An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients

Creative Ceutical Report, revised by the Commission to include stakeholders' comments

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The content of this report represents the views of the contractor and is its sole responsibility; it can in no way be taken to reflect the views of the European Commission and/or EAHC or any other body of the European Union. The European Commission and/or EAHC do not guarantee the accuracy of

the data included in this report, nor do they accept responsibility for any use made by third parties thereof.

The content of this report represents also views of different stakeholders (PPTA, IPFA, EBA, PLUS, CoE, EDQM) and the statements for which they have been referenced are their sole responsibility; these can in no way be taken to reflect the views of Creativ-Ceutical. Creativ-Ceutical does not guarantee the accuracy of the data included in this report, when directly related to a stakeholder's statement, nor does Creativ-Ceutical accept responsibility for any use made by third parties thereof.

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List of Abbreviations

ANSM	Agence nationale de sécurité du médicament et des produits de santé
BE	Blood establishment
CAF-DCF	Département Central de Fractionnement de la Croix-Rouge
C-C	Creativ-Ceutical
CD-P-PH	European Committee on Pharmaceuticals and Pharmaceutical Care
CD-P-SC	Consumer Health Protection Committee
CD-P-TO	Steering Committees on Organ Transplantation
CD-P-TS	European Committee on Blood transfusion (Partial Agreement) of the Council of Europe)
CEP	Certification of suitability of the Monographs of the European Pharmacopoeia
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CJD	Creutzfeldt-Jakob Disease
CoE	Council of Europe
CPMP	Committee for Proprietary Medicinal Products (replaced by CHMP in 2004)
DAF	Administration and Finance Division
DBO	Healthcare Department
DC	Donor Center
DCEP	Certification of Substances Division
DG SANCO	Directorate General for Health and Consumer Affairs
DH-BIO	Committee on Bioethics of the CoE
DLab	Laboratory Department
DOMAINE	Donor Management Program in Europe
DPM	Publications and Multimedia Department
DRK	German Red Cross
DRS	Reference Standards and Samples Division
EBA	European Blood Alliance
EC	European Commission

ECDC	European Centre for Disease Prevention and Control
EDQM	The European Directorate for the Quality of Medicines and Healthcare of the Council of Europe
EFS	L'Etablissement Français du Sang
EFTA	European Free Trade Association
EHC	European Haemophilia Consortium
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPD	European Pharmacopoeia Department
EQUAL	EU-Q-Blood-SOP Project
EU	European Union
EuBIS	European Blood Inspection Project
EUOBUP	EU Optimal Blood Use Project
EU-Q-Blood-SOP	Pan-European standard operating procedure methodology reflecting European best practice within the area addressing the quality and safety of blood
FDA	Food and Drug Administration
FVIII	Coagulation Factor VIII
FIX	Coagulation Factor IX
GBS	Guillain-Barré Syndrome
GDP	Gross domestic product
GHS	Non-Homogenous Stay Group
GMP	EU Good Manufacturing Practice
HAEi	International Patient Organization for C1 Inhibitor Deficiencies
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IG	Immunoglobulin
IPFA	International Plasma Fractionation Association

IPOPI	International Patients Organization for Primary Immunodeficencies
ITP	Idiopathic thrombocytopenic purpura
IU	International Unit
IVIG	Intravenous immunoglobulin
KEELPNO	Hellenic Centre for Disease Control
LFB	Laboratoire français du Fractionnement et des Biotechnologies
MAA	Marketing Authorization Application
MEP	Member of the European Parliament
MoH	Ministry Of Health
MR	Magnetic Resonance procedures
MS	Member States
NAT	Nucleic Acid Test
NCA	National Competent Authorities
NHS	National Health Service
OMCL	Network of Official Medicines Control Laboratories
PDMP	Plasma Derived Medicinal Products
PID	Primary Immunodeficiency
PLUS	Platform of Plasma Protein Users
PMF	Plasma Master File
PPTA	Plasma Protein Therapeutics Association
PRDD	Public Relations and Documentation Division
QM	Quality Management
RBC	Red Blood Cells
SCIG	Subcutaneous immune globulin
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TTI	Transfusion Transmissible Infections

US	United States
VAMF	Vaccine Antigen Master File
vCJD	Variant Creutzfeldt-Jakob disease
VNRBD	Voluntary Non Remunerated Blood Donation
VUD	Voluntary Unpaid blood Donation
WB	Whole Blood
WFH	World Federation of Hemophilia
WHO	World Health Organization
WNV	West Nile Virus

Introduction

Background

Maintaining an adequate blood and plasma supply for patients requiring transfusion or plasma derived products, ensuring appropriate use and warranting safety of products for transfusion, together with the prevention of transmission of infectious diseases, are the main concerns of national health authorities, as well as for the European Commission, for international institutions, and for other stakeholders.

Every year millions of patients are transfused with blood, blood components or receive plasma derivatives to improve their quality of life and survival. In 2012, EU Member States reported that there were more than 1,350 blood establishments collecting more than 20 million whole blood and blood components donations (red blood cells, plasma or platelets) as well as millions of additional donations of plasma by apheresis, which are used for transfusion or as starting materials in the pharmaceutical sector to produce plasma derivatives.

Blood and plasma derivatives can only be obtained from human donors making them a limited resource.

At the European level, numerous initiatives related to the blood and plasma sectors have been undertaken since 1989 (initially Directive 89/381/ECC). Directives on standards were developed with regard to quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, including traceability requirements and notification of serious adverse reactions and events were also addressed (Directive 2002/98/EC[1] and the relevant implementing Directives 2004/33/EC[2], 2005/61/EC[3] and 2005/62/EC[4]).

Plasma derivatives follow mainly pharmaceutical regulations. Nevertheless, as blood components are used to produce plasma derivatives as starting material, the requirements on collection and testing of the abovementioned directives apply.

[1] Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003)

[2] Commission Directive 2004/33/EC of 22 March 2004 of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical for blood and blood components

[3] Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notifications of serious adverse reactions and events.

[4] Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishment.

Directive 2001/83/EC[5] as amended by Directive 2004/27[6] laid down specific requirements on manufacturing, storage and distribution of medicinal products.

Moreover, the Commission Directives 2003/63/EC[7] amending Annex I of Directive 2001/83/EC regarding documentation and 2003/94/EC laid down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.[8]

In addition, guidance is provided for the interpretation of the principles and guidelines of Good Manufacturing Practice (GMP) [9], for the requirements on the scientific data for a Plasma Master File (PMF)[10] and on Epidemiological Data on Blood Transmissible Infections.[11]

Directives 2002/98/EC and 2001/83/EC encourages Member States to take all measures to achieve self-sufficiency for blood and plasma through voluntary unpaid donations.

Major efforts must, therefore, be undertaken, starting with a general and comprehensive understanding of a number of challenges that stakeholders and national competent authorities are facing today to comply with requirements on safety and availability of blood and blood products.

Objective and scope

This report aims to provide insights on a number of topics closely related to the availability of blood components and plasma derived medicinal products to patients within the EU. We have contacted major stakeholders involved in the blood and plasma sectors and discussed, in full transparency, the following topics: voluntary unpaid donations, product shortages, movement of these products within and outside Europe (import/export), achievement of self-sufficiency (especially with a potentially

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[5] Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001, on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001)

[6] Directive 2004/27/EC OF THE European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 136, 30.4.2004)

[7] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

[8] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

[9] Eudralex - The Rules Governing Medicinal Products Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for human and veterinary use, Annex 14, Manufacture of Medicinal Products Derived from Human Blood or Plasma; http://ec.europa.eu/health/documents/eudralex/index_en.htm

[10] EMEA/CHMP/BWP/3794/03 Rev.1-
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003663.pdf

[11] EMA/CHMP/BWP/548524/2008 Committee for Medicinal Products for Human Use (CHMP);
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/10/WC500097728.pdf

increasing demand), as well as potential difficulties in the regulatory environment that may hinder access to patients.

Methodology

To address these issues, a survey was developed (see appendix, p112) and disseminated to a selected number of stakeholders (see below) and followed by more in depth discussions. The views and opinions expressed in this report are those of the stakeholders and intend to shed light on a number of complex and important questions for the European Commission.

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Figures

1. Background information

The main concerns of national health competent authorities, as well as for the European Commission, are to maintain an adequate blood supply for patients requiring transfusion, ensure appropriate use and to warrant safety of products for transfusion together with the prevention of transmission of infectious diseases.

With this regard, the Directive 2002/98/EC[12] was adopted in 2002. It aims to warrant the safety and quality of blood and blood components by means of establishing minimum common and homogeneous regulations in all Member States.

Article 20 of the Directive states that Member States should take the necessary measures to encourage voluntary unpaid donations (VUD). The aim of promoting VUD for blood products is to facilitate Member States achieving the maximum level of self-sufficiency for these products.

Directive 2002/98/EC requests Member States to report every three years to the Commission on the measures to promote VUD. With the data reported by Member States the Commission prepared the second report on voluntary and unpaid donation in EU that was published in March 2011.[13] This report gave an insight into legislative provisions, policies, incentives, promotion, collection and supply of blood components and blood products.

The principle of voluntary non remunerated donation (another term for VUD) is recommended by the World Health Organization and Council of Europe based on ethical and quality and safety issues for sustainable blood supply to guarantee patient needs.[14,15,16]

Quality and safety of the blood components and products has been linked to voluntary and unpaid donations. Studies[17] have shown that family replacement and paid donors are associated with a significantly higher prevalence of transfusion transmissible infections (TTIs) including HIV, hepatitis B,

[12] Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003)

[13] 2nd Report on VUD – Report from the Commission to the council and the European Parliament. Report on the promotion by Member States of voluntary unpaid blood donations. European Commission 2011

[14] World Health Assembly and Executive Board resolutions on blood safety and availability.http://www.who.int/bloodsafety/resolutions/en/, accessed 12-05-2014

[15] Resolution WHA63.12 Availability, safety and quality of blood products. Sixty-Third World Health Assembly. Genève, World Health Organization, 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf, accessed 12-05-2014

[16] Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non remunerated blood donation (VNRD). Genève, World Health Organization, 2012. http://www.who.int/bloodsafety/Expert_Consensus_Statement_Self-Sufficiency.pdf

and hepatitis C. In developing countries, these donors still provide more than 50% of the blood collected. [18,19,20,21]However, these conclusions are not supported by other authors, who claim that compensated and regular replacement donors are safer than VUD first time donors.[22,23]

In 2002, the European Agency for the evaluation of Medicinal products published a statement regarding the safety and supply of plasma derived medicinal products from non-remunerated and remunerated donors which stated: ….*There is no evidence from clinical studies and pharmacovigilance that donor remuneration increases the risk of viral transmission via plasma derived products, which have been subject to proper screening at donation and a validated viral inactivation/removal step….* [24]

It is however important to note that, while viral inactivation/removal steps are crucial for the safety of plasma derived medicinal products, their implementation needs to be well validated and these techniques cannot be applied to labile blood components.

The availability to patients of blood and blood products within EU depends on a number of public and private actors that are involved with the blood and plasma markets. Blood establishments, collecting units of blood and/ or plasma at hospitals or private centres and the different national authorities within the EU can affect product availability.

Reimbursement of plasma derived medicinal products may also affect availability to patients. Treatments with medicinal products manufactured with plasma (like intravenous immunoglobulins for autoimmune, infectious or idiopathic diseases) are not reimbursed in all Member States.

Over the last years, the plasma protein industry has developed a wide range of products for the treatment of specific groups of patients, following the progress made by medical sciences as

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[17] Hassam A., Asian J Transfus Sci. Jan 2010; 4(1): 9–13. doi: 10.4103/0973-6247.59385

[18] WHO website: www.who.int/bloodsafety/voluntary_donation/en/ , accessed 2013-07-24

[19] Abdel Messih IY et al. The degree of safety of family replacement donors versus voluntary non-remunerated donors in an Egyptian population: a comparative study. Blood Transfus. 2012 20:1-7 DOI: 10.2450/2012.0115-12.

[20] Jain R, Gupta G. Family/friend donors are not true voluntary donors. Asian J Transfus Sci 2012;6:29-31

[21] PAHO Website: http://www.paho.org/hq/index.php ?option=com_content&view=article&id=7600%3Asangre2009&catid=4243%3Ahsd0107x-cd-media-center&lang=es, accessed 2013-09-24

[22] Van der Poel CL et al. Paying for blood donations: still a risk? Vox Sang. 2002 83(4):285-93

[23] A.Farrugia et al. Payment, compensation and replacement – the ethics and motivation of blood and plasma donation. Vox Sang. 2010 99, 202-211

[24] CPMP Position Statement, Non remunerated and remunerated donors:safety and supply of plasma derived medicinal products, European Agency for the Evaluation of Medicinal Products (EMEA),Doc. ref: EMEA/CPMP/BWP/1818/02/final;
http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/10/WC500004488.pdf

immunology, thrombosis and haemostasis, indicating the potential therapeutic applications of plasma protein fractions. As a consequence, the manufacturing of these medicinal products has significantly raised the demand for the plasma used by the pharmaceutical industry. It is important to understand the impact of this increased need and how it affects the blood donation and supply. The availability for all these products is limited by the scarce availability of donors.

In order to further develop the EU policy and legislation with regard to self-sufficiency and quality and safety of these products for transfusion and their availability to patients, the Commission has contracted Creative-Ceutical (C-C) to further gather information regarding the landscape of blood, blood components, plasma and plasma derived medicinal products in the EU, mainly the 27 EU Member States.

2. Current European initiatives

At the European level, numerous initiatives related to the blood and plasma sector have been undertaken, including recommendations and directives on standards set for quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components[25], as regards technical requirements for blood and blood components[26], traceability requirements and notification of serious adverse reactions and events[27], and standards and specifications relating to a quality system for blood establishments.[28]

The first report on promotion by Member States of VUD published in 2006 by the European Commission[29] summarized the measures taken by Member States to encourage VUD and identified measures to be taken by the Commission such as an integrated approach to address blood shortages and promote self-sufficiency. The second report on VUD of blood and blood components published in 2011 provided an overview of the practice of VUD of blood and blood components in the EU, focusing on (1) legislative provisions/guidelines and policies, (2) incentives, (3) promotion, (4) collection, supply and further issues.[30]A third report is due in 2015.

[25] Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003)

[26] Commission Directive 2004/33/EC of 22 March 2004

[27] Commission Directive 2005/61/EC of 30 September

[28] Commission Directive 2005/62/EC of 30 September

[29] First Report from the Commission to the Council and the European Parliament on promotion by Member States of voluntary unpaid donations – COM (2006) 217 final;

http://ec.europa.eu/health/ph_threats/human_substance/documents/blood_com_0217_en.pdf

[30] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final;

The European Committee on Blood Transfusion of the Council of Europe conducts yearly surveys on the collection, testing, and use of blood and blood components in its Member States. Data were returned from 29 and 33 Members States in 2009 and 2010 respectively. They were compiled and presented in annual reports or evaluated for trend analysis. Publication made thereof by the European Directorate for the Quality of Medicines & HealthCare (EDQM/CoE) can be consulted under www.edqm.eu/blood-transfusion. In addition, a technical appendix to Recommendation N0.R(95)15, the "Guide to the preparation, use and quality assurance of blood components" is regularly updated. The 17th edition was published in 2013 by EDQM.

Several organisations throughout Europe have joined forces in projects that are co-funded by the European Commission focused on different parts of the blood transfusion chain:[31]

- The EU-Q-Blood-SOP Project (EQUAL) that formulated a set of Standard Operating Procedure (SOPs) to be used in blood banking. Standard pan-European SOP methodology was developed reflecting European best practice addressing the quality and safety of blood. [32]
- The European Blood Inspection Project (EuBIS) that developed pan-European standards and criteria for the inspection of blood establishments. [33]
- The Donor Management Program (DOMAINE) which identified and recommended good donor management practices to create a safe and sufficient donor population in Europe.[34]
- The EU Optimal Blood Use Project (EUOBUP) that aimed to improve clinical transfusion process by promoting optimal blood use. [35]
- The Competent Authority Training Programme for Inspectors of Blood Establishments in Europe (CATIE).[36]
- Euro Blood Substitutes (BOTIA) – A research project on blood substitutes for 21st Century Europe, as a potential help to face transfusion risks.[37]
- Rapid SPR for parallel detection of pathogens in blood (RaSP) – This research project aimed to develop a method to detect HIV, Hepatitis B and C pathogens.[38]

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http://ec.europa.eu/health/blood_tissues_organs/docs/blood_reportdonation_en.pdf

[31] Transplantation, Transfusion - Projects and Actions for saving and improving the quality of life of citizens by facilitating transplantation and blood transfusion in the European Union and Actions. Executive Agency for Health and Consumers, European Union 2013

[32] http://www.equal-blood.eu/SOP/EU_Q_Blood_SOP_Manual_Ed_1_0.pdf, accessed 2013-07-24

[33] http://www.eubis-europe.eu/blood_manual.php, accessed 2013-07-24

[34] http://www.domaine-europe.eu/Manual/tabid/56/Default.aspx, accessed 2013-07-24

[35] http://www.optimalblooduse.eu/content/optimal-blood-use, accessed 2013-07-24

[36] http://www.catie-europa.eu/

[37] http://www.ec.europa.eu/research/fp6/botia_enhtm

[38] http://www.rapid-spr.com/

- PRIONSCREEN - The development of a blood screening assay for diagnosis of prion diseases in humans

In addition, the European Commission and the Council of Europe cooperate under a direct agreement on quality systems in the blood transfusion field and on specific matters related to human substances (blood).
As for the plasma sector, Plasma Users Coalition (PLUS) has organized 'Dublin consensus meetings' for the past three years grouping more than 20 organizations to discuss and agree on a number of principles such as, the commitment to guarantee a sufficient supply of safe and effective blood components to meet patient needs, to prevent adverse reactions including transmission of pathogens, to respect blood and plasma donors, to cooperate with all actors to collect adequate supplies of blood components, and a global utilisation of donated blood and plasma.[39,40]

3. Report Objective

This report aims to map the landscape, main trends and challenges in the blood and plasma sectors.

It brings together facts and figures, where these are available, and opinions of the main stakeholders to present a balanced view on different challenges in these sectors.

4. Methodology

4.1 Stakeholders selection

To understand the landscape of blood, blood components and plasma derived medicinal products, Creative Ceutical has contacted and interviewed representatives of main stakeholders, for-profit and non-for-profit, operating in and outside Europe to participate in the study providing input on a specific number of topics.

Representatives of all actors in the chain, from collection (EBA) to manufacturing (PPTA/IPFA), and of patients (PLUS) were invited, as well as of some international organisations (EDQM/CoE and WHO) who have a holistic view on the sector. In order to fully grasp the challenges of the blood and plasma sectors, we aimed to provide an overview of opinions by interviewing the main stakeholders on a number of issues that matter to policy makers in Europe. All stakeholders that positively replied to our invitation were included in this project. The views of each stakeholder will be expressed and supported by the documents that they provided.

[39] Mahony B.O et al Dublin Consensus Statement 2010. Vox Sanguinis

[40] Mahony B.O., Turner A. Dublin Consensus Statement 2011. Vox Sanguinis

4.1.1 Stakeholders involved in blood and blood components sector

4.1.1.1 The European Blood Alliance

The European Blood Alliance (EBA) is an association of not for profit Blood Establishments, with 23 members throughout the European Union and European Free Trade Association States (EFTA).

The EBA mission is to contribute to the availability, quality, safety and cost-effectiveness of the blood and tissue supply, as indispensable therapy to help patients, based on the public and professional awareness of voluntary and unpaid donation of blood and blood components. As well as assisting blood establishments to improve and promote collaboration between European blood services. .

EBA has been involved in some of the above mentioned projects such as EuBIS, DOMAINE and EU-Q-Blood-SOP, as well as workshops, such as platelet supply chain management.

EBA is registered on the Joint Transparency Register.[41]

4.1.1.2 The European Directorate for the Quality of Medicines and HealthCare (www.edqm.eu)

The European Directorate for the Quality of Medicines and HealthCare (EDQM) is a Directorate of the Council of Europe (CoE), an inter-governmental organisation of 47 Member States. Among several duties, the EDQM is in charge of the Secretariat of the European Pharmacopoeia Commission that elaborates the European Pharmacopoeia, an integral part of the European medicines regulatory framework. The EDQM comprises several departments some of which are directly contributing to the quality and safety of blood, blood components and medicinal product derived from human blood or plasma:

- the European Pharmacopoeia Department (EPD)
    - Secretariat of the European Pharmacopoeia Commission elaborating the European Pharmacopoeia, a legally binding instrument for quality and safety requirements for medicinal products including those derived from human blood or plasma.
- the Biological Standardization, Official Medicines Control Laboratories (OMCL) and HealthCare Department (DBO)
    - Secretariat of the European Committee on Blood Transfusion (CD-P-TS) elaborating the "Guide to the Preparation, Use and Quality assurance of Blood Components"

[41] http://ec.europa.eu/transparencyregister/public/consultation/displaylobbyist.do?id=14985501062 1-40&isListLobbyistView=true

describing harmonised guidelines for blood transfusion to be used by health authorities, blood establishments and hospital blood banks in the 37 Member States Parties to the European Pharmacopoeia Convention of the Council of Europe
    - Operates the Biological Standardization Programme that contribute to the European Pharmacopoeia by establishing standardised analytical methods and official European Pharmacopoeia Biological Reference Preparations for products derived from human blood or plasma
    - Coordinates the Official Medicines Control Laboratory Network
- Laboratory Department (DLab)
    - Establishes official European Pharmacopoeia Reference Standards

The EDQM/CoE promotes public health by setting provisions for legally binding standards for medicines throughout their entire shelf life and by developing common guidelines in the areas of blood transfusion to be used by health authorities, blood establishments and hospital blood banks.

4.1.1.3 Competent Authorities

All Member States have designated Blood Competent Authorities as required by Article 4 of Directive 2002/98/EC. This report took account of the national competent authorities' responses to the mandatory EU reports on the application of the Blood Directives and on the promotion of voluntary unpaid donations.

4.1.2 Stakeholders involved in the plasma for fractionation and plasma derived medicinal products sector

4.1.2.1 Plasma Protein Therapeutics Association

Plasma Protein Therapeutics Association (PPTA) identifies itself as the primary advocate for the world's leading source of plasma collectors and producers of plasma-based and recombinant biological therapies. The PPTA headquarter is located in Annapolis, USA and the European branch is located in Brussels, Belgium.

PPTA promotes the availability and access to safe and effective plasma protein therapeutics. The association cooperates with patient groups, policymakers, regulatory agencies and other stakeholders. A main goal is to bring together industry experts for quality, safety and efficacy improvement of plasma therapeutics.

The PPTA members are related to different regional associations such as to global members, European members, North American members, source members or associated members. The European members are:

- Baxter Healthcare SA
- Biotest AG

- CSL Behring GmbH
- Grifols International, SA
- Kedrion SpA

The PPTA members are large and international actors which produce more than 60 percent of the plasma protein therapies manufactured in Europe.[42]

4.1.2.2 International Plasma Fractionation Association

The International Plasma Fractionation Association (IPFA) represents not-for-profit organizations from 13 countries around the world involved in the collection of human blood and plasma based on voluntary non remunerated blood donation (VNRD) and in plasma fractionation. IPFA defines as its main priority to *maximise the availability of plasma recovered from whole blood donations, and* considers *the donations of plasma obtained via plasmapheresis techniques as an important and additional source of plasma for the manufacture of plasma-derived medicinal products*.[43].

The members are smaller actors with a typical focus within one country or market:

- Belgium Red Cross Central Fractionation Facility (CAF-DFC), Belgium
- Bio Products Laboratory, England
- Blood Source, USA
- L'Etablissement Français du Sang (EFS), France
- Hellenic National Blood Centre, Greece
- Héma-Québec, Canada
- Hemobras, Brazil
- Japanese Blood Products Organisation (formerly Japanese Red Cross Plasma Fractionation Centre) Japan
- LFB Biomédicaments, France
- National Bioproducts Institute, South Africa
- New Zealand Blood Service, New Zealand
- Sanquin Blood Supply Foundation, The Netherlands
- UNC Hemoderivados, Argentina

The IPFA supports its member organisations in their goal to secure a national supply of safe and high quality plasma products, for the benefit of patients in their communities. The association organises International Workshops on surveillance and screening of blood borne pathogens in different countries and is actively involved in many international meetings, organized by other stakeholders of the blood component and plasma product sectors.

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[42] http://www.pptaglobal.org/about-us/about-ppta, accessed 2014-05-06

[43] http://www.ipfa.nl/about-us, accessed 2014-05-06

4.1.2.3 Plasma Users Coalition

Plasma Users Coalition (PLUS) is a coalition of organisations, including:

- the European Haemophilia Consortium (EHC)[44]
  - Organization that gathers the European national haemophilia patient associations (National Member Organization) from 43 countries in Europe including all EU Member States and Turkey
- the World Federation of Hemophilia[45] (WFH)
  - A global network of patient organisations in 122 countries, officially recognised by the World Health Organization, that aims to improve and sustain care for people with inherited bleeding disorders around the world.
- the global organization IPOPI (International Patients Organization for Primary Immunodeficencies)
  - Association of national patient organizations from 50 countries, including 19 EU Member States plus Iceland and Norway, *dedicated to improving awareness, access to early diagnosis and optimal treatments for primary immunodeficiency (PID) patients worldwide.*[46]
- the HAEi (International Patient Organization for C1 Inhibitor Deficiencies)
  - Dedicated to raising awareness of C1 inhibitor deficiencies around the world. It is a non-profit international network of 27 national HAE patient Associations including 15 Member States plus Norway.[47]
- GBS/ CIDP Foundation International
  - Patients' organisation of 30,000 members in 33 countries aiming *to improve the quality of life for individuals and families worldwide affected by GBS (Guillain-Barré Syndrome), CIDP (Chronic Inflammatory Demyelinating Polyneuropathy) and variants*.[48]
- ITP Support Association,
  - Independent UK registered charity which *aims to promote and improve the general welfare of people with Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura).*[49]
- Alpha Europe

[44] http://www.ehc.eu/about-the-ehc.html, accessed 2014-05-06

[45] http://www.wfh.org/en/about-us, accessed 2014-05-06

[46] http://www.ipopi.org/, accessed 2014-05-06

[47] http://www.haei.org/, accessed 2014-05-06

[48] http://www.gbs-cidp.org/home/about/mission/ , accessed 2014-05-06

[49] http://www.itpsupport.org.uk/ , accessed 2014-05-06

- Patient-driven organization dedicated to identify individuals affected by Alpha-1 disease.

