EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical Products: quality, safety, innovation

Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)

22 June 2017

Summary Minutes

The purpose of these ad-hoc meetings is to provide an opportunity for an informal exchange of views between key stakeholders, representatives of Member State (MS) Competent Authorities on Substances of Human Origin (CASoHO E01718) and the Commission services on topics of mutual interest. The Commission services published a call to stakeholders for expressions of interest in October 2016. The list of approved stakeholder organisations meeting the criteria defined in the agreed Terms of Reference for these meetings was first published in November 2016 and is updated regularly. The call for expression of interest remains open[1].

PARTICIPATION:

Competent Authorities from all EU-28 MS were invited, as were competent authorities from Norway, former Yugoslav Republic of Macedonia, Montenegro and Turkey. Representatives of the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), the Council of Europe and the World Health Organisation were present as observers.

Stakeholders: European Blood Alliance (EBA), European Haemophilia Consortium (EHC), International Federation of Blood Donor Organisations (FIODS), Plasma Protein Therapeutics Association (PPTA), International Plasma Fractionation Association (IPFA), International Patient Organisation for Primary Immunodeficiencies (IPOPI), Platform of Plasma Protein User (PLUS) and International Haemovigilance Network (IHN).

European Commission/DG SANTE: Ms A-E Ampelas, Mr S. Van der Spiegel (chair), Ms D. Fehily, Mr R. McGeehan, Ms I. Pucinskaite-kubik, Mr P. Catalani

ICF Consulting, a company contracted by DG Santé to support its ongoing evaluation of the blood, tissues and cells legislation[2] was also represented.

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[1] https://ec.europa.eu/health/blood_tissues_organs/consultations/call_adhocstakeholdermeeting_en
[2] https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

1 WELCOME

The chair welcomed participants to this ad-hoc meeting, stressing the importance of these exchanges in the context of the ongoing evaluation of the blood, tissue and cell legislation[3] and inviting all stakeholders to focus their comments on issues of relevance to multiple or all Member States and avoiding discussions of single MS level topics.

2 INTRODUCTION OF STAKEHOLDERS PRESENT

Seven stakeholder organisations had been invited to this meeting on the basis of the agenda topics agreed in advance with the national competent authorities. Each organisation briefly introduced their aims and activities as follows:

FIODS: The International Federation of Blood Donor Organisations represents 18 million blood donors from 81 countries in 5 continents and promotes regular, anonymous, voluntary, non-remunerated blood donation in all countries of the world. More information at: http://www.fiods-ifbdo.org/

EBA: The European Blood Alliance represents non-profit Blood Services in Europe. Together these organisations collect the majority of EU blood donations, around 17 million annually, and supply blood and blood components for around 470 million EU citizens. More information at: http://www.europeanbloodalliance.eu/

PPTA: The Plasma Protein Therapeutics Association is a global trade and standards setting association representing commercial manufacturers of plasma-derived and recombinant biological therapies, collectively known as plasma protein therapies. PPTA also represents for-profit collectors of Source Plasma. Their members provide around 70% of the world's needs for Source Plasma (600 plasma collection centres based in North America and more than 100 in the EU) and >80% of the world's plasma protein therapy products. More information at: http://www.ppta.org/

IPFA: The International Plasma Fractionation Association represents not-for-profit plasma fractionators and national blood services collecting plasma for the manufacture of medicinal products. It supports the supply of plasma from Voluntary Non-Remunerated Blood Donors (VNRBD). More information at: http://www.IPFA.org

IPOPI/PLUS: The International Patient Organisation for Primary Immunodeficiencies, created in 1992, is an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for primary immunodeficiency patients worldwide. IPOPI has 61 National Member Organisations, 23 of which are in the EU and it represents 60.000 patients worldwide. The same participant represented the platform of plasma protein user (PLUS), an umbrella for patient organisations bringing together patients dependent on plasma Derived Medicinal Products (PDMP) supplied by manufacturers. More information at: https://ipopi.org/

