to plasma aims to address two main issues, namely: manage avoidable risks for donors and manage the EU's vulnerability when it comes to interruptions in the supply of plasma. Dr. Van der Spiegel noted that only 5% of the global population, corresponding to the US population, is collecting 60% of all plasma utilized in the world.

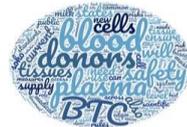
DG SANTE is exploring options to manage the supply issues through strengthening supply monitoring and emergency supply measures, since Europe is highly dependent on plasma collected from the U.S.

Dr. Stefaan Van der Spiegel also outlined that initially the COVID-19 pandemic had a negative impact on collection which resulted in a significant reduction of the plasma collections in plasma centres. In that context, the call of the EU Health Commissioner Kyriakides for blood and plasma donation in 2020 contributed to redress this and improve the collection levels.

The key steps in the revision of the BTC legislation are the following: The Inception Impact Assessment

Feedback received on IIA

- 80 contributions (free text)
- Overall, the revision of the BTC legislation is welcomed and the objectives of the revision are supported
- Many comments about the plasma dependency + need to take measures to tackle shortages (regulatory flexibility for collecting more plasma, avoiding off-label use without efficacy proven, differentiating blood for transfusion vs plasma for further manufacturing, more frequent donations, donors' compensation, donor campaigns...)
- Some comments about the fact that the envisaged measures of monitoring sufficiency data do not really tackle the supply/dependency issue
- Some comments about sharing best practices



launched in December 2020, the public and targeted consultations aimed at stakeholders, open until 15 April and two studies with dedicated workshops on key issues to gather further evidence. These workshops will take place between end of April and June 2021. The Commission received 214 submissions related to the public consultation and 160 to the targeted consultation.

Dr. Stefaan Van der Spiegel finally reminded the limited competence of the EU Commission from a legal perspective

in the field. He observed that a broader effort from all stakeholders and national decision-makers, also beyond the Blood Directive, is necessary to tackle the current issues and increase plasma collection in Europe.

2.3. Patient's perspective

Ms. Leire Solis (IPOPI, Health Policy and Advocacy Senior Manager) shared the issues faced by patients with primary immunodeficiencies and the expectations of the patient organization, IPOPI, regarding the revision of the EU Blood, Tissues and Cells legislation

She underlined the many challenges faced by all patients relying on PDMPs, which are primarily related

to plasma availability, directly impacting the development and availability of these products.

With regards to the COVID-19 crisis, Ms. Leire Solis emphasized the impact of the pandemic on the availability of immunoglobulins, which were highlighted in a recent survey conducted by IPOPI. In 7 out of the 13 surveyed countries, patients faced significant shortages, resulting, among others, in increased duration between treatments, changing the route of administration or brand and decreased dosages.

Ms. Leire Solis made five main recommendations with regard to the revision, which would benefit the patients who rely on PDMPs:

- Developing guidelines for legislation based on science, facts and studies;
- Avoiding the waste of plasma; the European Commission report of 2016 highlighting that insufficient plasma was recovered from whole blood donations;
- Strengthening the development of plasmapheresis programs across Europe;
- The need for awareness and information campaigns on plasma and addressing plasma and blood donors;
- Differentiation between blood products and plasma for manufacturing to develop more targeted policies and legislation.

Finally, Ms. Leire Solis pointed out the wish of IPOPI to see an increase in the collection of plasma in Europe in order to impact medicines' (PDMP) production.

2.4. IPFA's perspective

Dr. Françoise Rossi (IPFA, Director Scientific and Regulatory Affairs), explained the two existing ways for collecting plasma. She stated that the public health system needs a sustainable model to collect both whole blood and plasma and to protect both patients and donors. Dr. Françoise Rossi further explained that from the European Commission Inception Impact Assessment, several stakeholders noted their preference for the policy option 2, where designated 'Expert Bodies' define rules governing blood and plasma collection (Policy option 2: EU-level safety and quality requirements defined by European Expert Bodies and strengthened national inspection, EU audits and classification advice).