As mentioned above, in 2010, PLUS organized a conference in Dublin bringing together major stakeholders. The meeting led to the publication of the Dublin Consensus Statement[50], a set of principles in relation to blood and plasma collection globally. It sets out key principles in relation to patients, donors, cooperation between all the sectors and global utilization of donated blood and plasma. The three published Dublin Consensus statements are part of the documentation that PLUS has shared with us. Their analysis is included in the chapters below.

The PLUS Steering Committee organizes every year the annual PLUS (Platform of Plasma Protein Users) membership meeting to exchange information, share viewpoints on common issues and objectives and to review latest achievements.

4.2 Stakeholders' consultation

The stakeholders' consultation was conducted in two phases:

1. **A pre-questionnaire** was distributed to EBA, EDQM, WHO (Blood Transfusion Safety (BTS)), PPTA, IPFA and PLUS and served as support to express views regarding supply/availability of blood components and plasma derived medicinal products, product availability, differences in national health policies, implementation of a voluntary unpaid donation system, developments in the market for blood and plasma products, etc.
   These observations were laid out in their responses and supported by a number of confidential, proprietary and public documentation. (see appendix 1a)
   The first questionnaire was sent in April 2012 and responses were gathered in July 2012.
2. **An additional questionnaire** (content in table 1, see appendix 1b) was distributed to PPTA and IPFA targeting a number of topics specifically related to the landscape of the plasma sector in Europe. The second questionnaire was disseminated in October 2012 and responses were gathered in January 2013.

[50] Mahony B.O et al Dublin Consensus Statement 2010. Vox Sanguinis

Table 1 - List of topics addressed in the questionnaire

Voluntary unpaid donations	Aspects related to the voluntary unpaid donations of plasma for fractionation and donor remuneration.
Plasma collection	Aspects related to identification of plasma collection sources for plasma manufacturers (self-collection, agreement(s) with organizations, purchase system).
Plasma import/export	Aspects related to identification of plasma derived medicinal products exported, exporting countries and volumes exported.
Shortages	Aspects related to any insufficiency of supply of products, whether temporary or permanent and implementation of third party agreements.
Demand and need in IG	Aspects related to increasing demand and need of immunoglobulins (IG) due to the continuing growing number of clinical indications or for better access to existing indications.
Availability of clotting factors	Aspects related to the availability of recombinant and plasma derived factors and possible product waste.
Barrier to trade/restricted practices	Aspects related to barriers to trade/restricted practices due to governmental monopolies on certain products.
European regulations	Aspects related to European regulations in force. Impact on cost and accessibility

Furthermore, data from the survey conducted by the EDQM/CoE TSTS003 Working Party[51] on red blood cell (RBC) supply chain conducted in 2012 were kindly provided by EDQM/CoE and were used to prepare chapter 5.3.2 of this report.

The data relevant to the 27 EU Member States was extracted from this survey, analysed and structured with the fundamental help of EBA. Several face to face meetings and phone meetings were organized with all stakeholders to discuss the results of the consultation phase, examine the

[51] Blood Supply Management in Europe, Report of the TS003 Working Party, published by the EDQM/CoE (2013), in press

structure of the Executive Report and provide to all stakeholders the possibility to comment on the different drafts of the Executive Reports.

5. Survey results

5.1 Introduction

Blood components and plasma derived medicinal products are two widely used groups of therapies to save lives or to improve patient's quality of life that can only be obtained through blood and plasma donation.

In the United States, according to Pfuntner *et al*[52], *blood transfusion was the most common procedure performed during hospitalizations in 2011 (12 percent of stays with a procedure). The rate of hospitalizations with blood transfusion more than doubled since 1997* and *increased by 129 % for adults aged 18–44 years and 45–64 years, by 111 % for adults aged 65–84 years, and by 97 % for adults aged 85 years and older*.

Statistics on hospital-based care in the United States show that blood transfusions were given in one in every ten hospital admissions in which a procedure was performed, corresponding to a 140% increase from 1997, making transfusion the fastest growing common procedure in hospitals in the US.[53]

There are important differences between blood components and plasma derived medicinal products regarding collection, testing, processing and manufacturing, licensing, branding, distribution, clinical use, regulatory oversight, i.e. EU Directives and European Pharmacopoeia.

These differences result in a different management of the life cycle of these two groups of therapies.

- While blood and blood components are mainly held by public non-for-profit institutions and issued from voluntary unpaid donations, plasma derived medicinal products are mainly controlled by both not for profit and private organizations and plasma can be purchased in

[52] Pfuntner A. et al Most Frequent Procedures Performed in U.S. Hospitals, 2011, Agency for Healthcare Research and Quality. STATISTICAL BRIEF #165 HCUP;
http://www.hcup-us.ahrq.gov/reports/statbriefs/sb165.pdf

[53] Agency for Healthcare Research and Quality. HCUP Facts and Figures: Statistics on Hospital-Based Care in the United States, 2007. 2010. Rockville, MD, Agency for Healthcare Research and Quality.

an open market including from remunerated donors in Germany, Czech Republic, Austria and Hungary.[54]

- In general, blood and blood components are sourced and used locally whereas plasma derived medicinal products are sourced and distributed both locally and internationally.

Despite the differences outlined above, there are equally commonalities to both product groups, in particular as both product groups result from donations by human donor, and also as a significant part of plasma for fractionation is recovered from whole blood donations.

Considering the differences between both systems, the list of issues that were highlighted and discussed by the stakeholders is divided into 2 sections: issues related to blood and blood components and those related to plasma derived medicinal products.

Statements that voice the opinion of an organisation without referencing a published material will bear the following statement in the footnote: Statement from 'Organisation'.

5.2 Definitions

There is a strong need and demand by stakeholders to define and agree on commonly used terms that lack an official definition. To avoid misinterpretations and confusion around such terms, C-C and the involved stakeholders have made the effort to propose commonly accepted definitions.

These definitions are presented in this section as part of the results of both questionnaires and subsequent meetings with stakeholders.

5.2.1 Self-sufficiency

Regular and sufficient supply of blood components and plasma derived medicinal products is by far the biggest concern for all actors involved in making these products available for patients.

It is important to remember the following statement in the preamble, Recital (4) of Directive 2002/98/EC "…Member States should take measures to promote Community self-sufficiency in human blood or blood components…".[55]

[54] First Report from the Commission to the Council and the European Parliament on promotion by Member States of voluntary unpaid donations – COM (2006) 217 final

[55] Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003, p 30)

However, no definition of self-sufficiency has been established by European Regulators, making it difficult to answer questions addressing self-sufficiency in the Reports on Voluntary and Unpaid Donation of Blood and Blood Components.

So far, the only published definition for "self-sufficiency in safe blood and blood products" (based on voluntary unpaid blood donation) has been proposed by an expert panel of World Health Organization (WHO), as follows: "Self-sufficiency in safe blood and blood products (based on Voluntary Non Remunerated Blood Donation - VNRBD) means that the national needs of patients for safe blood and blood products, as assessed within the framework of the national health system, are met in a timely manner, that patients have equitable access to transfusion services and blood products and that these products are obtained from VNRBD of national, and where needed, of regional origin, such as from neighbouring countries".[56]

The means to achieve self-sufficiency in the blood and blood components may be different from that in the plasma derived medicinal products system.

Waller C et al. states in ''Blood, Plasma and Plasma Proteins: A unique contribution to modern healthcare – Volume 7'' that Europe is far from being self-sufficient in plasma. More than 50% of Europe's need for plasma-derived medicinal products comes from plasma donors in the USA.[57] This is in particular the case of UK (including Ireland) and Portugal where plasma collected in these countries is not used for fractionation or transfusion as a precautionary measure against the risk of variant Creutzfeld Jakob Disease transmission. It needs to be noted that this import from US plasma triggers concerns regarding quality and ethical principles in some EU Member States as plasma donors in the US are usually remunerated.

An update with newer more accurate data is needed to obtain a good analysis of supply and future needs in the EU.

Since 1994 and after the Adare meeting of European Ministers of Health Care, several documents have been issued by the European Council and the European Commission on self-sufficiency, aiming for Community self-sufficiency in blood and plasma products.[58]

Self-sufficiency has been achieved for blood components in most EU countries, but remains an aspirational goal for plasma derivatives in most countries. IPFA and EBA advocate the vitally

[56] WHO Expert Group. Expert consensus statement on achieving self-sufficiency in safe blood and blood products based on voluntary non remunerated blood donations (VNRBD). Vox Sanguinis 2012. 103:337-342

[57] Waller C. Historical Perspective on blood & plasma products, the stakeholders and the issues. In: Pharmaceuticals Policy and Law 7 (2005-2006) 7-19 (eds Valverde JL). IOS Press.

[58] Preamble, recitals (6) and (7) of Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003)

important contribution of recovered and source plasma from EU blood establishments in meeting the national and regional needs of patients in the EU and considers that EU policies should continue to reinforce the need to maximise the availability of this strategically important resource from VUD within the EU and minimise its dependence on imports from US donors.[59]

At the same time European governments should focus on implementing policies that enables patient diagnosis (especially of rare conditions) and access to treatment in accordance to state of the art clinical guidelines in order to meet patients' clinical needs.

5.2.2 Shortages

When mentioned, the term "shortage" was one of the most debatable terms among all interviewed stakeholders.

It needs to be noted that no legal definition of "shortage" and "regular shortage" has been established which makes ti difficult to address related questions. Several stakeholders recommend that such definitions should be established.

The EBA recommended that, for blood components, the definition of "shortage" could be based on that provided by national shortage plans (e.g. UK), which, based on potential consequences for patients, distinguishes serious and critical shortages with definitions as follows.

- Serious blood shortage ("amber phase" of the shortage plan): the blood inventory is insufficient to continue with routine transfusion practices and hospitals/Health Authorities will be required to implement specific measures, in order to reduce blood usage (mainly for elective surgeries).
- Critical blood shortage ("red phase" of the shortage plan): blood inventory levels are insufficient to ensure that patients with non-elective indications for transfusion will receive the required transfusion(s).

Along the same line, IPFA recommends a clear definition of the term "shortage" identifying the parameters needed to measure self-sufficiency and shortages.

Based on differences in health care policies and the lack of a pan-European consensus on the treatment of patients who suffer from a disease which can be treated with plasma derived

[59] Rossi et al. How expanding voluntary non-remunerated blood donations would benefit patients, donors and healthcare systems? Vox Sang. 2011, 102: 269-70

medicinal products, the treatment differ between Member States. The term "shortage" should not be confused with these differences in treatment level.[60]

All organisations, except PPTA, agreed that the term "shortage" covers collection, production, distribution and availability of products to end users. PPTA also highlighted the lack of definition of this term for the plasma sector and suggested instead the definition from the Food and Drug Administration (FDA): *a product shortage occurs when a product is not commercially available in sufficient quantity to meet the demand*[61]:

5.2.3 The principle of voluntary and unpaid (VUD) donations

5.2.3.1 VUD in blood and blood components

The principles governing voluntary and unpaid donation of blood and blood components are set out in Article 20 (1) of Directive 2002/98/EC. It states that Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensure that blood and blood components are provided from such donations to the extent possible.

It is important to remember the following statements in the Recitals (20) and (23) of Directive 2002/98/EC:

- (20) "Modern blood-transfusion practice has been founded on the principles of voluntary donor services, anonymity of both donor and recipient, benevolence of the donor, and absence of profit on the part of the establishments involved in blood transfusion services".
- (23) Voluntary and unpaid blood donations are a factor which can contribute to high safety standards for blood and blood components and therefore to the protection of human health. The efforts of the Council of Europe in this area should be supported and all necessary measures should be taken to encourage voluntary and unpaid donations through appropriate measures and initiatives and through ensuring that donors gain greater public recognition, thereby also increasing self-sufficiency. The definition of voluntary and unpaid donation of the Council of Europe should be taken into account".

The Council of Europe definition of "voluntary non-remunerated donation" (Recommendation No. R (95) 14)[62] has been endorsed by the European Union, World Health Organization, International

[60] Statement by IPFA

[61] http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm

[62] Article 2 of RECOMMENDATION No. R (95) 14 OF THE COMMITTEE OF MINISTERS TO MEMBER STATES ON THE PROTECTION OF HEALTH OF DONORS AND RECIPIENTS IN THE AREA OF BLOOD TRANSFUSION (Adopted by the Committee of Ministers on 12 October 1995 at the 545th meeting of the Ministers' Deputies);

https://wcd.coe.int/com.instranet.InstraServlet?command=com.instranet.CmdBlobGet&InstranetImage=536539&SecMode=1&DocId=527032&Usage=2

Society of Blood Transfusion, International Federation of Red Cross and Red Crescent Societies and International Federation of Blood Donor Associations. :

"Donation is considered voluntary and non-remunerated if the person who gives blood, plasma or cellular components of his/her own free will and receives no payment for it, either in the form of cash or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation".

It is fundamental to underline that the promotion of voluntary unpaid donations is based, not only on safety issues, as reminded in the Directive 2002/98/EC, but also on ethical principles. The European Convention on Human Rights and Biomedicine of 1997 ("Oviedo Convention")[63], ratified by 16 EU countries, "prohibits any financial gain from the human body and its parts". The "prohibition on making the human body and its parts as such a source of financial gain", has further clearly been integrated in the Nice Charter of Fundamental Rights of the European Union.[64]

5.2.3.2 VUD in plasma

Article 20 of Directive 2002/98/EC states that Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations.

Moreover, Article 110 of Directive 2001/83/EC[65] (Community Code relating to medicinal products for human use) lays down that Member States should encourage the production and use of products derived from human blood or human plasma coming from VUD.

Nevertheless, PPTA and PLUS imply that whole blood collections should be ensured by a voluntary and unpaid system whereas plasma for fractionation collected through plasmapheresis as well as other blood components collected through aphaeresis (e.g. platelets) would not be included in this definition.

[63] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine**,** Oviedo, 4.IV.1997 http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm

[64] http://www.europarl.europa.eu/charter/pdf/text_en.pdf , accessed 2013-07-24

[65] Directive 2001/83/EC of the European parliament and of the Council of 6 of November 2001 on Community code relating to medicinal products for human use (OJ L 311, 2811.201, p 67)

5.2.3.3 Incentives, compensations and payments related to blood/plasma collection

The principle of voluntary and unpaid donations does not exclude compensation for donors, if it is compliant with the definition of VUD, as laid out above. Most reporting countries have some form of incentive structures for blood donors.

The principle of using incentives to recruit, retain and recognise donors is recognised by the Member States, yet its concrete interpretation differs across. Thus, among the incentives mentioned in the European Commission reports on VUD, it is unclear which incentives are considered to constitute a payment for donations.[66,67]

As stated above, the distinction between paid and unpaid donation remains imprecise in Europe. In USA however, this question was addressed by the Food and Drug Administration in 1978, which issued Guidance *for FDA Staff and Industry Compliance Policy*[68] in a Federal Notice requiring that blood and blood components intended for transfusion include a donor classification statement on the labels to indicate whether the products were collected from paid or volunteer donors.

The guidance defines a "paid donor" as a person, who receives monetary payment for a blood donation and volunteer donor who does not receive monetary payment for a blood donation and benefits that do not constitute monetary payment. According to the guidance, time off from work, event tickets and replacement fee are not considered benefits as long as they are not readily convertible to cash. How these labels are applied is defined in the Code of Federal Regulations. [69]

5.2.3.4 Compensations versus payments

Sixteen countries (Belgium, Bulgaria, Estonia, Finland, France, Germany, Greece, Italy, Lithuania, Luxembourg, the Netherlands, Poland, Romania, Spain, Slovakia and the United Kingdom) previously reported “some form of guiding principles concerning the possibility of giving incentives to donors of blood and blood components”.[70]

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[66] First Report from the Commission to the Council and the European Parliament on promotion by Member States of voluntary unpaid donations – COM (2006) 217 final

[67]2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

[68] Guidance for FDA Staff and Industry Compliance Policy Guides Manual Sec. 230.150 Blood Donor Classification Statement, Paid or Volunteer Donor 1978 (43 FR 2142)

[69]Code of Federal Regulations, Title 21, Volume 7, revised as of April 1, 2013, 21 CFR 606.121(c)(5);

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=606.121

[70]2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

Incentives mentioned in the 2nd report on VUD are as follows:

- Reimbursement of medical costs
- Compensation linked to loss of earnings
- Food vouchers
- Free physical check-up
- Time off work (private sector)
- Time off work (public sector)
- Reimbursement of travel costs
- Small tokens
- Refreshments
- Other forms of incentives

Clarifying the issues mentioned above would greatly help in both assessing the VUD practices and reducing the risks of polemics and complaint about the interpretation of data. One approach could be the one presented in the Nuffield Council on Bioethics report on "*Human bodies: donation for medicine and research"(*2011), [71] provided specific terminology and the "intervention ladder" regarding transactions made in connection with human bodily material, including blood and plasma:

- *"Payment:* a generic term covering all kinds of transactions involving money, and goods with monetary value, whether those transactions are understood as recompense, reward or purchases;
- *Recompense* is a payment to a person in recognition of losses they have incurred, material or otherwise. This may take the form of either *reimbursement* of direct financial expenses incurred in donating bodily material (such as train fares), or *compensation* for non-financial losses (such as inconvenience, discomfort and time).
- *Reward* is a material advantage gained by a person as a result of donating bodily material, which goes beyond "recompensing" the person for the losses they incurred in donating. If reward is calculated as a wage or equivalent it becomes *Remuneration*. A *purchase* is a payment in direct exchange for a "thing" (a commodity).
- *Remuneration*. A purchase is a payment in direct exchange for a "thing" (a commodity).
- *Purchase:* payment in direct exchange for a 'thing' (e.g. a certain amount for a kidney, or per egg)".

EBA recommended using the terminology developed by the Nuffield Council the "Intervention ladder" scheme. The review of ethical principles and the proposed terminology about transactions of human bodily materials led the Nuffield Council to envisage shifting the attention away from the paid/unpaid donation dilemma towards making a distinction between altruistic and non-altruistic interventions. With the aim of seeking areas of shared consensus on what can be done by

[71] http://www.nuffieldbioethics.org/sites/default/files/Donation_full_report.pdf

institutions and organisations to "facilitate" donation of human bodily material (such as blood and plasma), the Nuffield Council suggested an 'Intervention Ladder' as a useful tool for analysing the ethical acceptability of different forms of encouragement for donating bodily material in various circumstances. The ladder defines six levels, levels one to four are considered altruistic, whereas five and six are non-altruistic:

1. *Information about the need for the donation of bodily material for others' treatment or for medical research;*
2. *Recognition of gratitude for altruistic donation, through whatever methods are appropriate both the form of donation and the donor concerned*
3. *Interventions to remove barriers and disincentives to donation experienced by those disposed to donate*
4. *Interventions as an extra prompt or encouragement for those already disposed to donate for altruistic reasons*
5. *Interventions offering associated benefits in kind to encourage those who would not otherwise have contemplated donating to consider doing so*
6. *Financial incentives that leave the donor in a better financial position as a result of donating*

The Nuffield Council on Bioethics does not consider that refunding expenses involved in donation or providing minor tokens as a "spur" to donation involve ethical compromises in a way that information campaigns or letters of thanks do not.[72,73]

The comparison of each of the six "rungs" of this "*Intervention Ladder*" with the above-mentioned CoE definition of VUD[74] shows that rungs 1-4 (encompassing, for example, information campaigns, letters of thanks, small tokens, refreshments and reimbursements of direct travel costs incurred in donating), having been classified as altruist-focused, are interpreted by EBA as fully compatible with the CoE definition whereas on the other hand, rungs 5-6 (encompassing payment either in the form

[72] Nuffield Council on Bioethics. Human bodies: Donations for medicine and research. Chapter 6. Actions affecting individuals.

[73] http://www.nuffieldbioethics.org/sites/default/files/files/Donation_Chapter6_Recommendations_affecting_individuals.pdf , accessed 2013-07-24

[74] Article 2 of RECOMMENDATION No. R (95) 14 OF THE COMMITTEE OF MINISTERS TO MEMBER STATES ON THE PROTECTION OF HEALTH OF DONORS AND RECIPIENTS IN THE AREA OF BLOOD TRANSFUSION (Adopted by the Committee of Ministers on 12 October 1995 at the 545th meeting of the Ministers' Deputies);

https://wcd.coe.int/com.instranet.InstraServlet?command=com.instranet.CmdBlobGet&InstranetImage=536539&SecMode=1&DocId=527032&Usage=2

of cash or in kind, which could be considered a substitute for money), having been classified as non-altruist-focused, clearly do not comply with the CoE definition.[75]

The PPTA suggested that compensated plasma donation fits with level 3 while some blood donation activities in Europe are best aligned to level 5.

This and other models could be explored and assessed.

Intensive academic research in Italy and Greece, for example, has shown that not offering days off work would act as a strong disincentive and result in lower blood inventories.[76].

While some studies have shown a negative economic and psychological impact from paying for blood donations which may reduce the number of blood donors in long term[77,78], others contradict this conclusion.[79]

Recent discussions with IPFA, PPTA, and also the Committee on Bioethics of the CoE (DH-BIO) and Ethics and Health Team of WHO tend to indicate that such a consensus could be reached.

Finally, it needs to be reminded that different possible interpretations and understandings of terms like compensation, incentives, remunerations or payments add a lot of confusion to already sensitive and political debates.

For the sake of the 3rd Commission report on VUD, due in 2015, following definitions were used:

- Compensation: a reparation strictly limited to making good the expenses and inconveniences related to the donation
- Incentive: an inducement/stimulus for donation with a view to seeking financial gain or comparable advantage (going beyond compensation)

[75] Folléa et al. Renewed considerations on ethical values for blood and plasma donations and donors. Blood Transfus [Epub ahead of print] DOI 10.2450/2013.0011-13

[76] Lacetera et al. Time for Blood: The Effect of Paid Leave Legislation on Altruistic Behavior (J Law Econ Organ 2012) doi:10.1093/jleo/ews019, Tranfus Med 2007;17:443-450)

[77] Frey BS et al Motivation crowding theory: A survey of the empirical evidence. J Econ Surv. 2001;15:589–611

[78] Ariely D et al. Doing good or doing well? Image motivation and monetary incentives in behaving pro socially. Am Econ Rev. 2008;99:7–9

[79] Lacetera N, Macis M. Incentives for altruism? The case of blood donation. Research-based policy analysis and commentary from leading economists. 2008. Nov. http://www.voxeu.org/index.php?q=node/2512, accessed 12-05-2014.

5.2.4 Barrier to trade/Restricted practices

PPTA recognised the presence of barriers to trade within EU which consist in a practice whereby support for one product comes from profits generated by another product. Therefore a subsidized product would be offered on better terms than would otherwise be possible, typically at a lower price. Cross-subsidization, especially when engaged in by government monopolies, is widely regarded by PPTA, as reducing price transparency.

IPFA recognised that arrangements exist for profit and for not-for-profit organisations in some EU countries in which domestically collected plasma from voluntary donors is processed into plasma derivatives for use in the country of origin aiming to ensure safety and quality. The public need for a guarantee of a national supply for these essential products may result in plasma supply costs higher than those of the global plasma market.

5.3 Blood and blood components supply chain

5.3.1 Introduction

Outcomes regarding shortages (Section 5.3.3) and Voluntary unpaid blood donations mainly came from the second EC report on VUD[80]. Outcomes regarding donor Management Programs (Section 5.3.4) mainly came from the DOMAINE survey and manual[81], and from the EDQM/CoE reports on the collection, testing and use of blood components for 2009 and 2010. Outcomes on systems to prioritize indications and optimise blood and blood component use mainly came from the EDQM/CoE reports on the collection, testing and use of blood components for 2009 and 2010 (Section 5.3.6).

5.3.2 Blood supply management chain organisations and practices in the EU

This report on blood supply management chain organisation and practices in the EU[82] was prepared by extracting and compiling data collected during the survey organized by the TS003 Working Group "Blood Supply Management" of the European Committee (Partial Agreement) on Blood Transfusion of the Council of Europe. Data from the European Commission Implementation Survey in 2013 is also

[80] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

[81] http://www.domaine-europe.eu/Manual/tabid/56/Default.aspx , accessed 2013-07-24

[82] TS003 – Abridged Report of the Survey Limited to the EU Member States, CD-P-TS, Council of Europe, June 2013

included.[83] The authors of this report did not verify or assess the methodology of data collection and extraction within these surveys.