EHC: the European Haemophilia Consortium (EHC), is a non-profit umbrella patient organisation representing around 90,000 patients dependent on clothing factors and other

[3] https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

types of plasma derivatives (PD) supplied by manufacturers. More information at: www.ehc.eu

IHN: The International Haemovigilance Network is a network of professionals, bringing together 38 national haemovigilance programmes and many interested individuals. Its aims are sharing experience and knowledge, benchmarking, the development of international definitions and international collaboration on haemovigilance. More information at: http://www.ihn-org.com/

3 PROTECTION OF BLOOD AND BLOOD COMPONENT DONORS IN THE EU

Five stakeholder organisations had been asked to give 10 minute presentations on this topic: FIODS, EBA, PPTA, IPFA and IHN.

FIODS presented regular voluntary unpaid donation as the basic principle to ensure the safety of donors and recipients. They noted that the differences between requirements and procedures in blood collection can lead to a diversity in the service given to the donor, especially in cases of serious adverse reactions and events and argued that MS should agree upon common principles/rules on the management and reporting of these events, and build from that a further developed culture of donor protection, also taking into consideration the difference between whole blood and apheresis donation. They also presented their training and cooperation initiatives as well as their approach to the education of donors on having healthy lifestyles. They described how this approach benefits donors themselves but also recipients as it raises awareness of donors regarding their responsibility not to cause harm to recipients. They stressed that the community of blood donor associations can play a crucial role to that end, with a complementary action to that of public health authorities, given their close relationship with donors.

EBA argued that the EU blood legislation does not adequately address donor health and protection. They pointed, in particular, to Directives 2004/33/EC and 2005/61/EC where they consider that more preventive measures to protect donors and comprehensive donor vigilance to monitor their safety are required, respectively. The provisions should address vaso-vagal reactions and iron deficiency and be evidence-based, with reference, for example, to the ISBT/IHN/AABB Standard for Surveillance of Complications Related to Blood Donation. They consider that further data is needed on donor iron stores for blood donation and appropriate IgG levels for plasma donation. This impacts the appropriate volume and frequency of whole blood and apheresis donations; haemoglobin levels alone are not considered sufficient. They pointed to the adequacy of the new General Data Protection Regulation (GDPR) for covering donor data confidentiality. They called for all organizations to be required to describe their donor panels, both for whole blood and apheresis, including numbers, frequencies of donation, infectious disease markers, length of active careers by gender and age, and turn-over rate of the donor panel.

PPTA presented donor health as a top priority for the plasma collection industry, reporting the collection of over 130,000,000 plasma donations globally over the past 5 years with an extraordinary safety record. Their representative affirmed that the health of the donor should not be compromised by their donation. Two major studies, conducted in Germany, on long-term donor safety were presented. The first, SIPLA I, was a prospective multi-centre study on

the safety of long-term intensive plasmapheresis in donors (Schulzki et al. 2006[4]). It included 3,783 experienced donors that donated 304,836 donations over a 3-year period. The study was completed by 24.4% of the donors with the majority dropping out due to socioeconomic or medical reasons. Of the latter, 16% of the reasons for drop-out were plasmapheresis-related, primarily involving low IgG, low total protein or low haemoglobin. Five severe reactions related to donation were reported, 4 related to vein puncture and 1 to metacarpal fracture after dizziness. At the end of the study, average IgG was significantly lower compared to the beginning but was well above the lower limit. The safety of intensive donation had also been confirmed in more in-depth study of a smaller number (75) of frequent (average. 48 donations/year) donors (Bechtloff et al. 2005[5]).