Currently, the rules including donor acceptance criteria are defined by the EU Blood legislation. The most recent version of the European Directorate for the Quality of Medicines (EDQM) 'Blood Guide' has amended some of these criteria. Recently, in the context of the COVID-19 pandemic, IPFA, as did PPTA, has proposed to the Commission and the European Medicines Agency (EMA) to take temporary measures to maintain access to PDMPs in Europe. Among various IPFA recommended actions, the revision of some of the current donor acceptance criteria was proposed. The revised criteria should be based on science and should continue maintaining high standards for safety for patients and donors.

Dr. Rossi further stressed that scientific literature has shown that there is no increased risk of transmission of blood-borne diseases when people with tattoos, body piercings or who undergo acupuncture in a regulated setting donate plasma.

Similarly, the eligibility criteria for sexual 'at risk behavior' (i.e. Men having Sex with Men) should be clarified and considered equivalent across the EU if based on epidemiology. Following the IPFA's recommendations in this regard over the years, the EMA published a position statement on quality and safety assessment for the Plasma Master File (PMF) certification with regard to donor deferral criteria for sexual risk behavior.

The regulation to protect donors should also be amended through the BTC legislation (such as frequency of donation, number of donations, volume collected). There is a need to amend the current donor acceptance criteria, based on science, assuring donor protection.

Criteria for quality and safety of plasma for fractionation should be addressed in the same body of legislation, and specifically addressed as such in the experts' bodies recommendations, whether it is collected by apheresis or recovered from whole blood.

Dr. Françoise Rossi concluded by recommending that expert bodies, which will advise the European Commission, should work together with industry (collectors and fractionators) taking part in setting the rules. This should be a collaborative process.

2.5. PPTA's perspective

Dr. Jens Rehbein (Chairman of the PPTA Regulatory Affairs Steering Committee, CSL Behring) pointed to a well-developed EU regulatory environment for plasma. However, he remarked that there is room for improvement, in particular after many years of little progress.

Dr. Jens Rehbein stressed that this mainly concerns the administrative regulatory framework: Throughout the years, the regulatory procedures about notifying the authorities on changes in both blood and plasma collection organizations became much more rigid. This rigidity does not match with the dynamic landscape of blood and plasma collection, in particular in times where various EU Member States are experimenting new ways of collecting plasma, aiming at increasing the volume of plasma in order to meet the patient demands.

Dr. Rehbein stressed that the revision of the Blood Directive should be seen as a new opportunity to:

- I. Differentiate between blood collected for transfusion purposes and plasma collected for manufacturing plasma-derived medicinal products (PDMPs);
- II. Increasingly take into account the new processes which allow for the inactivation and removal of potential pathogens;
- III. Adapt the eligibility criteria of donors according to the new scientific knowledge and new technical developments.

Because of some major differences in terms of eligibility criteria between European Member States, Dr. Jens Rehbein emphasized the need for an EU-wide harmonization of donors' inclusion criteria. He also highlighted the need to align with requirements in other countries since minor differences in the requirements imply major burden from a logistical, regulatory and manufacturing perspective.

From a PPTA perspective, an optimal regulatory framework would entail a more flexible approach towards plasma registration dossiers for marketing authorizations while allowing a fast and pragmatic update of plasma collection center information. This would, in turn, remove hurdles for manufacturing of PDMPs and their subsequent supply to the patient, while ensuring both quality and safety for the patients.

3. Discussion and Q&A

Mr. Brian Maguire, Independent Journalist and moderator of the roundtable, introduced the Question & Answers (Q&A) session.

He asked Dr. Van der Spiegel from DG SANTE whether there is enough investment in the healthcare workforce employed in collection of blood and plasma, and whether this is an element to include in the long-term approach of the Commission to address supply issues. He replied that there is a general awareness of this, but the organization of healthcare professionals remains a national (Member State) competence.