5.3.2.1 Introduction

All countries face challenges in making sufficient supplies of blood and blood products available and sustainable, while also ensuring the quality and safety of these products in the face of known and emerging threats to public health.[84]

5.3.2.2 Blood supply chain organisations and practices in the EU

5.3.2.2.1 Blood supply management assessed as a real process

In hospital, patients mostly are at the heart of transfusion medicine activities, all aiming at providing them with the missing vital blood component(s). This patient-centred vision leads to conceiving all transfusion medicine activities as a "blood supply chain", starting with patients' needs and ending with transfusion of needed blood components to patients. This blood supply chain comprises two main sectors: the hospitals – where transfusion is ordered by clinicians and administered to patients; and the suppliers, acting from donor management to blood component distribution, usually blood establishments (BE).

Cooperation between hospitals and BEs for transfusion related matters is vital to ensure that the healthcare professionals and patients are satisfied with the products and services provided by the Blood Establishments.

Although optimising blood utilisation greatly impacts both patient safety and blood supply security, the blood supply management (BSM) itself is the top mission exerted both by BEs, supplying blood components, and hospitals, storing, issuing, prescribing and transfusing blood components to patients, to make safe blood supply available for patients. This subject has been investigated by a working group (TS003 WG) of the European Committee (partial agreement) on blood transfusion (CD-P-TS), with the objective of helping countries to assess and improve their BSM, focusing on red blood cell concentrates (RBC).

A major outcome from TS003 WG was to conceive the BSM as a real process with the following steps for RBC supply management:

[83] Third Report on the application of Blood Directive 2013 – to be published

[84] Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD) – WHO report. Vox Sang. 2012, 103: 337-42. DOI: 10.1111/j.1423-0410.2012.01630.x

1. Assess past hospital RBC use for patients;
2. Establish a forecast for overall annual supply (BEs) and use (hospitals);
3. Establish annual blood collection program (BEs);
4. Weekly balance RBC use and supply in both BEs and hospitals;
5. Review and update the patients' RBC needs and their satisfaction.

This process has been used as a basis to elaborate a questionnaire to investigate each step of the BSM process in the Council of Europe countries, and Council of Europe observers (Australia, Canada, New Zealand and USA). The survey was conducted in 2012 at the country level, through persons designated to the Council of Europe by each country Authorities. As systemically done by the Council of Europe for its surveys, all data have been checked by countries. The full results of the survey will be published later, but the main outcomes for the 27 EU countries -all have responded- are presented below.

5.3.2.2.2 Blood supply chain organisations in the EU

In 2012, the 28 EU Member States plus Norway and Lichtenstein reported a total of 1,363 blood establishments, 731 satellite and 534 mobile sites on their territories.[85]

The general questions of the TS003 survey led to identify three main types of countries' organisations of blood supply chain.

- 7 countries (26 %) in which one National BE collects, manufactures and distributes all the blood components to hospital blood banks in which they are stored and then issued to patients in response to orders from clinicians: FI, FR, HU, IE, LU, MT, NL;
- 4 countries (15 %) in which the transfusion activities are all included in hospitals that are responsible for all activities from donors to patients: DK, EE, IT, SE. Competition between hospital based suppliers takes place only in SE, not in the 3 other countries;
- 16 countries (59 %) in which the organisation comprises a mix of the bodies described above: AT, BE, BG, CY, CZ, DE, ES, GR, LT, LV, PL, PT, RO, SI, SK, UK. In seven of these countries (AT, BG, CZ, DE, LT, PT, SK) variable proportions of the RBC supply (ranging from 13 % to 92 %) come from hospital based BEs.

In the 16 countries with more than one RBC supplier, competition between different suppliers takes place in Austria and Lithuania. As a whole, competition between RBC suppliers is observed in only 5/27 (18.5 %) countries.

[85] Third Commission Report on the implementation of Blood Directives, 2013 – to be published

23/27 (85 %) EU countries have nationally coordinated blood and plasma programmes. 22/27 (81.5%) EU countries have nationally coordinated "vein to vein" (donor to patient) integrated blood supply management process.

In all EU countries, blood transfusion therapy (costs of blood components) is Government / Public Health insurance funded, although mixed funding (e.g. private insurance) could exist in a few countries.

5.3.2.2.3 Assessment of past hospital RBC use for patients

WB / RBC use was monitored in all EU countries. This was assessed as either WB/RBC units transfused, in 11 countries (40.7 %), and WB/RBC units distributed by BE to hospitals, in 16 countries (59.3 %) in which the number of transfused units was not available. Monitoring of WB / RBC annual use was performed at national level in 26 countries (17 countries used an IT-based system for this monitoring), and annual use trends have been analysed in the last past years in 21 countries (77.8 %). This monitoring and analysis involved governmental body (ies) in 21 countries (77.8 %). The data monitored at national level and their analyses were published by 17 countries (63 %).

5.3.2.2.4 Forecast for overall annual supply (BEs) and use (hospitals)

A WB / RBC annual supply forecast was established in 19 countries (70.4 %). A WB/RBC annual use forecast was established in 16 countries (59.3 %). A reconciliation of WB / RBC annual use and supply forecasts was operated in 14 countries (51.9 %). This reconciliation was operated at national level in 10 countries (37.0 %).

5.3.2.2.5 Annual blood collection programmes (BEs)

22 countries established blood collection/supply programmes, including the expected numbers of units collected for every moment and location, were established in 22 countries (81.5 %). The blood collection/supply programmes were prepared on an annual basis for the next year in 18 countries (66.7 %).

5.3.2.2.6 Weekly balance RBC use and supply in both BEs and hospitals

(a) On the BE/supplier side

Regularly balancing WB/RBC use and supply implies to regularly monitor WB/RBC inventories, and to regularly assess (per day, week, month) WB/RBC collected, WB/RBC units distributed to hospitals in the service area(s), RBCs expired/outdated in the BE(s), and other losses in the BE part of the supply chain. To streamline this balancing process, it is important to pre-determine "normal range" for inventories and to define in advance ways to adapt in case of expected shortage or excess, and also to prevent the occurrence of such situations.

The WB/RBC inventories were monitored:

- With the total number of RBCs in inventory, in 25 countries (92.6 %);
- With RBCs in inventory classified by RBC type (e.g. paediatric, irradiated, CMV negative, washed) in 17 countries (63.0 %);
- With RBC inventory classified by age in 14 countries (51.9 %).

WB/RBCs collected were monitored in 23 countries (85.2 %). WB/RBCs distributed to hospitals in the service area(s) were monitored in 20 countries (74.1 %). WB/RBCs expired/outdated were monitored in 19 countries (70.4 %).

Limits for WB / RBC in inventories have been determined:

- For normal range in 24 countries (88.9 %);
- For shortage in 22 countries (81.5 %);
- For excess in 16 countries (59.3 %).

Where determined the inventory limits varied widely from country to country. An IT-based system was used to monitor WB / RBC inventories in 20 countries (74.1 %). SOPs for the management of the stock supplying process were available:

- For regular situations, to maintain adequate inventory levels in 20 countries (74.1 %); regular calculation and forecast of the WB / RBC inventory for a specified period in the future (estimate in the future, based on present data and trends) were implemented in 16 countries (59.3 %);
- For shortage situations, with description of measures to replenish inventory up to adequate levels, in 19 countries (70.4 %);
- For excess situations, with description of measures to keep inventory within adequate levels in 12 countries (44.4 %).

Procedures to prevent a foreseeable shortage from their forecast were available in 15 countries (55.6 %). Procedures to prevent a foreseeable excess from their forecast were available in 14 countries (51.9 %).

(b) On the hospital side

Regularly balancing WB/RBC use and supply implies to regularly monitor WB/RBC inventories, and to regularly assess (per day, week, month) WB/RBC entries in inventories, issues for patients and losses (mainly RBCs expired/outdated in the hospital). To streamline this balancing process, it is important to pre-determine "normal range" for inventories and to define in advance ways to adapt in case of expected shortage or excess, and also to prevent the occurrence of such situations.

The WB/RBC inventories were monitored:

- With the total number of RBCs in inventory, in 20 countries (74.1%);
- With RBCs in inventory classified by RBC type (e.g. paediatric, irradiated, CMV negative, washed) in 11 countries (40.7 %);
- With RBC inventory classified by age in 10 countries (37 %).

WB/RBCs supplied by the BE/supplier were monitored in 13 countries (48.1 %). WB/RBCs issued for patients were monitored in 13 countries (48.1 %). WB/RBCs expired/outdated were monitored in 14 countries (51.9 %).

Limits for WB / RBC in inventories have been determined:

- For normal range in 21 countries (77.8 %);
- For shortage in 21 countries (77.8 %);
- For excess in 12 countries (44.4 %).

Where determined the inventory limits varied widely from country to country. An Information technology (IT) -based system was used to monitor WB / RBC inventories in 15 countries (56.6 %). A computerized vendor management system was used to automatically trigger the replenishment of hospital inventories in 5 countries (18.5%) for a percentage of hospitals in the country varying from ca 20% to more than 85%. Standard Operating Procedures (SOPs) for the management of the stock supplying process were available:

- For regular situations, to maintain adequate inventory levels in 16 countries (59.3 %); regular calculation and forecast of the WB / RBC inventory for a specified period in the future (estimate in the future, based on present data and trends) were implemented in 6 countries (22.2 %).
- For shortage situations, with description of measures to replenish inventory up to adequate levels, in 13 countries (48.1 %);

- For excess situations, with description of measures to keep inventory within adequate levels in 9 countries (33.3 %).

Procedures to prevent a foreseeable shortage from their forecast were available in 4 countries (14.8 %). Procedures to prevent a foreseeable excess from their forecast were available in 4 countries (14.8 %).

(c) Cooperation between BEs and hospitals

Cooperation between BEs / RBC suppliers and hospitals concerned:

- Exchange of blood inventory and blood demand data in 21/27 countries (77.8 %);
- Analysis of blood inventory and blood demand data in 17/27 countries (63.0 %);
- The process of regularly balancing the use / demand and supply in 13/27 countries (48.1%);
- SOPs in 11/27 countries (40.7 %)
- IT systems in 11/27 countries (40.7 %).

When existing, the collaboration between BEs / RBC suppliers and hospitals was active at the following levels:

- Local, in 21/27 countries (77.8 %);
- Regional, in 17/27 countries (63.0 %);
- National, in 11/27 countries (40.7 %). A national effective coordination of BSM could be found in countries with any of the three organisation types (see 3.3.2.2): one national BE, 100 % hospital based BEs, mixed BEs. A “vein to vein” IT system covering the entire blood supply chain appeared to be of major importance to achieve such national coordination of BSM.

National contingency plans for blood supply management in special circumstances (e.g. earthquakes, pandemics, floods, wars, heat waves, financial/economic/political crises) were existing in 25/27 countries (92.6 %). All countries but three (IT, MA, SI) indicated Government/Ministry of Health/Competent Authority as institutions responsible for contingency planning.

5.3.2.2.7 Review and update the patients’ RBC needs and their satisfaction

Blood product needs for patients were assessed and updated annually in 22/27 countries (81.5 %). This assessment was made at national level in 12/27 countries (44.4 %). Hospital transfusion committees and BEs were the institutions most frequently mentioned as involved in this assessment. Methods used to assess and update the patient’s blood product needs were a regular review of evaluations of RBC transfusion settings (e.g. scientific studies, new/updated guidelines) in 13/27 countries (48.1 %), and/or reference to national guidelines in 13/27 countries (48.1 %).

Satisfaction of needs and/or demand of RBC for patients was assessed in 17/27 countries (63 %). In countries practicing such assessment, the indicators used to assess satisfaction of needs and/or demands of RBC for patients were as follows.

- Reviewing/benchmarking RBC ordering and use by clinics in 13/27 countries (48.1 %);
- Monitoring the unmet demand (requests), in 13/27 countries (48.1 %);
- Postponed transfusions (delays), in 10/27 countries (37.0 %)
- Cancelled surgeries, in 5/27 countries (18.5 %);
- Need to import RBC, in 4/27 countries (14.8 %);
- Export of RBC, in 3/27 countries (11.1 %).

To the question on assessment of self-sufficiency for WB / RBC (meeting the patient's need), 20/27 countries (74.1 %) responded they were 100% self-sufficient, 3/27 countries (11.1 %) responded they were less than 100 % self-sufficient (CY, GR, RO), and 2/27 countries (7.4 %) they were over 100 % sufficient (FI, IE).

25/27 countries (92.6 %) indicated they decided on actions in case of deficit or surplus of WB/RBC. In these countries, the decision on actions was made at local level in 14/27 countries (51.9 %), at regional level in 17/27 countries (63.0 %), at national level in 18/27 countries (66.7 %). The main institutions mentioned as involved in such decision making were BEs and hospitals. Major examples of such decisions/actions taken in the last 3 years were as follows.

- Development and implementation of transfusion guidelines for optimizing blood use at national level, in 16/27 countries (59.3 %);
- Development of training programme for clinicians/nurses for optimising blood use at national level, in 16/27 countries (59.3 %);
- Actions to benchmark the blood use between hospitals in order to reduce consumption, in 10/27 countries (37.0 %).

An assessment of the percentage of WB/RBC origin from VNRBD (according to the Council of Europe definition) was performed or available in all EU countries. The percentage of WB/RBC from VNRBD was assessed as 100 % in 23/27 countries (85 %) and less than 100 % in 4/27 countries (15 %), BU, GR, LT, PO.

Most frequent major decisions/actions taken to improve the Blood Supply Management effectiveness and efficiency in the next 3 years were: developing nationally coordinated programmes, developing IT systems, improving BE – hospital collaboration.

5.3.2.2.8 Good practices of blood supply management

A symposium organised by the Council of Europe with interested parties in October 2012 has allowed the presentation and discussion of the main results of the study, with experts from the 39 participating countries (the results presented above were limited to the EU countries). This

symposium also provided an opportunity to evaluate the validity of the use of the TS003 questionnaire, combined with a SWOT (strengths, weaknesses, opportunities and threats) analysis, to self-assess the current status of the Blood Supply Management in a given country. This was done in 8 countries (7 EU: ES, FI, FR, IE, PT, RO, UK), and gave rise to presentations prepared for each country according to a common template containing the following items: general organisation of Blood Supply Management, main strengths, weaknesses, threats, opportunities and recommendations as "good practice in Blood Supply Management". The method was much appreciated by both the speakers who used it and the attendants.

From this experience, a major outcome from the symposium was to recommend the use of the TS003 questionnaire, after a few modifications, as a self-assessment tool to evaluate current situation of Blood Supply Management, deduce corrective measures for improvement and assess the implemented measures. [86]

Another major outcome from the symposium agreed by all participants was the strong encouragement to look for practical modalities to improve collaboration between hospitals and BEs, as a key factor for continuous improvement of Blood Supply Management. The follow up work after the symposium is expected to lead to a Council of Europe manual on Blood Supply Management with the following content: i) Finalised results of the survey; ii) Report of the symposium; iii) International "good practices of BSM"..

5.3.3 Shortages

Despite some successes, self-sufficiency is not yet a reality in many countries or regions. The 2nd Report on Voluntary and Unpaid Donation of Blood and Blood Components from the European Commission mentions that although 22 countries have national policies for self-sufficiency of blood and blood components, only 13 of them have defined the concept of self-sufficiency (Austria, Bulgaria, Czech Republic, Cyprus, France, Hungary, Italy, Malta, Portugal, Romania, Spain, Sweden and Croatia). [87]

With regard to shortages, because of the lack of a definition as pointed out in this report and by the EBA, for "shortage", the data from the 2nd Report on VUD should be taken with caution.

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[86] http://www.edqm.eu/en/Projects-1449.html?aMotsCles=a%3A1%3A%7Bs%3A0%3A%22%22%3Ba%3A1%3A%7Bi%3A0%3Bs%3A5%3A%22ts003%22%3B%7D%7D

[87] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

The 2nd Report on VUD had singled out:

- 4 countries that experienced 'regular shortages' in whole blood (CY, EE, SE, HR)
- 3 countries that experienced 'regular shortages' in red blood cells (CY, SE, HR)
- 2 countries that experienced 'regular shortages' in platelets (CY, BG)
- 1 country that experienced 'regular shortages' for fresh frozen plasma (CY)

When these shortages were experienced, quantities needed and consequences for patients were not mentioned.

For further information on shortages from the EDQM/CoE TS003 survey please see section 5.3.2.

5.3.3.1 Introduction

The second report on VUD provided an overview of the legislative provisions/guidelines and policies as depicted:[88]

- 24 MS have binding rules concerning voluntary and unpaid blood donation, laid down in national regulations (Austria, Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Poland, Romania, Slovenia, Slovakia, Spain, Sweden, Norway and Croatia).
- 2 MS: Hungary and the UK have a dual system with binding rules laid down by national regulations and rules set by the sector (self-regulatory), and
- 1 MS: Malta, binding rules concerning voluntary and unpaid blood donation are set by the sector (self-regulatory),
- 1 MS: The Czech Republic has a non-binding declaration in its national law (in line with Directive 2002/98/EC),
- 1 MS: Ireland has no legislative provisions or guidelines governing the principle of voluntary and unpaid donation of blood and blood components.

These legal provisions and guidelines appear to have remained relatively stable over time. Since 2006, when the 1st Report on the promotion by MS of VUD was issued by the Commission, Czech Republic, Croatia and Sweden have changed their provisions on voluntary and unpaid blood donation. However, two countries (Czech Republic and Estonia) state that they are planning to change their existing legal provisions or guidelines.

Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Spain, Sweden, the United Kingdom and Croatia have defined penalties for

[88] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

infringements of the legislative provisions on voluntary and unpaid donation of blood and blood components. None of these countries have imposed such penalties.

Across Member States, practices can vary on two points: interpretation of the principle of "unpaid donation" and promotion of donation itself.[89]

Since the EU concept of unpaid donation, applicable to all EU countries, does not exclude some forms of financial compensation, interpretation of this latter concept may vary across Member States.

Even in countries with mandatory voluntary and unpaid donations, some financial compensations or incentives might be given. Given the absence of clear definitions in the 2nd report on VUD, it is therefore difficult to distinguish voluntary and unpaid from voluntary and paid donations.

Although compatible with European law, some donation practices are discouraged by several countries:

- Czech Republic, France, Hungary, Spain, Sweden and the United Kingdom have specific policies to discourage the practice of "replacement donors", which is the act to request the donation of a unit of blood from a family member or friend of the patient requiring transfusion.
- Czech Republic, Estonia, Luxembourg, Poland and Sweden report having some form of policy or guidelines to discourage the practice of trans-border blood donation. This latter is a practice where individuals donate blood outside their country of residence, e.g. in another Member States.

[89] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

5.3.3.2 Incentives for whole blood donors

The figure below shows incentives given to whole blood donors as described in the 2nd Report on Voluntary and Unpaid Donation of Blood and Blood Components.

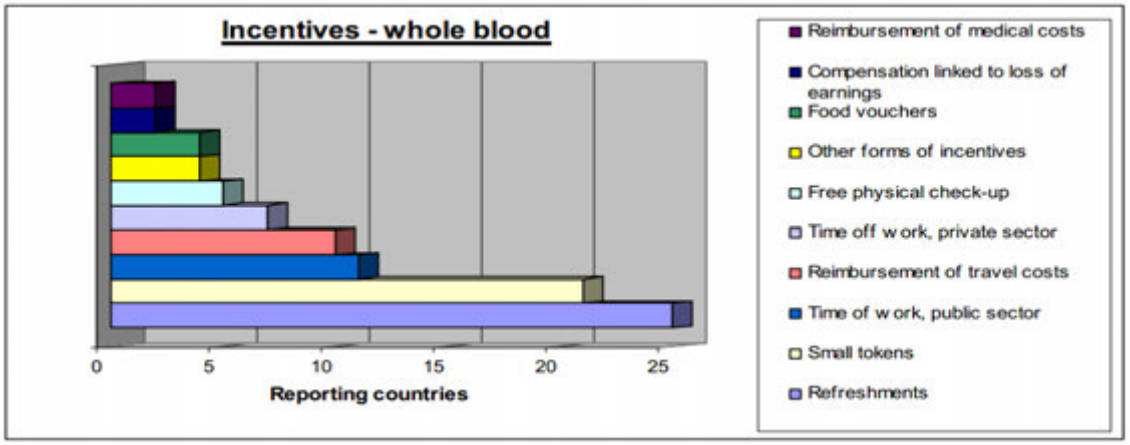

Figure 1 - Incentives for whole blood donation [90]

While some jurisdictions, such as France and the Netherlands, strictly allow time off work as that needed to donate and associated travel, in Italy, a paid day off work has been shown to increase the average blood donation rate on average by one extra donation per year, which represents an increase of around 40%[91].

5.3.4 Donors

5.3.4.1 Donors Management Program

''Blood donor management is the very first of many steps in the blood transfusion chain. Doing things correctly at this stage will facilitate all subsequent parts of the transfusion chain and make blood transfusion therapy safer and cheaper. Doing things incorrectly at this very first step will affect the entire chain, often in an irreparable way".[92]

The DOMAINE project has delivered a manual based on a wide survey across Europe to help blood establishments set up or adjust their policies and organisations in ways that will ensure a consistently safe and sufficient blood supply for their many patients. As this manual comes more as

[90] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

[91] Lacetera et al. Time for Blood: The Effect of Paid Leave Legislation on Altruistic Behavior (J Law Econ Organ 2012) doi:10.1093/jleo/ews019, Tranfus Med 2007;17:443-450)

[92] Donor Management Manual – Wim de Kort (2010) ISBN 978-90-815585-1-8

an advisory and not a mandatory guide, it provides a number of essential elements in the process of blood donor management that could help any blood establishment, regardless of their local cultural, organisational and budgetary differences, such as the following:

- Donor base, donor types and characteristics, donor management process
- Donor recruitment strategies and practices
- Donor retention strategies and practices
- Organisation of collections, donor deferral, bleeding procedures
- Donor safety issues: adverse events and reactions, donor care and counselling.

This guide was published in 2010 and is available online for free consultation[93]. A training course organised in Lisbon in 2011, gathering participants from 22 countries helped to disseminate the knowledge of the DOMAINE manual.

5.3.4.2 Donor population

According to EDQM/CoE reports[94] on "Collection, Testing and Use of Blood and Blood products in Europe'', there are 3 main types of donors:

- First time donors
- Registered donors (active/non active)
- Regular donors.

First-time donors are all donors that donate for the first-time. The number of registered donors is usually reported by the countries that hold either a national or regional registry. These donors can be divided into two sub-populations: active and non-active. Non-active donors refer to any donors that donated at least once in the past while active refer to donors that donate on a regular basis. Regular or recurring donors however are donors that donate blood or blood components regularly once or more in the same year.

The EDQM/CoE has communicated to our team, prior to the publication of the annual reports, 2010 data. Data from 2001-2005 were obtained from 'Trends and Observations on the Collection, Testing and Use of Blood and Blood Components in Europe' reports published by EDQM/CoE [no data on total donors] and 2006-2008 data were obtained from 'The Collection, Testing and Use of Blood and Blood Components in Europe' report. 2001-2008 reports are available online for consultation.[95]

[93] http://www.domaine-europe.eu , accessed 2013-07-24

[94] The collection, Testing and Use of Blood and Blood Components in Europe, 2010 Report, published by the EDQM/CoE (2013,) in press

[95] http://www.edqm.eu/en/blood-transfusion-reports-70.html, accessed 2013-07-24

Table 2 - Number of total donors from 2005-2010 in EU Member States (adapted from EDQM reports)

Country	2005	2006	2007	2008	2009	2010
Austria		349.918	495.193	338.958	234.837	334.066[(b)]
Belgium	306.660	304.950	338.559	299.505	311.836	365.813
Bulgaria	[1]	146.797	112.101	145.874	119.937[(a)]	119.110
Cyprus		69.483	48.520	48.544		
Czech Republic	345.000	319.100	286.321	363.197	414.500	376.176
Denmark		215.379	263.373	255.590	269.393	255.231
Estonia		32.254	34.051	34.063	19.773	44.805
Finland	159.969	163.670	179.525	163.287	168.643	154.602
France	1.506.082	1.527.209	1.617.478	1.639.773	1.689.495	2.125.786
Germany	2.602.600	2.846.415	2.978.888	2.946.183	3.143.222	3.074.037
Greece	369.538	343.530	407.015	413.148	471.757	533.015
Hungary	364.620	355.811	354.995	269.976	275.965	322.735
Ireland	97.481	118.590	97.777	96.991	97.662	96.737
Italy	1.493.000	1.539.454	1.570.000	1.619.000	1.690.426	1.722.503
Latvia	47.423	51.008	55.357	54.870	54.533	50.361
Lithuania	42.173	50.676		59.706		72.663
Luxembourg	15.322	14.567	13.392	14.169	10.367	
Malta			14.572	15.130	8.561	12.339
Netherlands	498.857	417.958	402.822	394.587	366.807	352.083
Poland	499.099[(a)]	826.193	616.974	897.687		703.561
Portugal		304.789				293.571
Romania	233.491	309.471			551.886	480.150
Slovakia	114.355	128.039	143.992	107.511	134.316	120.319
Slovenia	106.335	108.237	107.326	114.763	123.485	110.497[(a)]
Spain	1.109.563	1.116.016	1.118.018			1.133.040
Sweden	246.756	415.026	281.970	290.696	296.552	245.289
UK	1.566.841		1.438.611	1.605.609	1.437.147	1.566.463
Total	11.725.165	12.074.540	12.976.830	12.188.817	11.656.263	14.664.952

[(a)] Data provided by Competent Authority

[(b)] Calculated by multiplying donors/1.000 inhabitants (EDQM/CoE, 'Trends and Observations on the Collection, Testing and Use of Blood and Blood Components in Europe. 2001 – 2011 Trend Analysis Draft Report') per population/1.000 inhabitants (Eurostat 2010 data)

Table 3 - Percentage of first time donors – all donors who were actually tested for the first time, either at the time of donation or through pre-donation screening, or who donate for the first time - from 2001-2010 in EU Member States (adapted from EDQM reports)

Country	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Austria		16	8	26		16.9	10.9	15.6	13.8	
Belgium	16	16	14	17	18	16.9	14.6	17.4	20.5[(c)]	20.1 [(c)]
Bulgaria	24	23	21	21	21	21.6	29	21.2		29.5
Cyprus						30.7	12.1	9.3		
Czech Republic	10	11	9	8	9	7.2	9.2	13.7	14.8	14.7
Denmark	10		11	10		8.8	13.2	10.2	11.7	10.7
Estonia	31					22.4	27.1	27.1	25.5	19.3
Finland	12	11	11	11	10	11.1	10	13.8	12.1	12.6
France	25	22	22	25	23,4	23.7	23.8	25.1	25.1	20.3
Germany			24	18	21	18	18.4	19.3	20.5	18.2
Greece	28	18	16	12	15	16.9	17.1	17.1	17.0	14.1
Hungary	14	18		18	18	15.7	15.5	16.9	20.4	15.9
Ireland	32			15	27	19.9	13.4	15	14	15.7
Italy[(a)]	15	20	20	15	16	14.9	17.8	18.1	21.3	22
Latvia	24	23	27	27	26	29.2	30.7	28.3	28.5	
Lithuania	34	36		38	52	42.8		52.6		31
Luxembourg	10	7	6	6	12	7.9	7.6	7.2	11.2	
Malta							32.4	19.5	32.7	14.2
Netherlands	9	10	7	7	6	7.7	6.8	7.2	10.3	10.6
Poland[(b)]	39	39	37.8	38	39.8	40.5	40.1	41	38	35
Portugal	29					13.5				10.9
Romania	27	31	36	37	31	26.9			21.3	21.1
Slovakia	25	19	19	16	20	21.7	23.7	31	26.6	30.1
Slovenia	10	11	10	9	10	11	9.6	9.2	10.3	11,3[(c)]
Spain	30			30	30	26.7	24.2			21.5
Sweden	11	13	13	12	11	8.3	15.4	15.3	16.5	
UK	14	18	17	18	17		17.1	15.6	18.8	13.9

[(a)] In Italy, first time donors include donors who have donated more than 24 months ago.