This had been followed by a second study, SIPLA II, where the safety of experienced and first time donors in intensified plasmapheresis (up to 60 donations/year) was compared (Kießig et al. ISBT, 2013[6]) in 2,379 donors observed over a 1 year period. This study included mixed blood and plasma collection and confirmed that at the end, haemoglobin was low in 11,1% male and 10,4% female donors, total protein in 25,4% and IgG in 20,1%. With a very low rate of severe reactions, it was concluded that plasmapheresis under intensified conditions appears safe. Other studies were presented that indicated similar results.

In conclusion, PPTA consider that the published scientific studies have shown there is no significant adverse effect on donor health by long-term intensified plasmapheresis, if haemoglobin, total protein and IgG are monitored regularly; the risk for adverse reactions decreases with the number of donations and cardiovascular risk of donors remains unaffected by plasmapheresis. PPTA noted the industry's continued commitment to protecting donor health and minimizing any potential risk.

IPFA presented the donor selection criteria followed by their member organisations. The criteria aim to protect donor health. Apart from age and health check criteria, IPFA refers to a donation frequency of up to 5 and 3 times a year for whole blood donation by men and women, respectively, and to 23 times a year for plasma donation, with a maximum frequency of once every two weeks. In reality, the average yearly donation rates in their member organisations are 1.7 for whole blood and 5.5 for plasmapheresis. They noted significant differences between the donation volume rules defined in the EU legislation, in national rules and in the US.

They presented a published study comparing the donation volumes and protein status of unpaid, compensated and paid donors in the EU and the US[7]. The results showed that compensated and paid donors donate significantly larger volumes and have significantly lower protein levels (albumin and immunoglobulins) than unpaid donors, whether in the EU or the US. In particular, US high frequency donors were shown to donate 34% more plasma volume than EU unpaid plasma donors and to have lower total protein content (9%), up to

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[4] T. Schulzki, K. Seidel, H. Storch et al. (2006) A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA) *Vox Sanguinis* 91: 162–173

[5] Bechtloff S, Tran-My B, Haubelt H, et al. (2005) A prospective trial on the safety of long-term intensive plasmapheresis in donors. Vox Sang 88:189–195

[6] S.T. Kiessig ST, S. Teichmann, S. Schneider, et al. (2013) First results from the Study on Intensive Plasmapheresis II (SIPLA II) Abstract presented at the 23rd Regional Congress of the ISBT Amsterdam, The Netherlands, June 2 - 5

[7] Laub R, Baurin S, Timmerman D. et al. (2010) Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sang. 99(3):220-31

11% lower TRF (iron), RBP (protein status) and HPX (toxic haem scavenger) levels, 15% to 28% lower albumin and immunoglobulin (IgM and total IgG) levels and nutritional deficiency indicators (RBP, TRF and albumin) with levels 10%, 7% and 15% lower, respectively. They expressed concern that high frequency collection and high collection volumes (800 ml twice a week) do not allow a return to the normal physiological levels between donations.

IPFA noted that the EU legislation requires a 48 hour gap between plasma donations but that this does not appear to allow sufficient time for replacement of the proteins in the donor's plasma, even if the donor is on a healthy diet. They indicated that the low plasma protein levels in US frequent plasmapheresis donors might not be indicative of any disease, but demonstrate the presence of a not completely healthy condition based on laboratory findings. IPFA advised not changing the European rules in terms of volume and frequency of donations until further data and better understanding of the impacts on donor health are available.

IHN presented their concerns regarding the EU legislation and its current provisions for ensuring vigilance and safety of blood and blood component donors. They noted that Directive 2005/61/EC limits donor reaction reporting requirements to those serious adverse reactions having an effect on the quality and safety of the donated blood component. They strongly argue for broadening this requirement to the reporting of all serious adverse reactions in blood and blood component donors. They recommend that this reporting be based on the published Standard for Surveillance of Complications Related to Blood Donation developed jointly by the International Society for Blood Transfusion, the IHN and the American Association of Blood Banks[8] and endorsed by EBA. They pointed particularly to the 2 major safety issues to be considered: fainting reactions and iron deficiency.