The moderator asked the speakers what the EU can do to increase plasma collection in Europe. **Dr. Stefaan Van der Spiegel** highlighted that the starting point on how to collect plasma depends on national decisions. Indeed, there are few countries where private actors are allowed to collect plasma, next to national services and that there is a need to improve plasma collection in all EU countries, through both systems – public and private. Dr. **Françoise Rossi** answered that the European Commission took a big step by creating the Emergency Support Instrument to support COVID-19 convalescent plasma collection and providing blood establishments with the necessary equipment for plasma fractionation.

Mr. Brian Maguire asked **Ms. Leire Solis** how to tackle the fact that only a few EU member states collect plasma. She answered that applying best practices from countries could be a solution. Ms. Solis said that she hopes that the EU will take into account the specificities of the plasma sector when reviewing EU legislation. She stated that among the challenges experienced during the COVID-19 pandemic, an important one was the decrease in blood and plasma donations globally. The EMA and WHO stressed the importance of blood management of blood transfusions and the ECDC strongly underlined the importance of implementing the Blood Patient Management in order to address shortages.

The moderator asked if the European Commission and the European Parliament should consider 'Patient Blood Management' in the new legislation. **Dr. Van der Spiegel** acknowledged that while there is a trend to use blood more selectively, this falls under the individual member state mandate rather than under the EU mandate.

Finally, **Dr. Jens Rehbein** was asked whether in his opinion EU regulators are ready to adapt to technological and scientific innovation to increase plasma donations and collections. He answered that all relevant actors, including industry, are working on collecting plasma as efficiently as possible.

To conclude Q&A session, the speakers stressed the following aspects:

Dr. Jens Rehbein, remarked that the EU should pursue a more flexible regulatory environment, with the differentiation of transfusion products and plasma for further manufacturing, as well as with eligible donor criteria based on scientific progress. The main goal should be the removal of regulatory hurdles for both public and private sectors to ensure the supply of PDMPs.

Dr. Françoise Rossi highlighted the importance of a major flexibility for amending the rules mentioned. This should appear in the revised Directive. Further, a hemovigilance framework would improve the accessibility of donations as needed. She stressed that it is important to have a strategic autonomy in Europe, to avoid relying on plasma importation from third countries.

Dr. Karmin Saadat outlined the urgency of updating donor's eligibility criteria to keep it up to date while ensuring the safety and quality of the donors and PDMP quality.

Ms. Leire Solis remarked the need to avoid waste of plasma and increase best practices in some EU Member States. She further reiterated the urgency to ensure that more plasma is collected for patients relying on PDMPs.

Dr. Stefaan Van der Spiegel highlighted that there is not one only action from one single actor that will result in a solution; action will need to be taken by many stakeholders. He also outlined the importance of providing regulatory flexibility and facilitating access to therapies – which are part of the objectives of the revision.

4. Recommendations and concluding remarks

MEP Pietikäinen thanked the moderator and all speakers for their participation and underlined the importance of such varied discussions for decision makers.

The various speakers highlighted the importance of increasing plasma donation. Plasma shortages lead to barriers to the development of PDMPs. Therefore, the EU Blood Directive should remove the remaining obstacles which prevent individuals from donating plasma.

In light of the issues raised during the roundtable, **MEP Pietikäinen** made several recommendations according to which the revision of the EU Blood Directive should remove regulatory barriers and improve regulatory efficiency by:



1. Introducing a clear differentiation between whole blood and blood components for transfusion and plasma for manufacturing PDMPs;
2. Including a clear definition of “plasma for manufacturing”, “plasma for fractionation”, “plasma for transfusion” and “recovered plasma”:
3. Revising the existing eligibility criteria for plasma donors, taking into account the latest technological and scientific developments. These criteria should take into account the ability of the PDMPs manufacturing process to remove known and emerging pathogens, thus ensuring the highest quality and safety of the final product.

MEP Sirpa Pietikäinen concluded by pointing out that many issues in the blood and plasma field still remain to be addressed to ensure that important progress is made.