[(b)] In Poland, there are 23 blood establishments. The National Blood Centre receives data from 22 because one establishment is under the Ministry of Interior and has no obligation to transfer data to Ministry of Health.

[(c)] Data provided by Competent Authority

These data should be interpreted according to the donor segmentation as outlined in the DOMAINE manual[96]. Although for many reasons it is preferable to have a donor base with more regular donors, the DOMAINE survey showed that only in 21% of countries, regular donors were the largest

[96] http://www.domaine-europe.eu/Manual/tabid/56/Default.aspx , accessed 2013-07-24

subgroup, and in 29% the proportion of first time donors was higher than the proportion of regular donors. In average in 2010, first time donors still represent 24% of the donor base, excluding Member States where first time donors and repeat plus regular donors were not reported separately. The ratio of first time donors to the total number of donors in general, reflects the annual donor recruitment as well as the turn-over rate in the donor base. A system with a good retention capacity has sufficient donor numbers to ensure supply, a high percentage of which are regular donors. These figures are influenced by recruitment programs.

The number of first time donors, as compared to the total number of donors, becomes less meaningful in systems that only pre-qualify donors at their first visit and postpone their first donation after they have been pre-qualified.

In 2012, Members States reported, as part of the implementation survey, a total 13,180,568 active donors, 9,764,634 repeated and 2,238,858 first time donors.

Table 4 - Number of active, repeated and first-time donors across the EU (2012) - Implementation Survey (2013)[97]

	Active Donors	Active Donors/1000inh	Repeated donors	Repeated Donors/1000inh	First Time Donors	First Time Donors/1000inh
Austria	-		-		-	
Belgium	297.833	26,8	246.062	22,2	51.771	4,7
Bulgaria	122.779	16,8	43.245	5,9	34.595	4,7
Croatia	67.774	15,8	58.089	13,6	11.670	2,7
Cyprus	48.121	55,8	7.148	8,3	7.106	8,2
Czech Republic	272.152	25,9	227.175	21,6	49.252	4,7
Denmark	154.350	27,7		0,0	-	
Estonia	35.869	27,1	28.353	21,4	7.516	5,7
Finland	144.226	26,7	126.914	23,5	16.649	3,1
France	1.725.931	26,4	1.369.527	21,0	356.404	5,5
Germany	2.867.230	35,7	2.458.347	30,6	408.883	5,1

[97] Implementation Survey, 2012. Report to be published

Greece	333.335	30,0	276.668	24,9	56.667	5,1
Hungary	239.133	24,1	183.380	18,5	55.753	5,6
Ireland	117.511	25,6	102.101	22,3	15.410	3,4
Italy	1.739.712	29,3	1.443.770	24,3	295.942	5,0
Liechtenstein	5	0,1		0,0	-	
Latvia	36.113	17,7	24.108	11,8	12.005	5,9
Lithuania	56.332	18,8	32.962	11,0	22.922	7,6
Luxembourg	13.704	26,1	9.364	17,8	1.106	2,1
Malta	11.394	27,3	2.905	7,0	771	1,8
The Netherlands	379.846	22,7	295.891	17,7	37.468	2,2
Norway	100.052	20,1	83.463	16,7	16.589	3,3
Poland	627.847	16,3	456.526	11,8	171.321	4,4
Portugal	249.168	23,6	204.291	19,4	44.877	4,3
Romania	521.132	25,9	245.568	12,2	91.902	4,6
Slovakia	121.542	22,5	91.557	16,9	29.985	5,5
Slovenia	59.634	29,0		0,0	10.706	5,2
Spain	1.214.281	26,0	828.955	17,7	233.062	5,0
Sweden	247.549	25,9	247.549	25,9	-	
United Kingdom	1.376.013	21,5	670.716	10,5	198.526	3,1
Total	**13.180.568**		**9.764.634**		**2.238.858**	

[(a)] England, Scotland &Northern Ireland

Here below additional tables, adapted from the EDQM reports, provide data on the collection and use of blood components across the EU.

Table 5 - Collection and use of blood components across the EU (2010) (adapted from EDQM reports)

	Collection			Utilization for transfusion			
	Total Donors	Donors/1000 inhabitants	WB donations (U)	Use of WB (U)	Use of RBC (U)	Use of Plasma (U)	Use of Platelets (U)
Austria	334,066	28.17	472,206	301	425,537	74,420	37,245
Belgium	365,813	33.7	549,266	0	516,035	92,761	69,328
Bulgaria	119,110	16.2	162,658[(a)]	1,654	183,120	93,666	6,606
Cyprus*	48,544	63.3	49,294	0	44,283	15,735	11,167
Czech Republic	376,176	36.4	440,700	393	389,521	201,220	31,866
Denmark	255,231	45.9	337,000	0	316,733	66,110	33,907
Estonia	44,805	33.4	58,729	19	51,586	27,196	6,086
Finland	154,602	28.6	265,592	314	249,922	53,512	43,023
France	2,125,786	32.7	2,483,577	0	2,378,241	382,449	278,097
Germany	3,074,037	37.6	4,940,257	5,657	4,694,567	1,216,153	496,281
Greece	533,015	50.8	613,275	49	615,692	201,909	133,375
Hungary	322,735	32.3	418,794	0[(b)]	361,151[(b)]	93,987[(b)]	14,259[(b)]
Ireland	96,737	21.1	151,894	0	140,037	23,612	24,431
Italy	1,722,503	28.5	2,694,871	3,025	2,522,355	395,602	205,791
Latvia	50,361	25.2	55,702	0	52,017	36,758	6,131
Lithuania	72,663	22.1	68,324	25	79,012	29,682	11,020
Luxembourg*	10,367	21	22,105	0	20,272	4,410	2,315
Malta	12,339	29.5	14,548	0	14,051	6,161	1,609
Poland	703,561	18.4	1,179,668[(a)]	610[(a)]	1,095,838[(a)]	369,474[(a)]	93,184[(a)]
Portugal	293,571	27.8	414,268	116	336,421	10,990	66,428
Romania	480,150	25.3	400,285	109,597	396,490	249,245	22,664
Slovakia	120,319	22.2	205,246	957	186,978	87,690	16,023
Slovenia	110,497[(a)]	53.9[(a)]	95,601[(a)]	0	87,451[(a)]	29,879[(a)]	10,944[(a)]
Spain	1,133,040	24.7	1,740,091	140	1,618,419	200,583	192,332
Sweden	245,289	26.1	493,439	0	488,373	89,064	42,817
The Netherlands	352,083	21.1	542,160	619	548,793	81,742	56,165
United Kingdom	1,566,463	25.1	2,305,482	16	2,182,950	303,377	287,027
Total	14,664,952	29.38	21,175,032	123,492	19,995,845	4,437,387	2,200,121

*Austria and Luxembourg: data are for 2009; Cyprus data are for 2008

[(a)] Data provided by Competent Authority

[(b)] 2009 data

The EU five (DE, UK, FR, IT, ES) registered the highest numbers of donors, substantially more than the remaining 22 countries.

Table 6 - Collection of blood components across the EU (2012) – Implementation Survey (2013) [98]

	Number of Whole blood donations	WB collections/1000 inh	Number of Platelets Donations by Apheresis	Platelets apheresis Donations/1000 inh	Other donations by apheresis
Austria	-	-	-	-	-
Belgium	538.336	48,5	13.471	1,2	6.078
Bulgaria	167.851	22,9	2.714	0,4	
Croatia	179.305	41,9	2.646	0,6	118
Cyprus	57.847	67,1	272	0,3	261
Czech Republic	418.954	39,8	18.271(a)	1,7	
Denmark	293.765	52,6	1.232	0,2	
Estonia	5.812	4,4	105	0,1	804
Finland	246.434	45,6	483	0,1	
France	2.641.930	40,5	131.875	2,0	32.643(i)
Germany	4.785.048	59,6	196.106	2,4	35.245(b)
Greece	400.002(c)	35,9	18.123	1,6	
Hungary	425.637	42,9	3.573	0,4	825
Ireland	138.099	30,1	12.023	2,6	
Italy	2.683.127	45,2	80.051	1,3	26.147
Liechtenstein	5	0,1	0	0,0	
Latvia	5.559	2,7	3.461	1,7	

[98] Implementation Survey, 2012. Report to be published

Lithuania	79.367	26,4	1.049	0,3	2.221(d)
Luxembourg	20.631	39,3	679	1,3	
Malta	16.995	40,7	469	1,1	
The Netherlands	498.117	29,8	4.723	0,3	
Norway	198.584	39,8	51.000	10,2	4.654
Poland	1.173.050	30,4	34.133	0,9	600(e)
Portugal	387.222	36,7	4.568	0,4	346
Romania	399.848	19,9	6.830	0,3	1.037(f)
Slovakia	203.825	37,7	6.257	1,2	
Slovenia	93.099	45,3	2.343	1,1	125(g)
Spain	1.702.768	36,4	7.880	0,2	24.728(f)
Sweden	484.755	50,7	0	0,0	
United Kingdom	2.256.736	35,3	148.012	2,3	0
Total	**20.502.708**	-	**752.349**	-	**135.832**

(a) Platelets and red cell apheresis data

(b) Erythrocytes: 14,699 Granulocytes: 629 Multicomponents: 19,917

(c) 81% of whole blood collections

(d) Multicomponents

(e) Red Blood Concentrate – 488 • Granulocyte Concentrate – 102

(f) 128 eritrocytapheresis+ 909 combined apheresis procedures

(g) Granulocytes

(f) 128 eritrocytapheresis+ 909 combined apheresis procedures

(i) 32 255 multicomponent apheresis donations + 368 granulocyte concentrate apheresis donations

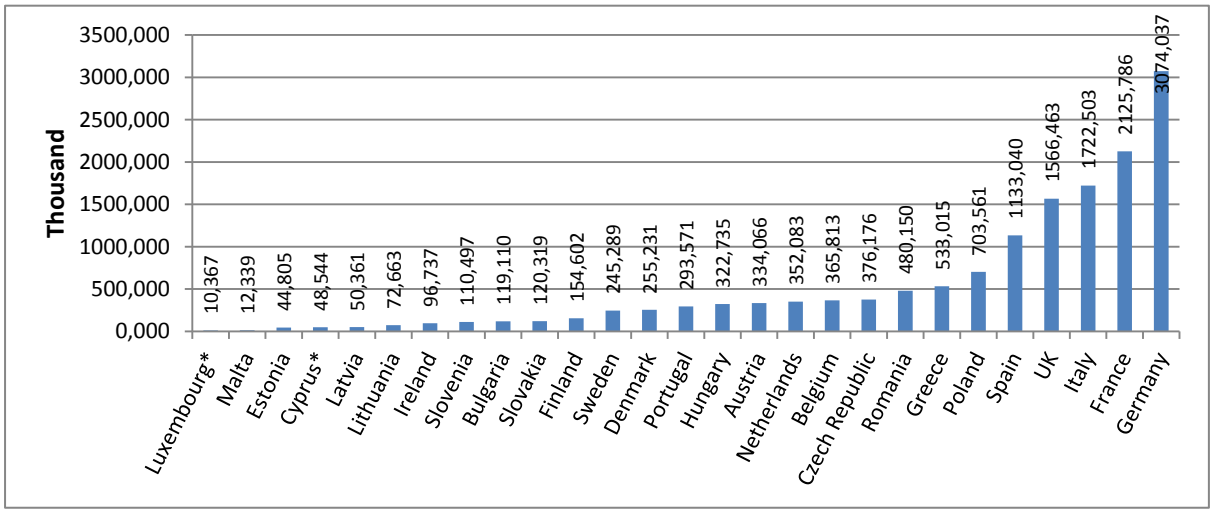

Figure 2 - Total Donors (2010) (adapted from EDQM reports)

***Austria, Luxembourg: data are for 2009; Cyprus data are for 2008

When the total population is taken into account (number of donors/1000 inhabitants) the picture though is completely different; Cyprus Slovenia and Greece reported more donors/1000 inhabitants than other EU countries.

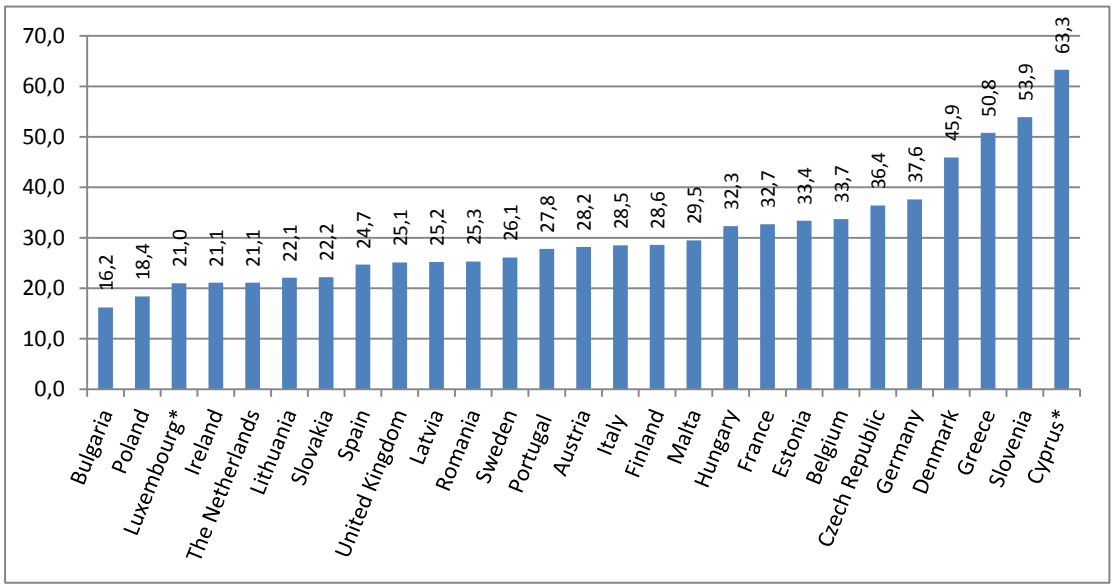

Figure 3 - Donors per 1000 inhabitant (2010) (adapted from EDQM reports)

***Austria, Luxembourg: data are for 2009; Cyprus data are for 2008

Differences among Member States regarding whole blood, platelets apheresis and plasma donations/million inhabitants are still observed as shown on figures 4 to 7.

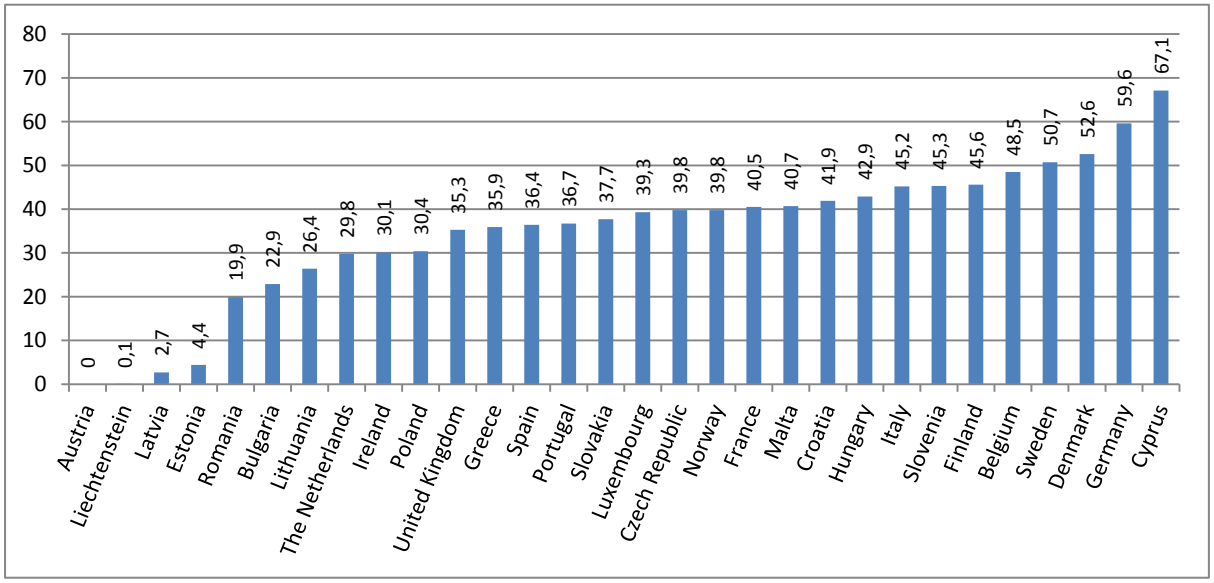

Figure 4 - Whole blood collections per 1000 inhabitant, 2012, implementation survey, 2013[99]

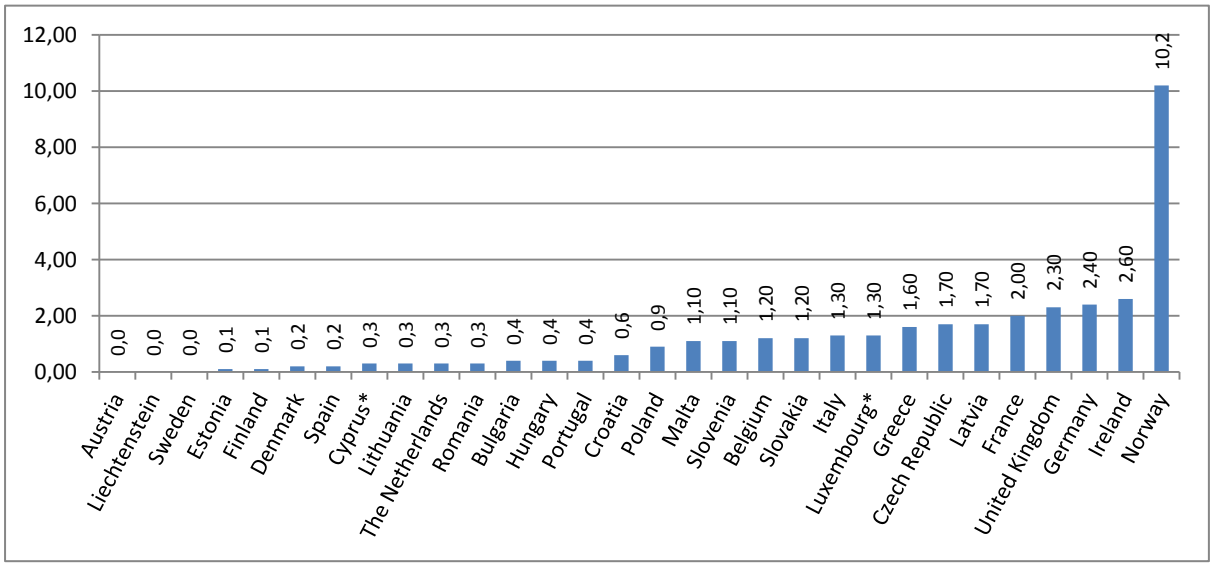

Figure 5 - Platelets apheresis donations per 1000 inhabitant, 2012, Implementation Survey, 2013

[99] Implementation Survey, 2013, Report to be published

Germany is the main consumer of blood components in Europe. Volumes used for transfusion are twice those of France and Italy (second main users of blood components).

It is important to note the significant gap in terms of transfused volumes between the five greatest users of blood and the rest of the EU Member States.

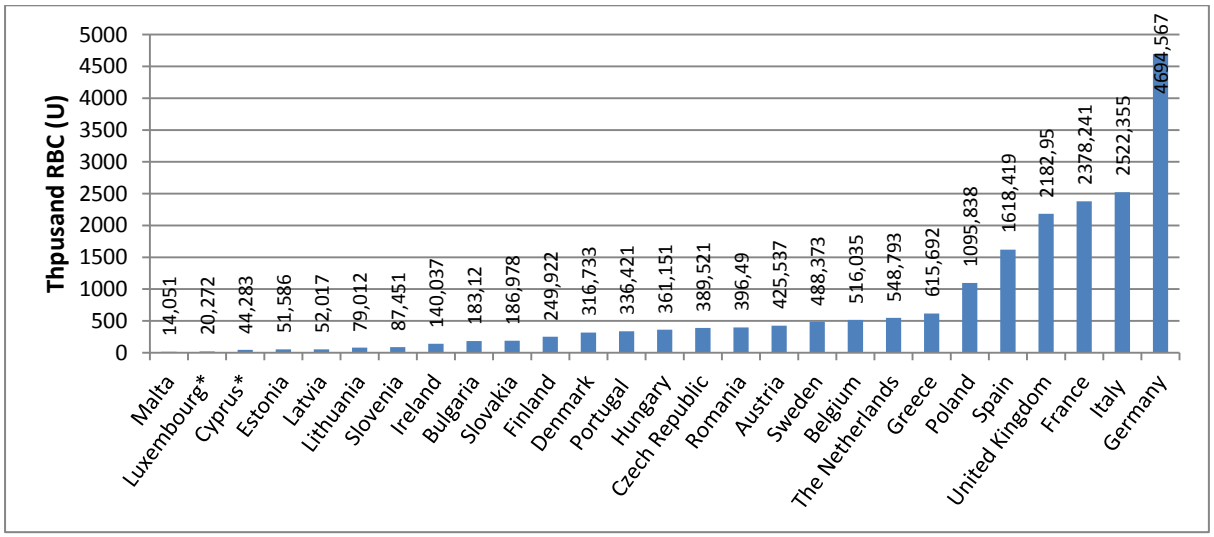

Figure 6 - Volumes of RBCs used for transfusion (2010) (adapted from EDQM reports)

*Austria, Luxembourg: data are for 2009; Cyprus data are for 2008

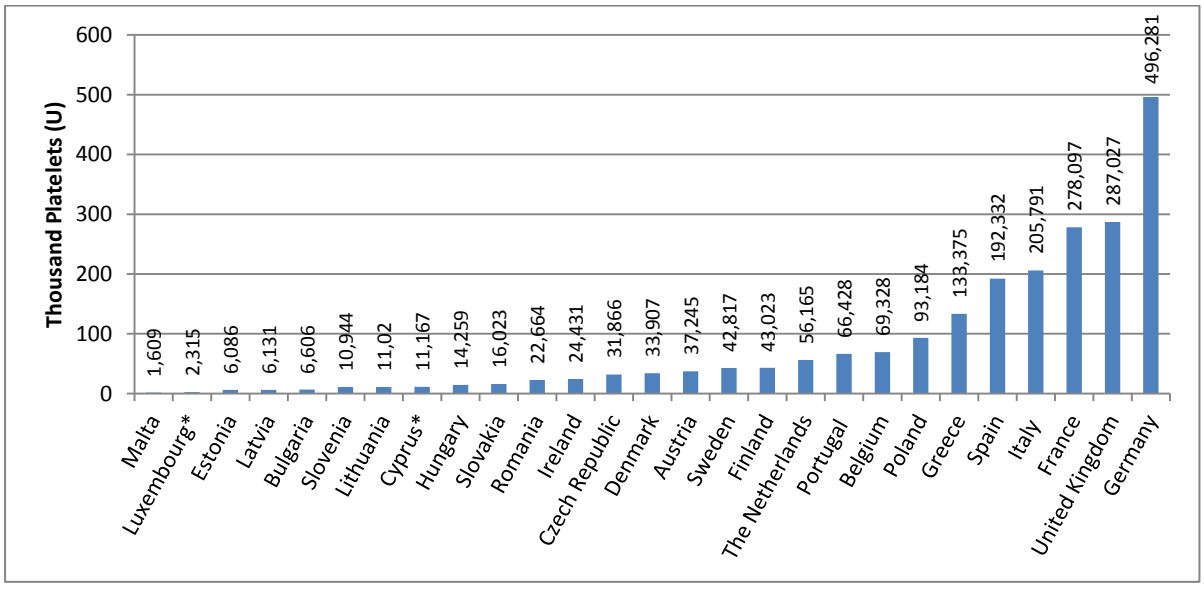

Figure 7 - Volumes of Platelets used for transfusion (2010) (adapted from EDQM reports)

***Austria, Luxembourg: data are for 2009; Cyprus data are for 2008**

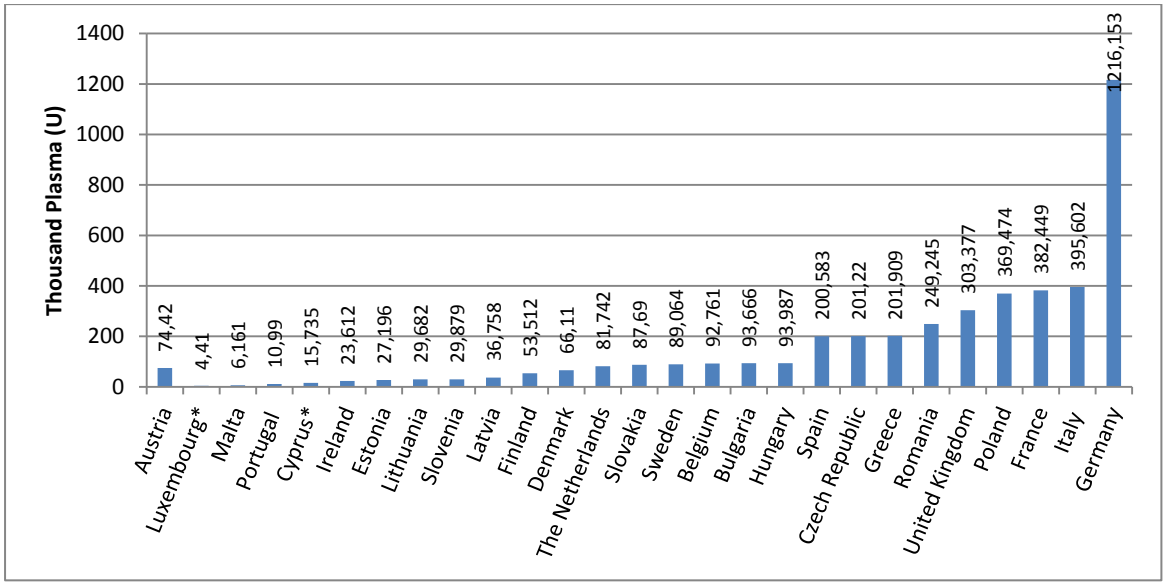

Figure 8 -- Volumes of Plasma used for transfusion (2010) (adapted from EDQM reports)

***Austria, Luxembourg: data are for 2009; Cyprus data are for 2008**

Whole blood is used for transfusion in 17 countries, mainly in Hungary (418,794 transfused units) followed by Romania (109,597 transfused units), Bulgaria (1,654 transfused units). In other countries using whole blood for transfusion is either negligible or not practiced at all.