French haemovigilance data show an average immediate fainting rate of 100 per 100,000 donations and an average delayed fainting rate of 12 per 100,000 donations, although rates are significantly higher in younger donors, in female donors and in first-time donors. Rates for whole blood and apheresis donation are similar. Recent studies have highlighted methods to mitigate this risk.

IHN quoted recommendations from AABB in 2017 reminding organizations that blood donation can induce significant iron depletion that may have deleterious health consequences, particularly in young donors, pre-menopausal females, frequent donors and those donors whose haemoglobin levels are close to the minimum for eligibility. AABB recommends blood establishments to take action for all at-risk donor subpopulations: the measurement of serum or plasma ferritin with subsequent defined actions for donors with low ferritin levels, evidence-based lengthening of the inter-donation interval and/or restriction of the number of donations per year and/or the development of programs to provide replacement iron in the absence of ferritin measurements.

IHN also called for the systematic collection of data pertaining to any possible long term deleterious side effects associated with frequent donations (in particular plasmapheresis), including cancer frequency, bone metabolism defects and low birth weight.

[8] http://www.isbtweb.org/fileadmin/user_upload/Donor_Standard_Definitions_Final_2014.pdf

IHN considers that the importance of protecting donor health mandates high quality harmonised blood donor vigilance programmes and evidence based donor deferral rules to protect donor health. They also called for a promotion of voluntary non-remunerated blood donation as a secondary means to promote donor safety.

4 SUPPLY OF PLASMA FOR PLASMA-DERIVED MEDICINAL PRODUCT MANUFACTURE IN THE EU

Five stakeholder organisations had been asked to give 10 minute presentations on this topic: IPOPI/PLUS, EHC, IPFA, PPTA and EBA.

IPOPI/PLUS stated that immunoglobulins (Ig) manufactured from donated blood and plasma are vital biological medicines for patients with primary immunodeficiencies (PID) fighting infection. Around 70% of these patients need lifelong treatment and have no alternative. Patients need Ig continually without a break, every 3 weeks when using intravenous Ig and weekly if using sub-cutaneous Ig.

Immunoglobulins are leading a global market with demand growing continuously. IPOPI/PLUS stressed that these products need to circulate freely and that a wide range of these products should be available to PID patients to ensure optimal care. Any shortage represents a severe risk for patients with PID. As patients, they are very grateful to both blood and plasma donors and they encourage that blood and plasma donations are made in the safest environment. For them, supply has become the major safety issue and, to meet the growing demand, they see a need to enrol more donors and to increase plasma collection without compromising the safety of blood and plasma donors; they consider that both compensated and uncompensated donations are needed. The underlined their view that blood and plasma are different, both from a donation and safety perspective, and that the donation rules should take this into account. Plasmapheresis is the most important source of plasma for manufacturing.

They applauded the efforts of the European Medicines Agency, together with the European Commission, in ensuring safety and efficacy of Ig therapies and called for Member States that nationally authorise plasma derived medicinal products to raise standards to those of the EMA and to gain centralised approval. Once an Ig therapy has been centrally approved, it should be possible for all patients to have access to it. IPOPI consider that patients should not have their right to treatment compromised on the basis of ethical principles that only hinder patients' rights. They stress that centrally approved plasma derived medicinal products, such as immunoglobulin, should circulate freely across the EU. They noted that EMA stated in 2002 that there was no evidence from clinical studies and pharmacovigilance that donor remuneration increases the risk of viral transmission via plasma derived medicinal products that have been subject to proper screening at donation and a validated viral inactivation/removal step and they pointed to an EMA view that a requirement for unpaid or non-remunerated donors would create major supply problems and product shortages without any justification on grounds of safety[9].