Table 7 - EU whole blood use (2010) (adapted from EDQM reports)

Country	Whole blood (U)	Country	Whole blood (U)
Austria*	301	Lithuania	25
Bulgaria	1.654	Poland	628
Czech Republic	393	Portugal	116
Estonia	19	Romania	109.597
Finland	314	Slovakia	957
Germany	5.657	Spain	140
Greece	49	The Netherlands	619
Hungary	418.794	United Kingdom	16
Italy	3.025		

5.3.4.3 Donor selection

Annex III of Directive 2004/33/EC sets out the eligibility criteria for donors of whole blood and blood components. Donor deferral criteria are also included in section 2 of the same Annex.

In recent years, two relevant documents related to donor selection have been prepared to address infectious outbreaks with potential impact on blood quality and safety and supply: (1) Commission Directive 2009/135/EC of 3 November 2009[100] to respond to a temporary situation related to the specific Influenza A(H1N1) virus to prevent potential blood shortage and (2) a preparedness plan to prevent transmission of West Nile Virus (WNV).[101]

In addition, the Council of Europe has published a Resolution on deferral of donors with risk sexual behaviours.[102]

5.3.5 Import/Export of blood and blood components

From the survey conducted by the EDQM/CoE TS003 Working Party "Blood Supply Management", 3/27 countries indicated they were not self-sufficient in RBCs: Cyprus, Greece and Romania. Amongst these three, import of RBC was known for one: Greece. In 2013, this came in the media, informing that the Swiss Red Cross annually exported 30,000 units of RBC to Greece for decades[103]. In 2012, Greece reported the import of 25,200 red cell concentrates from the Swiss Red Cross Blood Centre and IE, 2 red cell concentrates from the USA[104]. In accordance with the Greek Government, this program will be reduced to 15,000 units. The reduction will be stepwise by 2,000 to 3,000 per year, starting in 2015. In parallel, the Swiss Red Cross supports the Greek health system in upgrading their self-sufficiency (training in recruiting and retaining donors).

On the other hand, the Council of Europe TS003 survey has shown that two Member States were over 100 percent self-sufficient in RBC: Ireland and Finland. However, none of these indicated export to another country.

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[100] Commission Directive 2009/135/EC of 3 November 2009[100] allowing temporary derogations to certain eligibility criteria for whole blood and blood components donors laid down in Annex III to Directive 2004/33/EC in the context of a risk of shortage caused by the Influenza A(H1N1) pandemic

[101] Final working document – West Nile Virus and blood safety, introduction to a preparedness plan in Europe. June 2012. http://ec.europa.eu/health/blood_tissues_organs/docs/wnv_preparedness_plan_2012.pdf

[102] Resolution CM ResolutionCM/Res(2013)3 on sexual behaviours of blood donors that have an impact on transfusion safety (Adopted by the Committee of Ministers on 27 March 2013 at the 1166th meeting of the Ministers' Deputies).

[103] Confirmed by Swiss Red Cross blood established. Information is accessible at: http://www.swissinfo.ch/eng/politics/Red_Cross_to_send_less_blood_to_Greece.html?cid=35076310, accessed 2013-07-24

[104] 2013 Implementation survey – Report to be published

An informal working group was created in 2013 to develop a proposal for surplus blood exchange through Intra Member States agreements, particularly for emergent situations, after it emerged that some states have reduced their blood collection activities. [105,106]

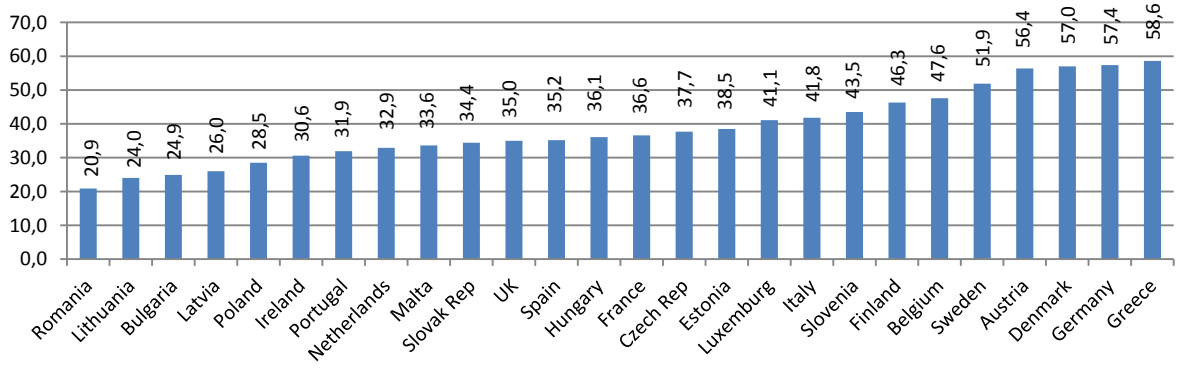
In 2012, Italy exported 126 red blood cell units to Congo, Paediatric Hospital of Kimbondo, for humanitarian aid and 70 red blood cell units to Republic of San Marino according to a bilateral agreement.

In the United Kingdom, blood establishments have agreements with Austrian establishments for the procurement fresh frozen plasma due to the presence of CJD in the UK population.

5.3.6 Systems to prioritize indications and optimise blood and blood component use

From the EDQM/CoE final report on the 'Collection, Testing and Use of Blood components' for 2010[107], the RBC consumption widely varied in the EU countries, from 20.9 to 58.6 RBC per 1,000 population. The provided data should be interpreted with caution (for some countries data reflect use; for other countries data reflect distribution by blood establishments).

Outside Europe, in New Zealand, after years of active policy to optimise the use of blood, and developing collaboration between blood establishments and hospitals, consumption was reduced to 28.8 RBC per 1,000 pop. As recently pointed out, institutional experience and national databases suggest that a restrictive blood transfusion approach, compatible with such a level of consumption, is being increasingly implemented as best practice in fully developed countries.



[105] Meeting of the Competent Authorities on Blood and Blood Components 17 and 18 April 2013 Summary Report. http://ec.europa.eu/health/blood_tissues_organs/docs/blood_mi_20130417_en.pdf

[106] Meeting of the Competent Authorities on Blood and Blood Components 6 and 7 November 2013 Summary Report http://ec.europa.eu/health/blood_tissues_organs/docs/blood_mi_20131106_en.pdf

[107] The Collection, Testing and Use of Blood and Blood Components in Europe, 2010 Report, published by the EDQM/CoE (2013,) in press

Figure 9 - RBC consumption in 26 MS in 2010 (adapted from EDQM report)[108]

When no data was available in the EDQM-CoE final report for 2010 (Austria, Hungary, Luxembourg, and Slovenia), data were taken from this report for the year 2009[109]. The relatively low numbers in Ireland and Netherlands follow projects focusing on optimizing blood utilisation. These experiences tend to indicate that optimisation of blood use should require at least the following factors:

- Assessment of consumption analysed by diagnostic related groups;
- Education of prescribers based on solid scientific evidence;
- Strong collaboration between blood establishments, hospitals and Ministry of Health to develop an active and coordinated strategy to optimise the use of blood.

5.4 Plasma derived medicinal products supply chain

5.4.1 Introduction

Plasma derived medicinal products are mostly used to treat patients with rare or very rare diseases.

Plasma for fractionation can be collected separately by apheresis techniques or recovered from whole blood donations. The majority of recovered blood components are provided by non-profit blood establishments and an important proportion of plasma for fractionation is provided by commercial companies. In the Dublin Consensus Statement, all involved stakeholders agreed upon the existence of two independent collection systems, upon cooperating to ensure the best community outcomes including sufficiency of plasma derivatives supply. In this consensus statement, with the patients' health as the main focus, providing safe blood and plasma products and protecting blood donor's health was recognised as fundamental.

In the seventies, the monograph "Human plasma, normal, liquid" of the European Pharmacopoeia laid down the first provisions for quality and safety requirements for plasma used in the manufacturing of medicinal products derived from human blood or plasma. This monograph was later suppressed following the adoption the new monograph "Human Plasma for Fractionation, *0853*" by the European Pharmacopoeia Commission during its 83rd plenary session.

Since 1989, plasma derived medicinal products are subject to EU pharmaceuticals legislation regarding quality, safety and efficacy standards, and require an authorization to be released on the EU market.[110 & 111] Collection and testing of plasma, the starting material for these products, is

[108] Questionnaire on the collection, testing and use of blood components -2010 Final report

[109] The collection, Testing and Use of Blood and Blood Components in Europe, 2009 Report, published by the EDQM/CoE (2013,) in press

[110] Note for guidance on plasma-derived medicinal products – 2001 - CPMP/BWP/269/95 rev. 3 accessible at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003613.pdf , accessed 2014-05-13

subject to EU legislation on substances of human origin. Although there is some overlap, blood and blood components for transfusion are subject to different regulations pathways, focusing on different safety and quality standards (Directive 2001/83/EC[112,113] regulates the storage, testing, distribution and manufacturing of plasma intended for manufacturing medicinal products). PPTA and PLUS have proposed that there be separate EU legislation for plasma collected by apheresis to be used as raw material for plasma derivatives products, than for whole blood and labile components. It needs to be noted though that plasma collected by apheresis can also be used for transfusion.

Annex 14 to the EU Guide to Good Manufacturing Practice has been developed to clarify safety and quality expectations on the blood establishments and consequently on the manufacturer of the medicinal product derived from human blood and plasma.

The advent of plasma fractionation in the 1940s, developed by Cohn and colleagues, led to the widespread use of plasma-derived medicinal products.[114]

Improvements in protein purification and molecular separation technology over recent years have made available a wide variety of products, with medical applications covering a large and growing field. The first manufactured product at an industrial scale was albumin in 1940's followed by intramuscular immunoglobulins (1960). A decade later, coagulations factors and Rho(D) specific immunoglobulin became available (1970) and it is only in 1990 that intravenous immunoglobulin (polyvalent) were introduced to the market. [115] Hyperimmune globulin such as anti-tetanus, anti-rabies, anti-hepatitis B, anti – cytomegalovirus and other specific immunoglobulin are also produced. In response to more recent epidemics hyperimmune globulins have been produced for HIV[116], SARS[117] and H1N1.[118]

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[111] Waller C. Historical Perspective on blood & plasma products, the stakeholders and the issues. In: Pharmaceuticals Policy and Law 7 (2005-2006) 7-19 (eds Valverde JL). IOS Press.

[112] Directive 2001/83/EC of the European parliament and of The Council of 6 November on the Community code relating to medicinal products for human use

[113] The rules governing medicinal products in European Union – Volume 4, Annex 14

[114] First note for guidance on plasma-derived medicinal products – 2001 - CPMP/BWP/269/95 rev. 3 accessible at: https://www.tga.gov.au/pdf/euguide/bwp026995r3en.pdf , accessed 2013-07-24 (replaced by replaced by EMA/CHMP/BWP/706271/2010)

[115] Market Research Bureau. Worldwide Supply and Demand of Plasma and Plasma-Derived Medicines. Iranian Journal of Blood and Cancer. 2011, 3(3)

[116] Stiehm ER et al, Use of human immunodeficiency virus (HIV) human hyperimmune immunoglobulin in HIV type 1-infected children (Pediatric AIDS clinical trials group protocol 273), J Infect Dis. 2000 Feb;181(2):548-54.

[117] MB Ali, MB, BS, FHKAM (Community Medicine) Advantek Biologics Limited Hong Kong Med J Vol 9 No 5 October 2003,

Following the HIV and hepatitis C epidemics in haemophiliac patients, and in response to the increasing demand of safe clotting factors to treat these patients, in 1992 two pharmaceutical companies started producing recombinant Factor VIII, eight years after the emergence gene cloning. First cloned in 1982, it was only in 1997 that the first factor IX recombinant was licensed. Several preparations of clotting recombinant factors are now available.[119,120]

This part of the report focuses on plasma-derived medicinal products produced on an industrial scale from pools of source material through various manufacturing procedures. They may be used as therapeutic medicines or as excipients.

In this reports are not directly addressed products derived from single donations or from small pools of source material (e.g. fresh frozen plasma and cryoprecipitate).

As products derived from human plasma are generally divided into the above two groups it is important to remind that there are discussion ongoing on clarifying the borderline between blood components and pharmaceutical products. In specific we remind a case before the European Court of Justice on the qualification of Fresh Frozen Pooled Plasma (Octaplas®) under French law, where it is argued by Octapharma AG whether plasma (a blood component) should not fall under the pharmaceutical legislation, given the need for an industrial scale step in its processing (large scale pooling and inactivation of large quantities), even if plasma is to be considered a blood component and not a pharmaceutical product. In 13 March 2014, the Judgment of the Court (First Chamber) hereby rules as follow[121]:

1. Directive 2001/83/EC of the European Parliament *and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, and Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood*

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[118] Hohenadl C. et al, Hyperimmune intravenous immunoglobulin containing high titers of pandemic H1N1 hemagglutinin and neuraminidase antibodies provides dose-dependent protection against lethal virus challenge in SCID mice, *Virology Journal* 2014, **11**:70 doi:10.1186/1743-422X-11-70

[119] Hemophilia: From Plasma to Recombinant Factors, American Society of Haematology 2007, http://www.hematology.org/About/History/50-Years/1524.aspx

[120] Powels J.S. Therapeutics and Clinical Risk Management 2009:5

[121] REQUEST for a preliminary ruling under Article 267 TFEU from the Conseil d'État (France), made by decision of 26 October 2012, received at the Court on 13 November 2012, in the proceedings Octapharma France SAS v Agence nationale de sécurité du médicament et des produits de santé (ANSM), Ministère des Affaires sociales et de la Santé.
http://curia.europa.eu/juris/document/document.jsf?text=Octaplas&docid=149130&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=531319#ctx1

components and amending Directive 2001/83 must be interpreted as meaning that plasma from whole blood which is prepared by a method involving an industrial process and which is intended for transfusions comes, in accordance with Article 109 of Directive 2001/83, within the scope of Directive 2002/98 with respect to its collection and testing, and within the scope of Directive 2001/83, as amended by Directive 2004/27, with respect to its processing, storage and distribution, on condition that it satisfies the definition of a medicinal product under Article 1(2) of the latter directive.

2. Article 4(2) of Directive 2002/98, read in the light of Article 168 TFEU, must be interpreted as meaning that it allows the maintenance or introduction of national provisions which make plasma which is prepared by a method involving an industrial process subject to a more rigorous regime than that to which medicinal products are subject solely with respect to its collection and testing.

French authorities note that the Court did not specify what an industrial process for plasma entails.

The tables below provide a picture per country of the plasma products' market whose values, according to the available data, is up 2958.4 million euros in the EU as of 2011. Germany is by far the major market for plasma derivatives in the EU the second is France.

It is quite important to notice how the EU five largest[122] plasma derivatives markets values[123] were 2268,7 million Euros, while the rest of the EU[124] is worth about 703,8 million euros, for populations of 317.2 and 178.3 million inhabitants respectively. The recombinant factors market was estimated at 1290.5 million euros. This market is larger than the plasma derivatives market in Denmark, Ireland and the Netherlands.

[122] Italy, France, Spain, United Kingdom and Germany

[123] MRB Country Reports

[124] Rest of EU: Bulgaria, Slovenia, Romania, Ireland, Slovakia, Hungary, Denmark, Czech Republic, Finland, Portugal, Greece, Austria, Poland, Belgium, The Netherlands, Sweden + (Estonia, Latvia and Lithuania) – Total Population 178.3 million inhabitants

Table 8 - Plasma products' market value in EU (2011) (adapted from MRB Country Reports)

Country	Plasma derivatives Market in million Euros	
	Plasma derived products	Plasma + recombinant products
Austria	68	95,4
Belgium	81	157,7
Bulgaria	5,5	6,8
Cyprus	NA	NA
Czech Republic	33,8	NA
Denmark	30,4	68,6
Estonia	NA	NA
Finland	37,3	57,3
France	575,8	841,4
Germany	900,5	1.332,6
Greece	51,5	74,2
Hungary	26,8	40,8
Ireland	18,9	52,8
Italy	395,2	674,8
Latvia	NA	NA
Lithuania	NA	NA
Luxembourg	NA	NA
Malta	NA	NA
Poland	78,1	90,1
Portugal	42,6	58,2
Romania	7,6	11,4
Slovakia	24,8	NA
Slovenia	6,9	NA
Spain	260,7	375,8
Sweden	88,3	156,9
The Netherlands	88,2	194,9
United Kingdom	203,7	416,6
Total	**3.025.6**	**4.706,3**

Data for Cyprus, Estonia, Malta, Luxembourg, Latvia and Lithuania not available.

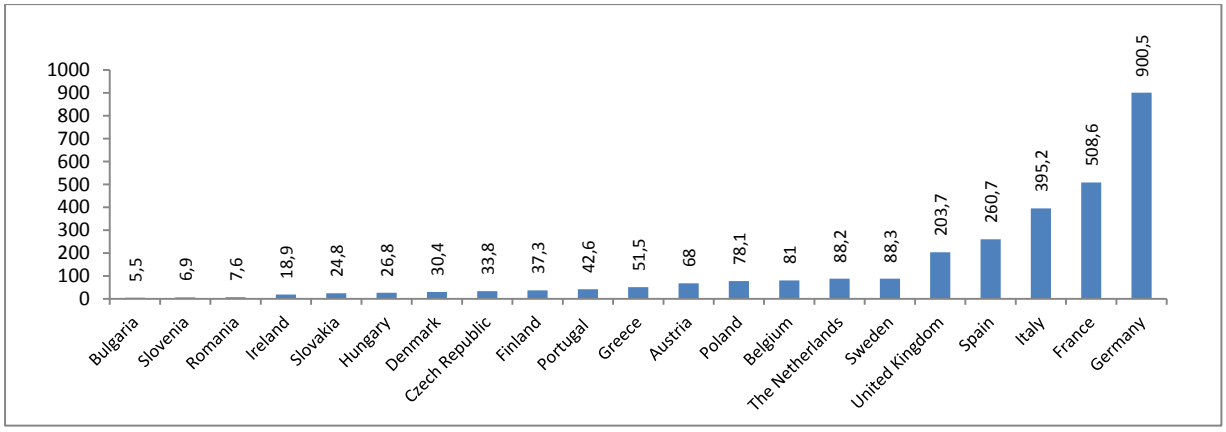

Figure 10 - Plasma products' market value in EU (2011) (adapted from MRB Country Reports)

Data for Cyprus, Estonia, Malta, Luxembourg, Latvia and Lithuania are not available.

5.4.2 Supply/demand and patient access to care

5.4.2.1 Supply and demand for plasma derived medicinal products

According to More *et al*[125] the supply and demand of plasma derived medicinal products is closely linked to global fractionation capacity and clinical need, which is influenced not only by the optimization of production methods, the economic and the regulatory environment.

In 2012, the reported activities[126] regarding plasma collection by apheresis, Czech Republic Germany and the Netherlands have the highest rates of plasma donations by apheresis (per million inhabitants). It needs to be noted however that no data were provided for Austria and Hungary, 2 countries where plasmapheresis activities are in general considered to be important. Twenty two out of twenty nine reporting countries have residual or none activity.

[125] More J & Bulmer M. Human Serum Albumin: A multifunctional plasma protein. In Production of Plasma Proteins for Therapeutic Use. Pp159-184. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA.

[126] Implementation Survey, 2012. Report to be published.

Table 9 – Number of plasma donations by apheresis/ country (2012). Implementation survey (2013)

	Number of Plasma Donations by Apheresis	Plasma Donations/ 1.000 inhabitants		Number of Plasma Donations by Apheresis	Plasma Donations/1.000 inhabitants
Austria	-	-	Liechtenstein	0	0,0
Belgium	104.545	9,4	Latvia	0	0,0
Bulgaria	232	0,0	Lithuania	11	0,0
Croatia	0	0,0	Luxembourg	3.132	6,0
Cyprus	1.507	1,7	Malta	0	0,0
Czech Republic	617.617	58,8	The Netherlands	321.184	19,2
Denmark	3.086	0,6	Norway	4.693	0,9
Estonia	1.028	0,8	Poland	21.042	0,5
Finland	4.127	0,8	Portugal	0	0,0
France	487.804	7,5	Romania	1	0,0
Germany	2.445.918	30,4	Slovakia	152	0,0
Greece	2.146	0,2	Slovenia	623	0,3
Hungary	-		Spain	22.564	0,5
Ireland	0	0,0	Sweden	9.929	1,0
Italy	403.554	6,8	United Kingdom	0	0,0
Total of plasma donations by Apheresis	4.454.895				

The plasma donation rate per million inhabitants varies significantly between Member States, possibly linked to the fractionation capacity or incentives for donation.

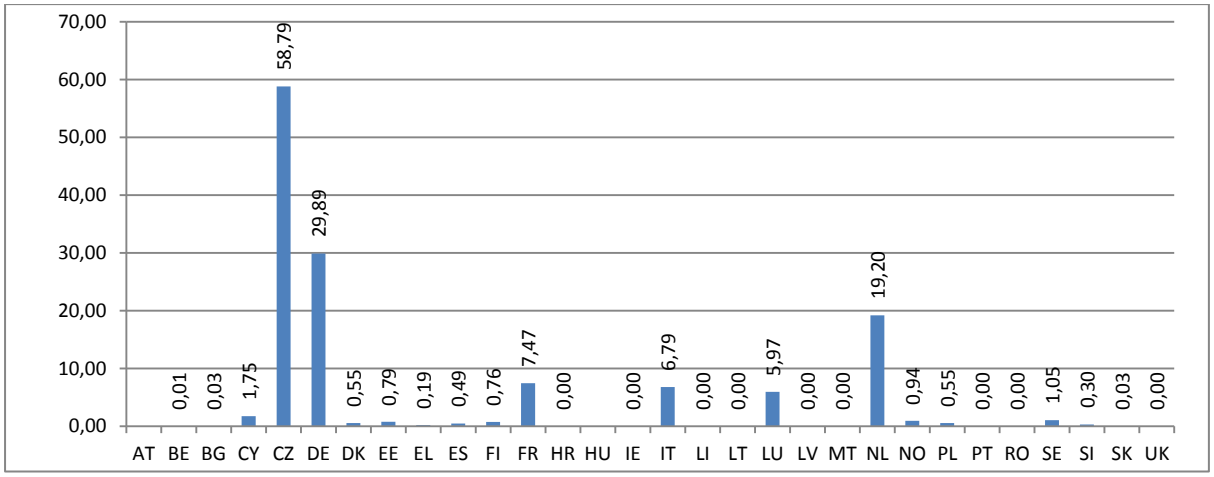

Figure 11 - Plasma donations per million inhabitants, 2012, Implementation Survey, 2013

In fact, most of EU countries do not have fractionation plants (12 countries out of the 27 have fractionation plants) as illustrated by the table below.

Table 10 - Fractionation plants in the EU (2011) (adapted from MRB Country Reports)

Country	Local fractionation plants	Number of fraction plants	Owner	location	Fractionation capacity/year
Austria	Yes	2	Baxter Octapharma	Vienna Vienna	NA NA
Belgium	Yes	2	CAF-DCF Baxter	Brussels Lessines	500,000 liters NA
Bulgaria	Yes	1	Ministry of Health	Sofia	NA
Cyprus	NA	NA	NA	NA	NA
Czech Republic	No	0	NA	NA	NA
Denmark	No	0	NA	NA	NA
Estonia	No	0	NA	NA	NA
Finland	No	0	NA	NA	NA
France	Yes	4	LFB (2) Octapharma Sanofi Pasteur	Paris and Lille Strasbourg Lyon	1.4 million liters Over 1 million liters 50,000 liters
Germany	Yes	3	CSL Behring (Biotest Octapharma	Marburg Dreieich Springe	2 million liters 700,000 liters 650,000 liters
Greece	No	0	NA	NA	NA
Hungary	Yes	1	Kedrion	Gödöllö	200,00 liters
Ireland	No	0	NA	NA	NA
Italy	Yes	3	Kedrion Baxter	Pisa and Naples Rome	Over 1 million liters 500,000 liters
Latvia	No	0	NA	NA	NA
Lithuania	No	0	NA	NA	NA

Luxembourg	NA	NA	NA	NA	NA
Malta	NA	NA	NA	NA	NA
Poland	Yes	1	Biomed	Lublin	50,000 liters
Portugal	No	0	NA	NA	NA
Romania	No	NA	NA	NA	NA
Slovakia	No	0	NA	NA	NA
Slovenia	No	0	NA	NA	NA
Spain	Yes	1	Grifols	Barcelona	2.1 million liters
Sweden	Yes	1	Octapharma Nordic AB	Stockholm	1.34 million liters
The Netherlands	Yes	1	Sanquin	Amsterdam	800,000 liters
United Kingdom	Yes	1	BPL	Elstree (London)	750,000 liters

NIHT: National Institute for Hematology and Transfusion; BPL: Blood Products Laboratory fractionates only US imported plasma

In 2010, the global fractionating capacity was about 48.4 million litres, with 29.1 million litres processed (source and recovered) by the commercial sector and 4.5 million litres by non-profit organisations. The larger size fractionation plants were operating in Europe (26) and the United States (8) (out of 78 plants globally). China had 25 plants[127]. From these numbers, it can be estimated that there was a spare capacity of about 30%. According to Waller C. *to understand supply and demand for plasma products requires an understanding of how much in volume is needed for each product*[128].

It was accepted by all interviewed stakeholders in the field that immunoglobulins are driving the market and dictating how much plasma is needed.

PPTA argued that fractionation capacity alone cannot supply for the need, when the starting material is not available. I.e. having a potential capacity to fractionate a certain amount of plasma is not sufficient if there is not enough starting material available to manufacture products.

Until the 1970's, albumin was the driver for plasma collection. The excellent outcomes treating haemophiliac patients with plasma-derived factor VIII in the late 1970's, led to an incredible increase of demand of this product and led to the need for larger volumes of plasma to meet demand. IVIG became the driver in the 1990's when plasma-derived factor VIII and factor IX started to be partially

[127] Robert P. Worldwide Supply and Demand of Plasma and Plasma Derived Medicines. Iranian Journal of Blood and Cancer. 3 (3): 111-120 (2011)

[128] Waller C. Historical Perspective on blood & plasma products, the stakeholders and the issues. In: Pharmaceuticals Policy and Law 7 (2005-2006) 7-19 (eds Valverde JL). IOS Press.

replaced by recombinant products. Over time, needs for albumin, Factor VIII and now IVIG have determined the wide variation of the volume of source plasma collected[129].

In response to the growing demand for IVIG, the amount of plasma processed has increased in Europe. The volume of source plasma varies, whereas that of recovered plasma remains stable as it stems from the demand for labile blood components. From 1993 to 2010, the volume of processed source plasma increased from 4.4 to 11.7 million litres, while the volume of recovered plasma remained stable from 4.! to 4.9 million litres (commercial companies and non- profit organizations).[130]

According to Robert[131], in 2009, the worldwide value of plasma derived medicinal products was estimated at $11.8 billion with polyvalent IVIG representing 46% of the total, albumin 10% and factor VIII 9%, hyperimune immune globulin (IM&IV) 4.5%, factor IX 1.8% and the remaining products 29.4%. Moreover, the European market (only 11% of the world population) represented close to 36% of the world market, while the Asian and Pacific market (58% of the world population) represented 15%".

As for all therapies, demand could be appropriate or inappropriate, thus it is important to distinguish demand and patients' needs, based on indications, usually defined in guidelines.[132] As underlined in the Dublin Consensus statement, "The needs of patients should determine the optimal collection of blood and plasma". [133]

[129] Robert P. Worldwide Supply and Demand of Plasma and Plasma Derived Medicines. Iranian Journal of Blood and Cancer. 3 (3): 111-120 (2011)

[130] Sampling of slides presented to various Industry Meetings from 2009 to 2012, April 2013. Market Research Bureau. http://marketingresearchbureau.com/wordpress/mrbSample.htm, accessed 15-05-2014

[131] Robert P. Worldwide Supply and Demand of Plasma and Plasma Derived Medicines. Iranian Journal of Blood and Cancer. 3 (3): 111-120 (2011)

[132] Folléa et al. Blood supply management (RBC): definitions, description as a process, tools for assessment and improvement. ISBT Science Series 2013, 8 : 37-40.

[133] The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang. 2010 98: 447-50 DOI: 10.1111/j.1423-0410.2010.01310.x

These discrepancies are illustrated by wide variations in per capita usage. According to Marketing Research Bureau, Inc[134], in 2007, Australia and Canada had the highest IVIG consumption per capita 125.5 and 118.0 kilograms per million inhabitants.

The lowest consumption per capita was in India (0.2 kg/pmp), Egypt (1.4 kg/pmp), Iran (1.9 kg/pmp) and Thailand 2.8 (kg/pmp).)

In Europe, Sweden was leading (93.8 kg/pmp), followed by France (79.3 kg/pmp), Spain (62.5 kg/pmp), Italy (52.5 kg/pmp), Switzerland (48.7 kg/pmp), UK (46.1 kg/pmp) and Germany (36.4 kg/pmp) (data from some Member States not available).

While a report on the Optimal use of blood and blood products published by EDQM recommended two International Units (IU) as the minimum acceptable consumption of Factor VIII at national level per capita[135], there are still many countries where consumption per capita is still extremely low, such as in India (0.01IU), Egypt (0.08IU), Thailand (0.13IU).

The consumption level in Europe varies as well. According to data published by O'Mahony *et al*. in 2013[136], the median consumption was 3.59IU, the mean 3.45IU, with a standard deviation of 2.6IU per capita (see more on point 5.4.2.2).
It was suggested by Robert P. in article "Worldwide Supply and Demand of Plasma and Plasma-Derived Medicines" that *low usage level recorded in the some countries is due to financial constraints rather than limitations in the availability of plasma (source or recovered) or in fractionation capacity and believes that it is possible to increase the collection levels of source plasma in the United States relatively easily, provided that the necessary funding is available*.[137]

5.4.2.2 Improving patient access to plasma derived medicinal products

The main barrier for access to plasma derived medicinal products remains the cost, especially in emerging countries. The use of recovered plasma, meeting the requirements to be used for manufacturing, which is currently not utilized by many blood centres, could alleviate some of these barriers. In many countries, including EU Member States, recovered plasma is not being used for

[134] Market Research Bureau. Worldwide Supply and Demand of Plasma And Plasma-Derived Medicines**.** Iranian Journal of Blood and Cancer. 2011, 3(3)

[135] Optimal Clinical Use of Blood Components, International Symposium co-organised by the EDQM & HealthCare/DBO – Transfusion Medicine, Council of Europe PEI, the German Official National Agency for Biologicals, The Transfusionsmedizin und Haemostaseologie, Klinikum der Universitaet Muenchen. April 24–25, 2009.

[136] O'Mahony B et al. Haemophilia care in Europe – a survey of 35 countries. Haemophilia (2013), 1–9, DOI: 10.1111/hae.12125

[137] Robert P. Worldwide Supply and Demand of Plasma and Plasma Derived Medicines. Iranian Journal of Blood and Cancer. 3 (3): 111-120 (2011)

manufacturing. All stakeholders involved in the Dublin Consensus statement 2012 agreed on the need to "implement measures to avoid the wastage of plasma recovered from whole blood".[138]

The European Medicine Agency (EMA) published in 2012 a *Reflection paper on medicinal product supply shortages caused by manufacturing/ Good Manufacturing Practice Compliance problems*[139] supporting a collaboration and cooperation within the network to address supply shortages of these medicinal products. PPTA agrees, as stated in the document, that medicinal product shortages are "public health crises" and that "clear and transparent communication" of shortage-related information by manufacturers is critical. They have, therefore, proposed a plan for sharing information on distributed products in Europe. PPTA reported aggregate country specific distribution data is now available.[140]

IPFA and PPTA are not aware of any product shortages or failures of supply impacting on patient care resulting from a shortage of plasma or available product supply. However periodic and specific interruptions to the supply chain have occurred, which have created restrictions in the flow of product. It is understood that these interruptions to supply were limited to a specific supplier compensated by increased supply from other suppliers.

According to IPFA, there is a general agreement that there have been episodes of shortages throughout the world in the past but there is not much evidence today of a systematic or chronic shortage.

PPTA reported immunoglobulin shortage in the late 1990s due to a combination of factors:

- Increased demand
- GMP manufacturing issues
- Disharmonized recall policies because of Creutzfeld Jakob disease.

In the years 2000-2001, there was a worldwide shortage of FVIII recombinant resulting from manufacturing issues with one main supplier. Haemophilic patients had to postpone elective surgery and in many cases were switched to plasma-derived factor VIII therapies. This effect was seen in many countries worldwide including European countries. According to the 2012 report "Registry of

[138] O'Mahony B. The Dublin Consensus Statement 2012 on optimised supply of plasma-derived medicinal products, Blood Transfus 2013; 11: 623-6 DOI 10.2450/2013.0044-13

[139] *Reflection paper on medicinal product supply shortages caused by manufacturing/ Good Manufacturing Practice Compliance problems*, European Medicines Agency, 22 November 2012, EMA/590745/2012, Patient Health Protection, at 2, 4.

[140] http://www.pptaglobal.org/safety-quality/european-programs/european-distribution-data.

Clotting factors Concentrates" *no shortages of factor VIII and factor IX concentrates were reported in the United States or Europe in 2011, nor were there any reports of breaches of safety*.[141]

The International Patient Coalition, the Plasma Users Group - PLUS - has suggested possible drivers for shortage in supply, namely:

- Biological origin of the source material (human plasma):
  - increasing the collection of plasma depends on increasing the number of donors (blood and plasma)
  - the supply of the raw material (plasma) can be impacted by viral epidemics (or other crises)
- Increasing diagnosis rates of patients in need of PDMPs
- Growing number of indications (particularly for immunoglobulins)
- Restrictive Member States policies that hinder the free circulation of PDMPs in the European Union: France article L5121-11 from the French Public Health Code restricts access to PDMPs manufactured from compensated plasma donations[142]. Evidence of such a shortage as result of this policy was not provided by PLUS. French authorities clarified that this article allows obtaining a marketing authorisation for these products in case of shortage or if no alternative PDMP, obtained from voluntary unpaid donations, is available. French authorities also refer to article 110 of Directive 2001/83/CE which calls on Member States to encourage VUD of blood and plasma. French authorities expressed the view that there is no hinder for free circulation and that PDMP from other EU Member States, obtained from VUD, as well as PDMP authorised at EU level, can be put on the market in France.

Plasma derived medicinal products are complex biological products, which can be subject to unexpected manufacturing problems or recalls. It is therefore important to ensure and maintain a wide range of options for manufacture and supplying including, importantly, EU capability and capacity.[143]

O'Mahony B et al.[144,145] has highlighted in recent studies differences in the level of care using plasma derived medicines throughout Europe. In 2011, this study focused on bleeding disorders patients

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[141] M Brokker, "Registry of Clotting factors Concentrates", Ninth Edition, 2012, World Federation of Haemophilia, http://www1.wfh.org/publications/files/pdf-1227.pdf, accessed 2014-05-05

[142] http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=171DAEA96FDAEF09CBB62DA0B804E046.tpdjo06v_1?idArticle=LEGIARTI000006689899&cidTexte=LEGITEXT000006072665&dateTexte=20120711 , accessed 2013-07-24

[143] http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=171DAEA96FDAEF09CBB62DA0B804E046.tpdjo06v_1?idArticle=LEGIARTI000006689899&cidTexte=LEGITEXT000006072665&dateTexte=20120711 , accessed 2014-05-14

[144] O'Mahony B et al. Haemophilia care in Europe: a survey in 19 countries. Haemophilia (2011), 17:35-40

and surveyed 19 countries seeking information about treatment availability following the recent promulgation of consensus guidelines designed to standardise the care of haemophilia throughout Europe. Those guidelines were drafted by an inter-disciplinary group of haemophilia physicians and were subsequently endorsed by the European Haemophilia Consortium and the World Federation of Hemophilia and were the subject of an official launch at the European Parliament in Brussels in January 2009.[146]

In 2012, 35 countries responded to a survey of European national haemophiliac patient organisations affiliated to the European Haemophilia Consortium (EHC) and the World Federation of Haemophilia regarding treatment and the availability of products. Table 11 summarises access to treatment for haemophilia and von Willebrand disease in Member States (from results published in the Haemophilia Journal by O'Mahony B et al).[147]

[145] O'Mahony B et al. Haemophilia care in Europe – a survey of 35 countries. Haemophilia (2011), 17:35-40

[146] Colvin BT et al. European principals of haemophilia care. Haemophilia (2008), 14:361-374

[147] O'Mahony B et al. Haemophilia care in Europe – a survey of 35 countries. Haemophilia (2013), 1–9, DOI: 10.1111/hae.12125

Table 11 - Breakdown of access to treatments for bleeding disorders in European Countries (data from O'Mahony B et al. Haemophilia (2013), 1–9, DOI: 10.1111/hae.12125)

	Haemophilia		Von Willebrand disease (vWD)	
Country	**Plasma-derived factor concentrate**	**Recombinant factor concentrate**	**Plasma-derived factor concentrate**	**DDAVP[148]**
Austria	🟩	🟩	🟩	🟩
Belgium	🟨	🟩	🟩	🟩
Bulgaria	🟩	🟩	🟩	🟨
Croatia	🟩	🟩	🟩	🟨
Czech Republic	🟩	🟨	🟩	🟩
Denmark	🟨	🟩	🟩	🟩
Finland	🟩	🟩	🟩	🟩
France	🟩	🟩	🟩	🟩
Germany	🟩	🟩	🟩	🟩
Greece	🟩	🟩	🟩	🟩
Ireland	🟥	🟩	🟩	🟩
Italy	🟩	🟩	🟩	🟩
Hungary	🟩	🟩	🟩	Unknown
Ireland	🟥	🟩	🟩	🟩
Latvia	🟩	🟨	🟩	🟩
Lithuania	🟩	🟩	🟨	🟨
Netherlands	🟩	🟩	🟩	🟩
Poland	🟩	🟨	🟩	🟩
Portugal	🟩	🟩	🟩	🟩
Romania	🟩	🟩	🟩	🟨
Slovakia	🟩	🟩	🟩	🟥
Slovenia	🟩	🟩	🟩	🟨
Spain	🟩	🟩	🟩	🟩

[148] DDAVP - desmopressin acetate (1-deamino-8-D-arginine vasopressin) is a synthetic derivative of the antidiuretic hormone, used for prevention and treatment of bleeding of some patients with mild haemophilia A and von Willebrand disease (VWD) and other bleeding disorders without the need of blood products - Mannucci PM et al, Desmopressin (DDAVP) in the Treatment of Bleeding Disorders, TREATMENT OF HEMOPHILIA, November 2012 · No. 11, World Federation of Hemophilia

	Haemophilia		Von Willebrand disease (vWD)	
Country	Plasma-derived factor concentrate	Recombinant factor concentrate	Plasma-derived factor concentrate	DDAVP[148]
Sweden	🟨	🟩	🟩	🟨
United Kingdom	🟨	🟩	🟩	🟩

🟩 Always available 🟥 Never available 🟨 Rarely available

Sixteen countries stated that recombinant factor concentrates and plasma-derived concentrates were always available together (Austria, Bulgaria, Croatia, Finland, France, Germany, Greece, Italy, Hungary, Lithuania, Netherlands, Portugal, Romania, Slovakia, Slovenia and Spain) for the treatment of haemophilia, while in Belgium, Denmark, France and UK plasma derived concentrates were rarely available. .

According to this survey, there were important variations in the treatment of haemophiliac patients regarding access to home care, prophylactic and immune tolerance treatments, which explains the different factor VIII consumption rates. Among EU Member States, Sweden reported the highest factor VIII consumption per capita (8.56 IU) whereas Romania (0.51 IU) and Latvia (1.70 IU) the lowest. In Bulgaria and Lithuania, the rate is now 2.14 and 3.37, while in 2009 the reported use was less than 2 IU. Based on GDP per capita used as a crude measure of economic strength the authors *concluded that the differences in access to replacement therapy are due in large part to economics and local wealth.*

An increased need and demand of clotting factors is expected, as there is still room for improvement in the health care of haemophiliac patients in some countries.

Discrepancies in the level of care and lack of standardised operating procedures / effectively implemented guidelines for usage of plasma-derived medicinal products or preparation in case of shortages that may impact on patient access to care create the need to:

- Define shortages with relation to patient access to care
- Define official optimum treatment levels (quantities of medicinal products) for the management of the different diseases

5.4.3 Systems to prioritize indications

5.4.3.1 Introduction

To our knowledge, two countries have implemented systems to prioritize indications in case of shortage of IVIG supply: the United Kingdom and France. Both countries were prompted by the need to mitigate the effect of potential shortages. Indications are classified (labelled or not) into groups of higher and lower priority.

The core summary for product characteristics (SPC) claims that IVIG is indicated for:[149]

- *Replacement therapy in adults, and children and adolescents (0-18 years) in:*
  - *Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).*
  - *Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.*
  - *Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.*
  - *Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).*
  - *Congenital AIDS with recurrent bacterial infections.*

- *Immunomodulation in adults, and children and adolescents (0-18 years) in:*
  - *Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.*
  - *Guillain Barré syndrome.*
  - *Kawasaki disease.*

5.4.3.2 Monitoring of IVIG and SCIG supply (France)

In 2008, the French MoH has issued a circular (DGS/PP/DHOS/E2/AFSSAPS/2008/92)[150] regarding the monitoring of normal human immunoglobulin supply and management of supply tension situations. A translation of the priority ranking system is provided in appendix of this document (Appendix 1).

This circular concerns both IVIG and subcutaneous IG (SCIG) and requires pharmaceutical companies to monthly report the available stocks and distributed quantities of IVIG and SCIG.

In France, in 2010, the Agence française de securité sanitaire des produits de santé (AFSSAPS) defined a hierarchy on indications on the use of immune globulins in case of shortage or risk of shortage[151], which defined three groups with different priority levels:

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[149] Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94038/2007 Rev. 4 Committee for Medicinal Products for Human Use (CHMP), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136433.pdf, accessed 15-05-2014

[150] Circular DGS/PP/DHOS/E2/AFSSAPS n°2008-92 issued 14 March 2008 accessible at: http://www.sante.gouv.fr/fichiers/bo/2008/08-04/ste_20080004_0100_0112.pdf , accessed 2014-04-24

[151] Proposition de hiérarchisation des indications des immunoglobulines humaines intraveineuses (IgIV) en situation de tension forte sur les approvisionnements pour le marché français ; http://www.ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Proposition-de-hierarchisation-des-indications-des-immunoglobulines-humaines-intraveineuses-IgIV-en-situation-de-tension-forte-sur-les-approvisionnements-pour-le-marche-francais-Lettre-aux-professionnels-de-sante

- Priority indications,
- Indications for vital emergency or failure from therapeutic alternatives,
- No priority indications, which could wait until end of shortage.

5.4.3.3 National Demand Management Plan (UK)

In 2006, the UK Department for Health initiated a 'National Demand Management Programme for Immunoglobulin' containing the following three elements:

- The Demand Management Plan, outlining procedures in times of IVIG shortages.
- The National Clinical Guidelines for Immunoglobulin Use, providing guidance on appropriate use of IVIG and a framework for evidence-based clinical practices.
- The National Immunoglobulin database, providing information for improving consistency in standards of care and to predict future use.

The Clinical Guidelines for Immunoglobulin Use provide a mechanism to prioritize, who should receive IVIG during acute shortages and – just as importantly – provide guidance for use of this costly product in routine clinical practice. Each clinical indication for IVIG is assigned a colour-coded designation as follows[152]:

- **Red** *signifies a disease for which treatment is considered the highest priority because of a risk to life without treatment.* A commission policy issued in 2008 aimed to ensure a timely and uninterrupted provision of IVIG/SCIG to an agreed set of patients who have life-threatening conditions for whom IVIG/SCIG is either the only or first line option for treatment.[153]
- **Blue** *indicates a disease for which there is reasonable evidence base, but where other treatment options are available.* The use of immunoglobulin in these indications should be modified in times of shortage.
- **Grey** indications are those for which the evidence base is weak, in many cases because the disease is rare; IVIG treatment should be considered on a case-by-case basis, prioritised against other competing demands; these indications have the lowest priority in times of shortage.

Leonard et al. from Federaal Kenniscentrum voor de Gezondheidszorg - Centre fédéral d'expertise des soins de santé (KCE), Belgium found difficulties using these systems and cast doubt on *the rationale behind the choice of classification is not always stated or rationalized, the categories need*

[152] Department of Health (UK). Accessed at http://www.ivig.nhs.uk/ , accessed 2014-05-14

[153] Commission Policy for all treating centres for the provision of intravenous and subcutaneous immunoglobulin to high priority patients. RED indications - Version 2 (2008-2009)

to be regularly updated, and the application of this prioritization is not always described: in the absence of shortage, should a patient from a last priority group receive IG or not?[154]

IPFA disagrees with the above statement and stresses that the UK system is regularly updated and the rationale for classification is undertaken by clinical experts. In any event, IPFA supports the use of evidence based clinical guidelines to manage demand and ensure good patient access. IPFA understands that following discussions at the Wildbad-Kreuth III initiative in April 2013[155], the adoption of such systems will be recommended for all EU Member States.

PPTA, on the other hand, believes that these doubts do not induce the evidence to introduce such a prioritization system in other EU Member States. Moreover, since physicians in this regard face individual patients with often a combination of co-morbidities, it must be left to the treating physician to finally decide if a product treatment is critical and should be prescribed. PPTA adds that governments should run functional systems ensuring adequate reimbursement for safe and efficacious products made available for physician prescription.

[154] Léonard C et al. Comment assurer l'autosuffisance de la Belgique en dérivés stables du plasma ? Federaal Kenniscentrum voor de Gezondheidszorg - Centre fédéral d'expertise des soins de santé (KCE) reports 120B. 2009

[155] Optimal use of clotting factors and immunoglobulins, European Directorate for the Quality of Medicines &HealthCareEuropean 26-27 April 2013 symposium proceedings, Wildbad Kreuth Germany,

5.4.4 Voluntary unpaid plasma donations

Article 20 of Directive 2002/98/EC[156] calls on Member States to "take all necessary measures to promote Community Self-Sufficiency in human blood or human plasma", and for this purpose, to "encourage the voluntary unpaid donation of blood and plasma". This subject remains until today at a centre of a controversial debate between proponents and opponents of paid donation that has been going on for several decades now.[157,158,159,160,161,162,163]

In most cases, national EU policies only permit an unpaid system of blood and plasma collection. This means that commercial plasma collections are limited to a few countries, which allow both compensated and not compensated donations including Germany, Czech Republic, Hungary and Austria[164]. The majority of Member States also import additional plasma products from the commercial plasma sector to fully meet their health needs[165] and/or because of the open competitive environment, which exists in the EU.[166]

According to the 2nd Report on VUD from the Commission to the council and the European Parliament, as regards aphaeresis (plasma, platelets…), the following countries provide some form of incentives to donors: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Malta, Poland, Romania, Spain, Slovenia, Sweden, the United Kingdom, Norway and Croatia. However, the nature of the incentives provided could be much variable, including refreshments, small tokens (such as mugs and t-shirts), reimbursement of travel costs and time off work (in the public sector and private sector). [167]

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[156] Directive 2002/98/EC of European parliament and of the Council of 27 January 2003 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 (O.J. L33,8.2.2003)

[157] Titmuss RM. From Human Blood to Social Policy, ed 2, expanded. New York: New Press; 1997. The Gift Relationship.

[158] Titmuss RM. Why give to strangers? Lancet. 1971 Jan 16; 1(7690):123-5.

[159] McLachlan HV. The unpaid donation of blood and altruism: a comment on Keown. J Med Ethics. 1998 Aug; 24(4):252-4; discussion 255-6.

[160] Rodriguez del Pozo P. Review Paying donors and the ethics of blood supply. J Med Ethics. 1994 Mar; 20(1):31-5.