EHC reiterated the critical importance of plasma derived medicinal products for patients, in their case for those suffering from rare clotting diseases such as haemophilia A (deficiency of

[9] http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/10/WC500004488.pdf

Factor VIII) haemophilia B (deficiency of Factor IX) and Von Willebrand's disease (deficiency of Von Willebrand Factor). These patients must be treated with replacement therapy using coagulation factors derived from human plasma or manufactured synthetically (recombinant) of with frozen plasma or cryoprecipitate. The consortium had surveyed 19 European countries to establish the dosage available per capita (international units, IU) for Factor VIII and Factor IX, the ratio of plasma-derived vs. recombinant product used and the types of products used (e.g. fresh frozen plasma, cryoprecipitate, plasma-derived coagulation factors).

The survey showed high variability in usage in Europe with the lowest usage of Factor VIII in Albania 0.46 IU/capita and a range within the EU from 0.97 IU/capita in Romania to 9.4 IU/capita in Hungary. The recommended minimum use is 3 IU/capita. A similar variability in access was evident for Factor IX across the EU with the lowest use in Romania (0.1 IU/capita) and the highest in EU in Ireland (2.4 IU/capita). The minimum recommended is 0.5 IU/capita. Similar variability is seen for the use of plasma derived clotting factors versus recombinant, with Estonia relying almost completely on plasma-derived while Ireland relies almost completely on recombinant. While fresh frozen plasma is now almost never used in most countries as it carries higher risks, not being subjected to pathogen inactivation, it is still the commonly used therapy in countries such as Estonia and Ukraine. EHC stressed that patients need is the same across all countries and access should be equal to the safest and most effective therapies.

IPFA presented data published by MRB that demonstrate a steady increase in the global demand for plasma derived medicinal products, the most dramatic increasing demand being that for intra-venous immunoglobulins (IVIg). Since 2005, the volume of plasma collected by apheresis has more than doubled, while the supply of plasma recovered from whole blood donations has remained essentially stable. Despite the continuing increasing demand for plasma for manufacture of medicinal products, they note that more than 9.3 million liters of recovered plasma remains unused and that the growth in plasma collection has occurred almost entirely in the US, with 5% of the world's population providing 60% of the plasma used for medicinal product manufacture.

IPFA consider that plasma for manufacture of medicinal products should be considered as a strategic resource, similar to energy or drinking water, and that there are unacceptable risks associated with reliance on one region to collect the majority for the globe. They pointed to interruptions in supply in the 1980's worldwide due to HIV and in different regions at different times due to variant Creutzfeldt Jakob Disease (UK, Ireland), West Nile Virus (La Réunion), Dengue virus (Puerto Rico) and Zika Virus (Puerto Rico). Increasing demand, combined with a shortage in the US due to an unexpected interruption, was described as a potential disaster for patients outside the US that might no longer have access to the products they need. IPFA called for initiatives to safeguard the supply in a country or a region, with the involvement and commitment of National Blood Transfusion Services, the authorities (EU Commission, EDQM, Ministries of Health, Policy Makers, and Inspectorates) and with the co-operation of all stakeholders. They pointed to the experiences of Canada and Australia where significant effort has been invested in developing strategies to reduce reliance on the US supply and mitigate the risk of supply interruption through increasing collection of plasma, without donor remuneration, and increased recovery of plasma from whole blood. They called for a similar approach in the EU.

PPTA also used MRB data to demonstrate the rapidly increasing demand for intravenous immunoglobulins and demonstrated wide variability in usage rates across Europe. While,

according to MRB data, the average usage of intra-venous immunoglobulins in Europe in 2014 was 82.1 grams/1000 population, this varied from less than 5.0 in Bulgaria to more than 100 in France, Belgium and Ireland. They pointed to the Council of Europe resolution that called for equal access in particular to immunoglobulins for all patients and for health technology assessment to evaluate the comparative outcomes of treatment with different immunoglobulin products.

In line with IPFA, they pointed to the global reliance on the US for plasma collection but noted that the EU has the greatest throughput of plasma in its fractionation facilities and has more fractionation facilities than the US. They summarized the history of closures of public fractionation facilities in many countries, suggesting that only the private sector has the investment resources to carry out the manufacturing of plasma derived medicinal products efficiently and to the required standards.