[161] Whyte G. Ethical aspects of blood and organ donation. Intern Med J. 2003 Aug; 33(8):362-4.

[162] Archard D. Selling yourself: Titmuss's argument against a market in blood. J Ethics. 2002; 6(1):87-103.

[163] Buyx AM. Blood Donation, Payment and Non-Cash incentives: Classical questions drawing renewed interest. Transfus Med Hemother. 2009 October; 36(5): 329–339.

[164] First Report from the Commission to the Council and the European Parliament on promotion by Member States of voluntary unpaid donations – COM (2006) 217 final

[165] Mahony et Turner "The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products", Vox Sanguinis (2010) 98, 447–450

[166] Statement by IPFA

[167] 2nd Report from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions on voluntary unpaid blood donations of blood and blood components COM (2011) 138 final

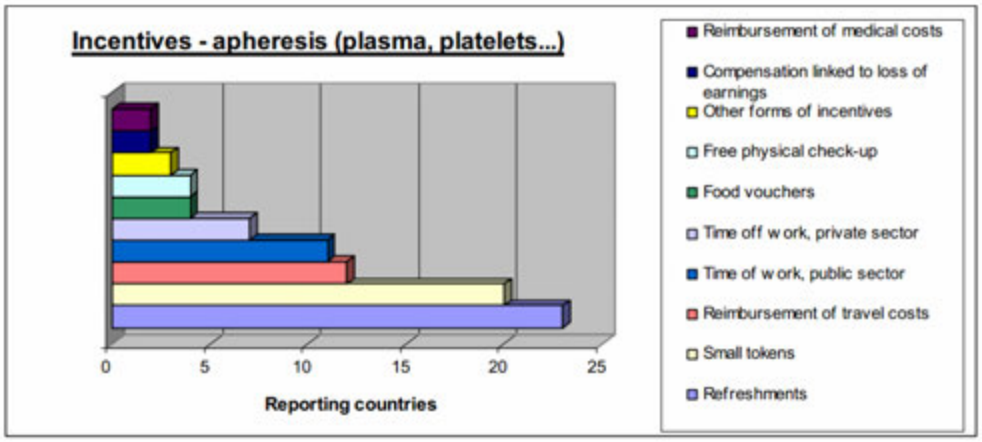

Figure 12 - Incentives for plasma donation

Farrugia A et al. reported in 2010 that in Germany, compensated plasma donations results in 12 units per donor yearly suggesting that apprehensions of 'crowding out' (i.e. a reduction in VUD donations where paid donations are introduced) through plasma donor compensation are unfounded.[168] There is a substantial amount of literature on donation of blood and plasma investigating whether providing incentives for donations of blood/plasma causes a "crowding-out" (introduction of new factor to an environment causes new competition with previously existing factor, radically changing the environment) that might lead to less donation overall.[169] Authors have found that incentives increase donations without leading to a decrease in donation quality.[170,171,172,173]

EBA on the other hand views this as a competition between non-for-profit blood centres and for-profit plasma sector that attracts donors using monetary incentives. EBA explains that this competition has caused blood supply issues in Austria and Germany. A blood supply shortage in Austria resulted from unregulated competition between a non-profit blood centre and a for-profit company in 2006 when a commercial blood service went bankrupt. In Germany, a

[168] Farrugia A. et al. Payment, Compensation and Replacement – the ethics and motivation of blood and plasma donations. Vox Sanguinis (2010) 99, 202–211; DOI: 10.1111/j.1423-0410.2010.01360.x

[169] Png IPL: Altruism and crowding out in the provision of public goods: cross-country evidence from blood donations(2008); http://www.comp.nus.edu.sg/~ipng/research/blood.pdf.

[170] Mellström C. et al. Crowding out in blood donation: Was Timuss right?. (2008) Journal of the European Economic Association 6(4):845-863

[171] Lacetera N. et al. Social Image Concerns and prosocial behaviour: Field evidence from a non-linear incentive scheme. Journal of Economic Behaviour and Organization (2010) 76 (2): 225-237.

[172] Lacetera N. et al. Do all material incentives for prosocial activities backfire? The response to cash and non-cash incentives for blood donations." Journal of Economic Psychology (2010) 31 (4):738–748

[173] Lacetera N et al. "Will There Be Blood? Incentives and Displacement Effects in Pro-Social Behavior." American Economic Journal: Economic Policy (2012) 4(1): 186–223

for-profit company that paid donors abruptly stopped collecting and supplying Prenzlau and Brandenburg hospitals with blood in 2007. Non-profit blood centres were forced to fill this gap on short notice, but could only regain one out of six donors that the for-profit company had previously attracted from the non-profit centre.[174]

Of the IPFA EU member organisations (LFB in France, Sanquin in Netherlands, CAF-DCF in Belgium and BPL in UK), Sanquin is responsible for the collection of its own plasma by its National Blood Bank division, being part of the same foundation. They collect whole blood (and thus produce recovered plasma) and source plasma from VUD. LFB and CAF-DCF purchase VUD plasma from their respective blood establishments. LFB also periodically purchase VUD plasma from the US and other EU countries. LFB also owns a plasma collection company in Austria, which collects plasma for supply to third parties. BPL purchases paid plasma from its plasma collection company in the US because of the ban on the use of UK plasma as a vCJD precautionary measure. Plasma processed or collected by IPFA EU member organisation is from VUD with the exception of LFB plasma collected in Austria and BPL plasma from the US where donors are compensated.

PPTA members Baxter, Biotest, CSL Behring (CSL plasma) and Kedrion collect plasma in Europe. In addition to the fractionators, the following PPTA EU Source members collect plasma to supply it to fractionators: Haema AG; Europlasma; Plasmapunkt Wien/Favoriten; Plasmaspendedienst Graz; Gesellschaft für Humanplasma (DGH); UNICAplasma; Ruhr-Plasma-Zentrum Bochum GmbH.

PPTA members collect plasma in:

- Austria
- Czech Republic
- Germany
- Hungary

PPTA members mention to compensate their donors for their time and inconvenience.

PLUS strongly believes that relying solely on VUD is not appropriate to guarantee an appropriate supply of PDMPs for the patients and would most definitely create a major public health issue. PLUS firmly believes that there is no conflicting interest in having both types of donors in a given country. A large majority of PDMPs currently distributed worldwide depends entirely on remunerated plasma donors (aphaeresis plasma 20-25€ per donation). PLUS opinion is that it would simply be irresponsible and unfeasible to guarantee appropriate supply without remunerated plasma donors.

The Dublin Consensus Statement 2010[175] on vital issues relating to the collection of blood and plasma and the manufacture of plasma products and The Dublin Consensus Statement 2012 “Optimised Supply of Plasma Derived Medicinal Products”[176] highlight the need for both recovered and aphaeresis plasma.

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[174] G Folléa et al. Why voluntary non remunerated blood donations are now more important than ever? Principals and perspectives of the European Blood Alliance. *In* G Folléa, J de Wit eds. Blood, tissues and cells from human origin: the European Blood Alliance Perspective. European Blood Alliance, Amsterdam, the Netherlands, 2013. ISBN 9789082031003.

As presented earlier in this report (p 26-28), EBA advocates for using the terminology and intervention ladder provided by the Nuffield Council on Bioethics report on "Human bodies: donation for medicine and research" [177] to reach a consensus on this sensitive topic of VUD for plasma donations.

PPTA would endorse this approach if plasma donation is not stigmatised in comparison with other activities. As stated above, PPTA suggested that compensated plasma donation belongs to level 3 (*Interventions to remove barriers and disincentives to donation experienced by those disposed to donate)* within the Nuffield Framework.

[175] The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang. 2010 98: 447-50 DOI: 10.1111/j.1423-0410.2010.01310.x

[176] O'Mahony B. The Dublin Consensus Statement 2012 on optimised supply of plasma-derived medicinal products, *Blood Transfus 2013; **11**: 623-6* DOI 10.2450/2013.0044-13

[177] Nuffield Council on Bioethics. Human bodies: Donations for medicine and research. http://www.nuffieldbioethics.org/sites/default/files/files/Donation.pdf , accessed 2013-07-24

5.4.5 Arrangements for collection, fractionation and distribution of plasma

5.4.5.1 Introduction

Third party agreements exist within EU MS covering collection, fractionation and/ or distribution of plasma and plasma derived medicinal products.

IPFA and PPTA members periodically undertake contract/toll manufacturing of plasma (for the preparation of plasma derived medicinal products) on behalf of organisations both within and outside the EU.

IPFA specifies that within such agreements, the plasma and manufactured products remain the property of the third party and typically cannot be described as 'agreements with third party groups for plasma collection'. These agreements consist of multiple types of bilateral contracts both within the EU and elsewhere for processing of plasma to intermediates or finished products for return to the supplying country/organisation.

Suppliers of plasma to PPTA and IPFA members for the manufacturing of plasma protein therapies in EU must comply with:

- Directive 2002/98/EC – Directive 2004/33/EC – Directive 2005/61/EC – Directive 2005/62/EC
- European Pharmacopeia monographs
- EU Commission guideline on Good Manufacturing Practice (GMP) annex 14
- Plasma Master File (PMF) requirements laid down in Directive 2001/83/EC- central EMA approval / national implementation (annual after 1st approval of PMF)
- Individual company and countries quality requirements

The details of the agreements are proprietary information.

According to MRB[178], in 2011, ten Member States had a plasma proteins market with an estimated worth close to 3 million Euro (see table 8, above).

The estimated worth decreased from 2008 to 2011 in Belgium, Czech Republic, Greece and Portugal, but in all other Member States there was an increase, ranging from 1.4% in Romania to 56.8% in Denmark.

The decrease in market values may be explained in some countries by the economic crisis, which led to a lowering of prices.

When recombinant factors were included, the estimated market value is up to 4.5 million euros.

Table 12 - Estimated plasma protein market. Variation from 2008 to 2011 and estimated market including recombinant factors in some Member State

	Plasma Proteins Market (million Euros)	% Variation from 2008-2011	Market including Recombinant factors (million Euros)	% Variation from 2008 -2011
Austria	68	+ 33.5	94,5	34.7
Belgium	81	- 5.9	157,7	- 0.4
Bulgaria	5,5	+ 10	6,8	+ 24
Czech Republic	33,8	- 9		
Denmark	30,4	+ 56.8 ($)	68,6	+ 39.2 ($)
Finland	37,3	+ 42.3	57,3	+ 37.9
France	575,8	+ 17,8	928	+ 7,5
Germany	900,5	+ 37	1.332,6	+ 36
Greece	51,5	-18.3	74,2	- 16.3
Hungary	26,8	+ 23.6 (Forint)	40,8	+ 12.8 (Forint)
Ireland	18,9	+ 12	52,8	+ 19
Italy1	395,2	+ 21.7	674,8	+ 20.0
Poland	78,1	+ 24	90,1	+ 24
Portugal	42,6	- 25	58,2	- 17
Romania	7,6	+ 1.4	11,4	+ 20
Slovakia	24,8	+ 55		
Spain	260,7	+ 15.3	375,8	+ 13.1
Sweden	88,3	+1.8	156,9	- 3.1
The Netherlands	88,2	+ 11.9	194,9	+ 14
United Kingdom	203,7	+ 8.4	416,6	

[(a)] Data provided by the Competent Authority

[178] Market Research Bureau (MRB) THE PLASMA PROTEINS MARKET IN (Country), 2011.

5.4.5.2 Not for profit fractionators

The list of plasma fractionation arrangements in EU is provided in Appendix 2.

Only France and UK have a state-owned fractionation plant. The Netherlands and Belgium (joint plant NL/BE close to Brussels) have independent not for profit organisations operating under license[179].

In France, the government owned Laboratoire Francais du Fractionnement et des Biotechonologies (LFB) has two sites in Les Ulis (near Paris) and in Northern France at Lille. Today, LFB contract fractionates for Morocco, Tunisia, Luxembourg and Brazil.

As no plasma is collected in the UK due to the risk for CJD, BPL (Bio Products Laboratory) imports plasma for fractionation and for supplying the local market.

Cooperation between Sanquin (Netherlands) and the Belgium Red Cross started in 1998 forming a joint venture to establish the fractionation plant CAF-DCF in Neder-over-Heembeek, Belgium. Later LFB has joined the joint venture. Sanquin has a 50% plus two vote majority in CAF-DCF.

No fractionation plants are located within the following countries: Denmark, Finland, Greece, Ireland, Luxembourg, Portugal, Bulgaria, Cyprus, Czech Republic, Estonia, Latvia, Lithuania, Malta, Romania, Slovakia and Slovenia.

In Denmark, the State Serum Institute had produced albumin from 1952 and small pools of coagulation factors from 1965[180]. The institute stopped fractionation in 2004. The American biotechnology company Hemasure acquired Novo's plasma products business in 1996 but the venture was a failure. Denmark now has a contract manufacturing arrangement with CSL in Bern.

Finland contracted the fractionation to Octapharma and Baxter. Until 2004 the Finnish Red Cross Blood Service fractionated Estonian plasma until 2004, when the plant was closed. The Finnish Red Cross Blood Service plant was closed in 2004. Sanquin then fractionated Finnish plasma until 2009. Estonian plasma was also fractionated by the Finnish Red Cross Blood Service.[181]

According to John Curling *et al* [182], the number of global not-for-profit plasma fractionation facilities dropped from 69 to 31 from 1990 to 2007 (in Europe dropped from 39 to 12). In the same period, the total plasma fractionated increased from approximately 5 million L to 6 million L in 2007 and consequently dropped to 4.5million L (44% recovered plasma) by 2010, corresponding to 29% (1990) and 24% (2010) of the total plasma fractionated. The developments in the processing capacity of EU not-for-profit fractionators between 1990 and 2010 included a

[179] Statement by IPFA.

[180] Jensen K. Bekæmpelse af infektionssygdomme. Statens Serum Institut 1902-2002 - ISBN 87-17-03659-3

[181] Curling J, Goss N and Bertolini J. The history and development of the plasma protein fractionation industry. In Production of Plasma Proteins for Therapeutic Use. Pp3-30. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA

[182] Curling J, Goss N and Bertolini J. The history and development of the plasma protein fractionation industry. In Production of Plasma Proteins for Therapeutic Use. Pp3-30. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA

decrease of capacity by LFB (1173 to 656 X103L/year), a retention of capacity for BPL and Sanquin (approximately 450 X103L/year and 250 X103L/year respectively) and an increase of capacity for CAF-DCF (200 X103L/year to 699 X103L/year). [183]

5.4.5.3 For-profit fractionation in Europe

Austria, Belgium, Germany, Italy, Spain, Sweden, Hungary, and Poland have privately owned fractionation plants.

In Poland, Biomed Lublin underwent privatisation in 2001.[184] The company was exporting its products to Belarus, Ukraine, Romania, Tajikistan, Uzbekistan, Moldova and Kyrgyzstan[185].

Many other plants however were absorbed during acquisitions by a limited number of private fractionators who significantly increased their fractionation capacity[186].

- From 1990 to 2010, CLS Ltd increased processing from 184 to 6200 x 10^3L/ year (figures include CSL Bioplasma) , acquired ZLB in 2000 and, in 2004 the Aventis Behring company, which previously was Centeon, formed by merging Armour Pharmaceuticals and Behrinwerke. Baxter Biosciences processed 3450x10^3L of plasma in 2002, and 5800x10^3L in 2010. In 1997, Baxter Biosciences acquired Immuno AG,[187] founded in AT in 1954 and mainly active in AT, DE and the US.
- In 2002, Grifols processed 1080x10^3L. This increased up to 3200x103L in 2010 and 5800x10^3L in 2011 following acquisitions of Alpha Therapeutics in 2003, and of Talecris Biotherapeutics in 2011 (which processed 3600 x103L in 2010).
- Octapharma is a privately owned company that was established in Austria in 1983. As its name implies, its initial focus was factor VIII products. Octapharma processed 815 x103L of plasma in 1990, which was increased to 3200 x103L in 2010. Octapharma had therefore acquired the German Red Cross (DRK) facility in Springe and the Aventis plant in Strasbourg in 1999. The former Kabi facility was acquired in 2002.

As explained below, according to MRB data, CSL Behring is the plasma derivatives manufacturer with higher market share in the EU, it is also the only company having market share in all the 27 countries). Also Oxctapharma and

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[183] Curling J, Goss N and Bertolini J. The history and development of the plasma protein fractionation industry. In Production of Plasma Proteins for Therapeutic Use. Pp3-30. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA

[184] About us section of Biomed Lublin website accessed at: http://www.biomed.lublin.pl/en/index.php?option=com_content&view=article&id=117&Itemid=113 , accessed 2013-03-24.

[185] Investors' and Exporters' Assistance Centre - Department of Economy and Innovation - Lublin Voivodeship Marshall's Office - http://lubelskie.coie.gov.pl/en/aktualnosci/a,103,biomed-lublin-expands.html

[186] Curling J, Goss N and Bertolini J. The history and development of the plasma protein fractionation industry. In Production of Plasma Proteins for Therapeutic Use. Pp3-30. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA.

[187] Curling J, Goss N and Bertolini J. The history and development of the plasma protein fractionation industry. In Production of Plasma Proteins for Therapeutic Use. Pp3-30. 1st Edition (Bertolini J, Goss N, Curling J eds.) John & Wiley Sons 2013, Hoboken NJ, USA.

Baxter have presences in many EU Member States. In Belgium, France, Netherlands and UK the local not-for-profit plasma fractionators are the main players, while the Spanish and Italian markets are mainly served by for-profit players originating from these countries.

According to Curling J *et al,* the number of commercial fractionation facilities increased from 33 to 45 between 1990 and 1999 and dropped again to 34 by 2007. Over the same period, fractionated volumes evolved from 12 (1990) to approximately 20 million liters (2007), corresponding to an evolution of 71% to 76% of the total plasma fractionation activity. By 2010, this had further evolved to more than 29 million L processed plasma of which 80% was source plasma.

Table 13 - Plasma derivatives manufacturers' Market shares (2011) (adapted from MRB Country Reports)

	CSL Behring	Biotest	Baxter	Octapharma	Kedrion	CAF-DCF	Ortho Clinical Diagnostics	Grifols	BulBio NCIPD	Sanquin	LFB	Nycomed Pharma	BPL	Other
Austria	48.50%	18.60%	17.50%	5.30%	4.60%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	5.50%
Belgium	26.00%	0.00%	16.50%	3.90%	0.00%	51.10%	1.90%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.60%
Bulgaria	5.00%	0.00%	30.00%	23.00%	0.00%	0.00%	0.00%	34.00%	8.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Czech Republic	2.00%	4.00%	48.00%	10.00%	0.00%	0.00%	0.00%	36.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Denmark	75.20%	0.00%	19.20%	2.80%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	2.80%	0.00%	0.00%	0.00%
Finland	38.60%	0.00%	16.90%	9.00%	0.00%	0.00%	0.00%	0.00%	0.00%	35.00%	0.00%	0.00%	0.00%	0.50%
France	18.30%	0.00%	16.60%	5.50%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	58.80%	0.80%	0.00%	0.00%
Germany	39.10%	15.00%	18.80%	11.80%	0.00%	0.00%	0.00%	10.70%	0.00%	0.00%	0.00%	0.00%	0.00%	4.60%
Greece	35.30%	0.00%	29.20%	0.00%	7.80%	0.00%	0.00%	16.50%	0.00%	0.00%	5.60%	0.00%	0.00%	5.60%
Hungary	11.00%	25.40%	19.00%	13.40%	31.20%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Ireland	11.00%	8.30%	47.00%	7.60%	0.00%	0.00%	0.00%	25.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.10%
Italy	9.00%	3.30%	16.60%	0.00%	57.80%	0.00%	0.00%	10.50%	0.00%	0.00%	0.00%	0.00%	0.00%	2.80%
Poland	25.00%	4.00%	47.00%	8.00%	0.00%	0.00%	0.00%	12.00%	0.00%	0.00%	0.00%	0.00%	0.00%	4.00%
Portugal	14.00%	0.00%	8.00%	47.00%	4.00%	0.00%	0.00%	25.00%	0.00%	0.00%	0.00%	0.00%	0.00%	2.00%
Romania	3.00%	3.00%	40.00%	41.00%	13.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Slovakia	7.00%	2.00%	37.00%	18.00%	0.00%	0.00%	0.00%	35.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.00%
Slovenia	3.00%	8.00%	20.00%	69.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Spain	13.30%	1.40%	13.10%	6.20%	0.00%	0.00%	0.00%	65.90%	0.00%	0.00%	0.00%	0.00%	0.00%	0.10%
Sweden	40.30%	0.00%	34.50%	24.00%	0.00%	0.00%	0.00%	1.20%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
The Netherlands	7.10%	0.60%	31.60%	2.80%	0.00%	0.00%	0.00%	0.00%	0.00%	57.90%	0.00%	0.00%	0.00%	0.00%
United Kingdom	12.20%	8.50%	23.40%	0.00%	0.00%	0.00%	0.00%	17.20%	0.00%	0.00%	0.00%	0.00%	32.10%	6.60%

Data for Cyprus, Estonia, Malta, Luxembourg, Latvia and Lithuania not available.
LFB: Laboratoire Français du Fractionnement et des Biotechnologies; BPL : Bio Products Laboratory

5.4.6 Barriers to trade and restricted practices

Barriers to trade, as PPTA prefers to name it, or Restricted Practices as IPFA chooses to define it (see complete definition in section 5.2.4), has been a subject of public debate for a long time.

IPFA has no detailed knowledge of specific commercial agreements between its members and their respective national stakeholders and other third parties. However, it is aware of arrangements in both not for profit and for profit organisations where national arrangements for fractionation of locally collected plasma preclude free market access to this plasma.

PPTA believes that cross-subsidisation creates a barrier to trade where countries have a legal monopoly to acquire and manufacture plasma collected by their establishments.

PPTA reports the following cases:

- Belgium: - Royal Decree of 18/6/1998 articles 2, 2bis and 2ter. The Belgian Red Cross receives a subsidy of 24,79 Euro/L for its plasma collection activities if it sells its plasma to CAF-DCF. – 0,25% of the civil liability insurance subscribed by any driver in Belgium is used to support the general activities of the Red Cross.
- The Netherlands: – A report by ConQuaestor that analyses the situation in the Netherlands and the different roles of Sanquin, private and public parts. However, according to the Dutch Competent Authority the ConQuaestor report concludes there is no cross-subsidization in NL.
- France: - Article L. 5124-14 of the French Public Health Code on acquisition and manufacturing of plasma
- United Kingdom: - Relation between UK Government, BPL (Bio Products Laboratories), and the National Health Service Blood and Transplant (NHSBT) within the UK National Health Service (NHS).

5.4.7 Recombinant and plasmatic coagulations factors (FVIII and FIX) across EU27

5.4.7.1 Factor VIII

The coagulation factor VIII can be produced either from human plasma (Plasmatic factor VIII) and as recombinant technology (Recombinant factor VIII). In EU, there are indications for the use of both forms:[188]

- Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)
- Management of acquired factor VIII deficiency

The emergence of the recombinant product has reduced the demand of the plasmatic derived products particularly in developed countries. Nonetheless, both forms are used and needed to meet the clinical needs, as describe on point 5.4.2.2, table 11. There is an increase in use in both plasma-derived and recombinant coagulation factors, as detailed in a report from the Instituto Superiore della Sanita', while describing the Italian situation.[189]

Prices of recombinant and plasma-derived FVIII in all EU member states are displayed in table 14. Recombinant factor VIII is more expensive in almost all EU Member States. France. However, in Denmark and Greece the recombinant form is cheaper than the plasmatic form. In France, the recombinant and the plasmatic form have the same price €183.78 / 250 IU.

The prices of recombinant factor VIII vary between the studied countries and the highest price is in Germany (€306.88 / 250 IU) and Italy (€287.22 / 250 IU) followed by Cyprus and Denmark.

In the following table, countries were ranked according to their GDP/Capita from the highest to the lowest.

[188] EMA - Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products - 24 May 2012 EMA/CHMP/BPWP/1619/1999 rev. 1 accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128995.pdf , accessed 2013-05-14

[189] Calizzani et Al. Analisi della domanda dei principali medicinali plasma derivati in Italia 2007-2011. Instituto Superiore della Sanita from 2012.

Table 14 - Retail prices of coagulation factor VIII in different EU countries based on 250 IU presentation

Country	*Average retail price of Plasmatic FVIII (€)	*Average retail price of Recombinant FVIII (€)	% difference	Rank (GDP/capita)[i]
Luxembourg	NA	NA	-	1
Denmark	415.44	253.3	-40%	2
Sweden	NA	188.13	-	3
Austria	206.41	236.92	15%	4
Finland	NA	224.24	-	5
The Netherlands	212.88	244.01	15%	6
Ireland	NA	NA	-	7
Belgium	223.76	246.88	10%	8
Germany	311.83	306.88	98%	9
France	183.78	183.78	0%	10
UK	NA	NA	-	11
Italy	173.34	287.22	66%	12
Spain	149.45	223.77	50%	13
Cyprus	NA	257.97	-	14
Greece	197.89	93.28	-53%	15
Malta	NA	NA	-	16
Portugal	NA	NA	-	17
Czech Republic	123.37	246	99%	18
Slovakia	108.29	191.00	76%	19
Estonia	NA	NA	-	20
Latvia	NA	NA	-	21
Poland	64[(a)]	78[(a)]	18[1]%	22
Hungary	97.24	168.26	73%	23
Romania	NA	NA	-	24
Bulgaria*	94.18	186.29	98%	25

***The reported prices represent an average of available retail prices for 250IU of plasmatic or recombinant factor VIII. The references used for price information are presented at the end of this document.**

[(a)]Data provided by the competent authority

5.4.7.2 Factor IX

The coagulation factor IX can be produced either from human plasma (Plasmatic factor IX) or as recombinant technology (Recombinant factor IX). Both forms are indicated for[190]:

- Treatment and prophylaxis of bleeding in patients with haemophilia B
- Management of acquired factor IX deficiency

The recombinant form of factor IX, as for the factor VIII, is more expensive than the plasmatic factor IX in almost all the EU countries studied except France. France is the only EU country where the plasmatic and recombinant forms, through state regulation, have the same price. Prices of the coagulation factor IX fluctuate in the European countries and range between €693.06 and €190.71 (Plasmatic Factor IX / 500 IU) and between €615.44and €273.33 (Recombinant factor IX / 500 IU). As for factor VIII, the highest prices of the recombinant form are in Germany (€615.44 / 500 IU) and Italy (€568.95 / 500 IU), followed by Denmark and Finland.