PPTA explored the question of plasma collection in relation to the compensation of donors, demonstrating that the small number of EU countries that contribute importantly to the supply of plasma for the manufacture of medicinal products are those that also compensate donors (Figure below).

	Global/Regional Plasma %	**Plasma***
USA	**61%**	Mostly Compensated
EU	**19%**	
Germany	39%	Mostly Compensated
Austria	8%	Mostly Compensated
Czech Rep.	6%	Mostly Compensated
France	10%	Non-Compensated
Italy	10%	Non-Compensated
Asia	12%	
China	66%	Compensated
Japan	17%	Non-Compensated
India & Korea	8%	Non-Compensated
Middle East and Africa	1%	
*Definition of non-compensation is subject to interpretation		

Focusing particularly on anti-D immunoglobulin, PPTA described the way in which the introduction of anti-D prophylaxis has almost eliminated haemolytic disease of the newborn in the EU. The manufacture of this product requires the immunisation and qualification of healthy donors, a process that can take up to 2 years. They claimed that different national legislative requirements, as well as partially conflicting or contradictory regulatory standards in nearly all 28 European Member States, make active immunisation of Rh-D negative volunteers with Rh-D positive cells virtually impossible in EU countries. As a consequence, the reliance of the EU on other countries, particularly the US, for this essential medicine is total.

To address the reliance on the US for plasma in general, they called for more collection centres to be opened outside of the US, allowing both public and private organisations to run these. They identified a need to increase efficiency in collection practices, with plasmapheresis as the primary method of collection, but also called for an end to the discard

of recovered plasma. They considered that allowing donor compensation is crucial to increasing the supply and called for the voice of patients in need of plasma derived medicinal products to be heard.

Referring to their published position paper on Self sufficiency for Plasma[10], **EBA** supported the position of IPFA and the call to consider plasma as a strategic resource for Europe to mitigate the risks of reliance on the US in the case of supply interruption. They consider that the strategy should be built on principles ensuring the dignity and safety of donors, based on voluntary non-remunerated donation, safe donation practices, transparency of costs and prices and equal access to plasma derived medicinal products for all patients. In relation to donor safety, they consider that more research is needed to understand safe donation patterns but call for all those involved in plasma collection to describe their donor panels: number, frequencies of donation, infectious disease markers, length of active donation careers by gender and age, and turn-over rate of the donor panel.

In 2015, EBA member organizations provided 8.8 million units of recovered plasma for medicinal product manufacture and 1.4 million units from apheresis. They consider that the priorities for their members are to develop efficient plasmapheresis programmes and to reduce wastage of recovered plasma. The main reason for wastage of recovered plasma was reported as non-compliance with the quality standards required by the plasma industry in the Plasma Master File (PMF). They consider that Directive 2016/1214/EU amending Directive 2005/62/EC with good practice guidelines is addressing this problem and that training programmes should be developed to reduce or eliminate the wastage of recovered plasma due to quality concerns. They suggested that the PMF certification procedure may present economic disincentives to the use of recovered plasma, especially in small countries.

EBA noted the decreasing demand for red blood cells resulting in a reducing potential for the supply of recovered plasma. In this context, they consider that blood donors must be converted to plasma donation and the efficiency of plasma collection by blood services must be increased. EBA members are developing programmes to improve the efficiency of plasmapheresis collection in some cases with demonstrable success (e.g. in Belgium, Denmark, France, Germany, Italy, the Netherlands). They called for support for these initiatives.

5 FINAL REMARKS

The chair closed the meeting, thanking the participants for the high quality of their inputs and underlining that they would form an important element of the evidence for the ongoing evaluation of the legislation.

[10] http://www.europeanbloodalliance.eu/wp-content/uploads/2016/11/EBA_Summary_Paper-EU_self_sufficiency.pdf