Table 15 - Retail prices of the coagulation factor IX in different EU countries based on 500 IU presentation.

Country	*Average retail price of Plasmatic FIX (€)	*Average retail price of Recombinant FIX (€)	% difference	Rank (GDP/capita)
Luxembourg	NA	NA	-	1
Denmark	NA	512.69	-	2
Sweden	350.63	405.81	16%	3
Austria	NA	NA	-	4
Finland	380.65	423.74	11%	5
Netherlands	437.555	NA	-	6
Ireland	NA	NA	-	7
Belgium	255.44	370.47	45%	8
Germany	693.06	615.44	-11%	9
France	367.56	367.56	0%	10
UK	NA	NA	-	11
Italy	412.6	568.95	37%	12
Spain	296.47	355.16	20%	13
Cyprus	NA	307.43	-	14
Greece	190.71	NA	-	15
Malta	NA	NA	-	16
Portugal[16]	NA	NA	-	17
Czech Republic[17]	243.29	273.33	12%	18
Slovakia[18]	222.64	NA	-	19

[190] EMA - Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products – 24 May 2012 - EMA/CHMP/BPWP/1625/1999 rev. 1 accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128994.pdf , accessed 2013-05-15

Estonia[19]	NA	NA	-	20
Latvia	NA	NA	-	21
Poland	52[1]	160[(a)]	-7%	22
Hungary[21]	NA	NA	-	23
Romania[22]	NA	NA	-	24
Bulgaria*[23]	197.73	NA	-	25

*The reported prices represent an average of available retail prices for 500IU of plasmatic or recombinant factor IX. The references used for price information are presented at the end of this document.

[(a)] Data provided by Competent Authority regards price of 250 IU of Factor IX plasma derived and recombinant

5.4.7.3 Management of surplus plasma-derived coagulations FVIII and FIX

Since the introduction of recombinant factor VIII and IX, there has been a significant uptake in different countries, partly driven by the perceived higher safety of recombinant factors compared to plasma-derived factors.

PPTA highlights that the consumption of rFVIII and rFIX is different in EU Member States. PPTA was not aware of any surplus of plasma derived FVIII and FIX.[191] Aiming to provide information to patients, manufacturers, regulators and other stakeholders on availability of products, PPTA announced the "European Data Program" on December 2013. PPTA started by reporting distribution data on the Recombinant Factor VIII, but informed to have intentions to expand to other products such as plasma derived clotting factors, albumin and imunoglobulines. [192]

IPFA does not have detailed data on the use of Plasma derived and recombinant coagulation factor products in all EU countries. However it is known that the majority of product used for the treatment of patients in the 15 countries of the former EU is from recombinant sources and there is a large potential surplus of plasma derived product available from domestically donated plasma in these countries for export within the EU or to other countries. For those EU countries which have a National Fractionator (i.e. France, UK, Belgium, Netherlands) the quantity of plasma derived FVIII and FIX available from their domestic and imported plasma supply significantly exceeds domestic product demand and can be exported within the EU and elsewhere.[193]

Despite the transition from the use of plasma derived coagulation factor products to biosynthetic analogues, there remains a significant group of haemophilia patients, who continue to be treated with plasma derived products. The reasons for this include personal preference, lower inhibitor incidence rate, perceived efficacy, lower price and the treatment of disorders such as von Willebrand

[191] Statement by IPFA.

[192] http://www.pptaglobal.org/media-and-information/press-releases/881-ppta-letter-to-stakeholders-re-european-data-program

[193] Statement by IPFA.

disease for which there is no currently available biosynthetic product. IPFA is not aware of any EU country which uses no plasma derived product although the ratio of plasma derived/recombinant varies between countries. Recombinant factors in general are perceived to be safer regarding infectious transmission risks as they do not depend on human donors.

Aiming to improve the care of European citizens with inherited bleeding disorders by a network of haemophilia centres, the European Commission provided 60 % of the funding for a project of the European Haemophilia Network (EUHANET)[194] (885 614,00€) under the EU Health Programme 2008-2013 -, running between 2012 to 1015. The remaining 40% was funded by industry.

An increasing demand for clotting factors may be expected due the increased life expectancy of patients with bleeding disorders as a result of health care improvements (including home care, prophylactic treatments and access to more complicated surgical procedures). Patients are treated for a long period of time, and are treated as adults which require greater and more frequent doses of clotting factors. In some countries, recombinant factors are being used as alternatives to plasmatic derived factors. Although there are still limitations, novel products are currently under development[195,196], such as biosimilars, long acting factor VIII and IX, which may one day change the present demand on plasmatic derived products.

5.4.8 Increasing demand in immunoglobulin (IG)

The driver for the required volume of plasma for manufacture is immunoglobulins. Its use continues to grow for three main reasons:

- The number of clinical indications for IG keeps increasing. Recently an indication for Alzheimer has been subject to clinical trial.
- Widespread off-label use (IVIG off-label use in US and Italy are provided in Appendix 3 as an example)
- Improved access to patients for existing indications.
- Chronic use in some indications, particularly for the treatment of some neurological illnesses in addition to immune deficiencies.

IVIG has indeed become an important treatment option in a number of clinical indications beyond primary immunodeficiency, including autoimmune and acute inflammatory conditions and off-label prescribing has crossed over into almost every medical specialty.[197]

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[194] http://www.euhanet.org/docs/EUHANETLEAFLET0407v3.pdf, accessed 14-05-2014

[195] http://www.hemophilia.ca/files/Pipeline%20-%20Factor%20VIII%20and%20VWF.pdf

[196] Shapiro A., Development of long-acting recombinant FVIII and FIX Fc fusion proteins for the management of hemophilia, Expert Opin Biol Ther. 2013 Sep;13(9):1287-97. doi: 10.1517/14712598.2013.819339

[197] Clinical guidelines for the use of IVIG – UK Department of Health

In England, according to the *Third National Immunoglobulin Database Report, (2012)*[198] neurological conditions are the most immunoglobulin consuming (43%), followed by immunological (33%), haematological (11%) and haemato-oncological (8%).

For some time, there has been concern over availability of IVIG to the NHS, due to a global supply shortage and issues specific to the UK and France. After which, both countries adopted special measures to prioritize a number of indications to prepare for shortages and risks of shortage (see section 5.4.3).

Although Alzheimer's disease was considered as one of the most promising indications for IVIG therapy, Baxter recently announced that its Phase III clinical study of immunoglobulin (IG) did not meet its co-primary endpoints of reducing cognitive decline and preserving functional abilities in patients with mild to moderate Alzheimer's disease[199]. Despite this off-label use cannot be excluded and an increase in overall IG consumption worldwide is to be expected in the upcoming years.

Hyperimmunes globulins used in the prevention and treatment of infectious diseases[200] are produced with plasma from previously immunized patients. The percentage of use in Europe represented 39% of global sales in 2009 (estimated at $768 million).

Efficient preventive health programmes, such as global hepatitis B vaccination or prevention of immunisation of pregnant Rh(D) negative women with specific immunoglobulin were implemented. As a consequence, the number of donors having the required titre of specific antibodies is decreasing at the same time that demand is increasing.[201]

Considering the above mentioned reasons, there is general concern about upcoming issues related to immunoglobulin supply to patients.

IPFA members recognise the potential future increased demand for plasma products but do not see the need to adopt any 'special measures' to increase the supply of IG. Indeed, the fractionation industry is familiar with changing patterns (both qualitative and quantitative) in the market for plasma derivatives. The industry has adapted to different product drivers throughout its history (albumin; then coagulation factors; now immunoglobulin) and will continue to do so. Manufacturers adjust their plasma collection and/or purchase (e.g. new donor recruitment programmes, purchase

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[198] *Third National Immunoglobulin Database Report, (2012)*
http://www.ivig.nhs.uk/documents/Third_National_Immunoglobulin_Database_Report_2011_2012.pdf

[199] Baxter announces topline results of phase III study of immunoglobulin for Alzheimer's Disease. May 7, 2013. Media@baxter.com

[200] Hsu J. L. et al, Polyclonal Immunoglobulins and Hyperimmune Globulins in Prevention and Management of Infectious Diseases Infect Dis Clin N Am 25 (2011) 773–788 doi:10.1016/j.idc.2011.07.005

[201] Robert P. Hyperimmunes Plasma Procurement and Products, Iranian Journal of Blood and Cancer. 3 (3): 147-149 (2011)

more and in more countries), as well as their production to match demand for their products and irrespective of future demand have an economic interest in maximising their yield.[202]

PPTA and IPFA member companies have different fractionation capacities and operate with different fractionation methods.

IPFA members in Europe also operate in a free and open competitive environment and match their procurement of plasma and production output to the specific domestic and export demand for their product. Individual companies have surplus capacity to meet potential increases in demand for all plasma products.

IPFA indicated that a range of factors will determine future demand including:

- Evolving clinical practice and indications
- Price
- Health care policy
- Priorities and funding
- Health Technology Assessments
- Emergence of alternative treatments

Both IPFA and PPTA do not forecast the demand for IG in the upcoming years.

There are independent projections and models of future demand and the most widely quoted of these are produced by The Marketing Research Bureau. Available reports are based primarily on past trends and future extrapolations, industry estimates and emerging possible future indications and therefore do not claim to be necessarily accurate or based on consensus clinical evidence.[203]

These forward projections offer models of future increases of demand of ~6% for the existing range and associated indications rising to a ~12% increase per annum in the event that IVIG receives regulatory approval for the treatment of Alzheimer's Disease[204], which nonetheless now seems unlikely.

A more recent study published in 2011 by Global Business Intelligence research estimates global consumption will reach 129 metric tons and $2.6 billion by 2016.[205] while Marketing Research Bureau predicted an increase to 150 metric tons by 2015 if indication for Alzheimer's Disease

[202] Statement by IPFA

[203] Statement by IPFA

[204] Robert P. Global Plasma Demand in 2015. Pharmaceuticals Policy and Law (2009) 11:359-367

[205] GBI Research. Immunoglobulins Market to 2017 – Off-Label Usage and Treatment of Primary Immunodeficiency Diseases and Neurological Disorders Stimulate Market Growth. Sept 2011

treatment was approved and 130.6 metric tons if not. The demand for Polyvalent IVIG was 68 metric tons by 2006.[206]

Robert P predicted that if IVIG could be used to treat Alzheimer's (a high-prevalence disease), the global demand would greatly increase and have serious consequences for plasma collections.[207,208]

5.4.9 Import/Export of plasma and plasma derived medicinal products

As previously mentioned by interviewed stakeholders, there is a movement of blood products including plasma and fractionation products within and outside EU (see sections 5.4.5).

In 2000, EMA has organised a workshop on the Plasma Master File tackling this subject where it was suggested to implement controls on import and export of plasma and fractionation products and on the distribution of plasma-derived medicinal products (need for inspection and licensing at every point). This also would require the need for a data-exchange system including a rapid alert system to inform all interested parties within the EU on deficiencies.[209]

In 2012, export of plasma for fractionation was reported by five Member States[210]:

[206] Robert P. – IVIG/SCIG: Global Usage Trends, Marketing Research Bureau, Inc. IPOPI Global Leaders meeting 2011 Nov. 4-5, London< England, - http://www.ipopi.org/uploads/Patrick%20Robert.pdf, accessed 14-05-2015

[207] Robert P. – IVIG/SCIG: Global Usage Trends, Marketing Research Bureau, Inc. IPOPI Global Leaders meeting 2011 Nov. 4-5, London< England, - http://www.ipopi.org/uploads/Patrick%20Robert.pdf, accessed 14-05-2015

[208] Robert P. Global Plasma Demand in 2015. Pharmaceuticals Policy and Law (2009) 11:359-367

[209] Report - EMA Workshop on the Plasma Master File – October 2001 – EMEA/CPMP/BWP/1737/02

[210] Implementation survey 2013, to be published

Table 16 - Countries reporting exported plasma for fractionation in 2012[211]

Country	Amount/Product	Destination
DE	3,399,419 L of plasma	Third countries (not specified)
DK	214.576 (60,9 metric tons)	Switzerland
FR	200 units of therapeutic lyophilized plasma	USA
EE	26 997 'doses' of plasma 7199 'doses' of plasma	Octapharma Biotest AG
SK	3063 L of plasma	Ukraine

IPFA explained that until today there are no reliable and authoritative data which describe the overall movements of plasma for fractionation and plasma derivatives within the EU or the level of imports from outside the EU.

EBA and IPFA agreed that Europe is not self-sufficient based on VUD. However, IPFA and EBA have shown that self-sufficiency of plasma from VUD was not so far away, as an analysis of plasma collection volumes and IVIG usage in 2008 (based on MRB and EDQM/CoE data) for the former 15 EU Member States indicated that at that time these member states collected sufficient plasma (paid, 30% and unpaid, 70%) to meet their collective demand for IG (99%)[212]. This analysis is being updated to reflect 2011 data. Data (plasma collection and IVIG usage) is not currently available for the new EU countries.

For PPTA, self-sufficiency for whole blood and labile blood components is a realistic goal while self-sufficiency for plasma protein therapies is not realistic.

To further increase security of supply and meet future potential increases in demand, IPFA advocated strategies which:

1. Ensure that recovered plasma available from all EU countries is collected to standards suitable for fractionation.
2. Eliminate wastage of recovered plasma from some countries.
3. Establish tactics to increase the supply of source plasma from VUD.

[211] Implementation Survey, 2013. Report to e published

[212] Rossi et al. How expanding voluntary non-remunerated blood donations would benefit patients, donors and healthcare systems? Vox Sang 2012, 102: 269-70. DOI: 10.1111/j.1423-0410.2011.01495.x

PPTA found that a regulated and flexible open system of import and export is the best way to ensure patients have sustained access to state of the art treatment.

IPFA confirmed that Sanquin and LFB export excess products from EU plasma for which there is no demand in Europe either because of competition or because there is a sufficiency of supply.

BPL ships plasma products prepared from US plasma both within the EU and elsewhere.

The members of PPTA are internationally operating companies and as such export therapies to many countries in the world (including Europe).

5.4.10 Flaws in legislation, regulations and policies

5.4.10.1 Legislations, financial health care policies that may limit the patient access to plasma derived products:

In many EU countries with relatively high GDP and developed health care systems guidelines exist for the appropriate use of plasma products (particularly IVIG).

IPFA was not aware of any high GDP countries in which patients have been denied treatment for approved indications.

PPTA learned from patient organizations (e.g. European Haemophilia Consortium (EHC), International Patient Organization for Primary Immunodeficiency (IPOPI), EURORDIS) about obstacles to access in EU Member States.

PPTA reported 'disharmonization' between EU MS sustaining that:

- France disagreed with the compensation of plasma donors and implement unfavourable regulatory provisions (L. 5121-11 of the French health code) for plasma-derived medicinal products from paid plasma donations. PPTA consider such practices as against the principles of free trade among the EU MS and not in the interest of patients in terms of availability of life-saving plasma derived medicinal products, although no further details were provided. French authorities clarified that this article allows obtaining a marketing authorisation for these products in case of shortage or if no alternative PDMP, obtained from voluntary unpaid donations, is available. French authorities also refer to article 110 of Directive 2001/83/CE which calls on Member States to encourage VUD of blood and plasma. French authorities expressed the view that there is no hinder for free circulation and that PDMP from other EU Member States, obtained from VUD, as well as PDMP authorised at EU level, can be put on the market in France.
- It is of extreme importance that physicians have the opportunity to choose between products, which cannot be guaranteed when the lowest acquisition cost should be used for purchasing plasma-derived and recombinant medicinal products. Policies attempting to cut

costs at the expense of good care will result in increased patient morbidity and hence increased medical costs.

- Legislation, such as the Blood Directive, addresses over-arching principles. For flexibility, specific requirements, such as donor eligibility criteria, should not be included in legislation but in regulation and guidance documents.

IPOPI (International Patient Organization for Primary Immunodeficiency) expressed concerns and worries regarding patient access to most efficient and adapted treatment. In particular, IPOPI criticized and warned about considering IG as 'generics'[213] contrasting the quotation from *Commissioning Immunoglobulin: Advice to the Commissioners and Commissioning Bodies* published in October 2011 which comments on the Second Edition Update: Clinical Guidelines for Immunoglobulin use as follows:

All immunoglobulin products are considered generic and therefore the commissioners insists that, when prescribers begin treatment on a new patient, the product with the lowest acquisition cost should be used unless compelling reasons for using the alternative have been specified as part of the IAP's approval (page 4, section 4). [214]

With effect from April 2013, there have been significant changes in the way healthcare services in England are commissioned. More recent information can be obtained from the Third National Immunoglobulin Database Report (2012), published in July 2013[215.]

According to this document, in England, immunoglobulin for patients with primary immunodeficiency, who are the subject of the IPOPI position statement, is not restricted. A patient with primary immunodeficiency is categorized as High Priority, and a treatment request made by their clinician is automatically approved. However, where there is no clinical reason for using a particular immunoglobulin product, clinicians would be expected to use the product with the lowest acquisition cost.

5.4.10.2 Regulations adding unnecessary costs to the plasma market at EU level:

IPFA recognised the essential requirement for robust and evolving regulation to maintain the safety, quality and efficacy of plasma products. However it can be argued that despite the widely accepted advocacy for 'risk based assessment' for regulation the additional application of the 'precautionary

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[213] IPOPI POSITION STATEMENT Access to Immunoglobulin Therapies for patients living with a Primary Immunodeficiency

[214] Ewart HE et al. Commissioning Immunoglobulin – Advice to commissioners and commissioning bodies. October 2011.

[215] *Third National Immunoglobulin Database Report, (2012)*
http://www.ivig.nhs.uk/documents/Third_National_Immunoglobulin_Database_Report_2011_2012.pdf

principle' can in some circumstances add cost and complexity without clear evidence of safety, efficacy or quality benefit.

The incremental costs of such approaches are particularly significant for smaller fractionators and plasma supply organisations. The following examples illustrated IPFA's concerns but are not an exhaustive list[216]:

- Clinical Trials: The progressive increase in the requirement for patient numbers in clinical trials of new or modified plasma products (particularly coagulation factor products) can be criticised on the basis of the statistical and scientific rationale for such increases. The escalation of such requirements decreases the feasibility and increases cost of clinical trials for rare diseases such as haemophilia and can act as a disincentive for product improvement and development contrary to the interests of patients. This concern has been argued in a recent review by Professor Mannucci[217].
- CJD/vCJD Exclusion and Recall Procedures: The EMA has issued guidance for the recall and destruction of plasma products associated with donations from donor known or suspected to be suffering from vCJD. In particular the guidance requires recall of products from all previous donations prior to a vCJD diagnosis. Although the likelihood of such an event is small, the impact on product supply for any affected manufacturer could be dramatic, leading to supply failure. IPFA believes that the precautionary action prescribed by the guidance do not take due account of potential supply (and cost) implications and in the absence of a scientific rationale for such action has expressed its concern to EMA and requested a review of this guidance. In addition to the above, the French regulatory agency (ANSM) is the only agency, which requires the recall of products associated with donors found to be suffering from sporadic CJD. This precautionary action which exists only in France is contrary to the position of other international regulatory authorities (including EMA and FDA) since there have never been any recorded cases worldwide of transmission of classic/sporadic CJD by pooled plasma products. However, the risk of transmission of variant CJD and other prion diseases by blood and plasma products is not yet conclusively established.[218&219&220&221]. French authorities express that such national practice aims to

[216] Statement by IPFA.

[217] Mannucci P M. Evolution of the European guidelines for the clinical development of factor VIII products: little progress towards improved patient management. Haemophilia 2012, 1-5

[218] Questions on variant Creutzfeldt–Jakob disease and blood transfusion, March 2010, updated July 2011 ECDC INTERIM RISK ASSESSMENT, accassed 20-05-2014

[219] Volume 49, August 2009 Supplement TRANSFUSION 49S

[220] Christopher A. Ludlam et al, British Journal of Haematology, 132, 13–24 doi:10.1111/j.1365-2141.2005.05796.x

[221] Soon-Tae L. et al Laboratory Investigation (2009) 89, 612–613; doi:10.1038/labinvest.2009.42

protect public health, in line with article 168, 4 (a) and 7, of the Treaty on the Functioning of the European Union.

IPFA advised that plasma collected in the UK, Ireland and Portugal is not used for the preparation of therapeutic plasma products as a precautionary measure against the risk of vCJD. The total plasma 'lost' to EU supply as a result of this action is approximately 700,000 litres per annum[222]. Although complete EU data is not available concerning the collection and use of plasma for fractionation in all EU member states, it was recognised that some EU countries are not able to contribute or cannot maximise their contribution to EU plasma supply because they are either unable to comply with current EU regulatory standards and/or they have yet to develop the necessary infrastructure and quality systems. Examples include Romania, Bulgaria, Greece and possibly other countries.

- Lack of Harmonisation of Regulations: Plasma from both the US and EU is used for the manufacture of plasma products to treat patients in EU countries. Regulation of donor selection and plasma collection procedures differs between US and EU regulators requiring substantial duplication of effort and cost by industry and plasma collection organisations where, for example, US plasma is used for product supply to the EU. Lack of harmonisation of regulation between the EU and US has been long recognised as an unnecessary burden to industry, which would wish to see an acceleration of progress towards harmonised systems between US FDA and EMA.

Epidemiological Surveillance: IPFA recognised the need for continuous epidemiological surveillance of blood and plasma donors. However, the increasingly complex requirements for data collection, reporting and analysis do not enhance the understanding or analysis of this safety parameter or contribute to product risk assessments.

At present plasma fractionators provide the European Medicine Agency with epidemiological data from donors as proprietary material, in their plasma master file.

This greatly differs from the blood establishments mandatorily providing the European Commission with donor epidemiological data in national annual reports. From this observation, EBA recommended to make available public aggregated anonymized epidemiological reports, including

[222] IPFA states that this is a purely estimate derived from knowledge of the volume of plasma collected in these countries prior to the emergence of vCJD. This estimate can also be derived from a calculation of the recovered plasma available from current whole blood collections.

paid plasma donations and voluntary unpaid plasma donations, to allow for a full comparison of voluntary unpaid and paid donors with regard to patient safety and also donor safety[223].

PPTA advocated a variety of means that would – altogether – improve patient access to plasma products in the EU:

- Plasma Master File (PMF) 2nd Step procedure: The PMF 2nd step procedure is not in line with the European Commission's better Regulation Initiative that aims to avoid unnecessarily complicated regulatory procedures as it is a purely administrative act after a centralized evaluation of the PMF, with no impact on public health and unnecessarily binds limited resources of national regulatory authorities and manufacturers, which could be more efficiently used in areas of real impact on public health.[224].

  The proposed adaption would require minor efforts, namely marginal updating of two regulatory documents (2nd step guideline, Guidelines on the details of the various categories of variations Regulation (EC) No 1234/2008 Article 4(1) (a)).

  A comparison of the 2nd step procedures before and after the implementation of EC/1234/2008 shows that the workload for the company and also the involved regulatory authorities increase significantly, because of this step "of purely administrative nature" (Guideline on PMF and Vaccine Antigen Master File (VAMF) "Second Step"), now each single product dossier has to be updated, resulting in an increase of electronic sequences from 1 to 100. In addition, the associated costs have increased to up to 740%, depending on the number of products and EU countries where these products are licensed. Over the years, PPTA member companies have gathered more experience with the 2nd step procedure and the additional workload and costs have accumulated to an unprecedented magnitude.
- Guideline on the scientific data requirements for PMF - EMEA/CHMP/BWP/3794/03 Rev.1 (Nov 2006): Requires the regular GMP inspection (every 2 years) of all plasma suppliers by an EU Competent Authority (regardless if suppliers are EU based or e.g. US based; FDA inspections are not recognized as sufficient).

  The approval of plasma suppliers in the EU PMF requires an inspection of each establishment by EU Competent Authorities every two years. This is also required for plasma centres in the USA that are licensed and regularly inspected by the FDA. The EU GMP inspections do not add demonstrated value over the FDA GMP inspections, and the number and risk level of the EU inspection findings in recent years do not justify the biannual, costly inspections. Major savings could be achieved, without adding any risk to the patient, by e.g. reducing the EU

[223] Folléa et al . Why voluntary non remunerated blood donations are now more important than ever? In Folléa et al. editors, Blood, tissues and cells from human origin: the European Blood Alliance Perspective, 2013, pp 102-125 http://europeanbloodalliance.eu/eba-book/

[224] IPFA supported this comment.

inspections to an initial qualification audit and to spot audits of a few plasma centres from one and the same company at an ongoing basis (risk based approach).

- Guideline on epidemiological data on blood transmissible infections – EMA/CHMP/BWP/548524/2008 (22 April 2010): Requires reporting, trending and alert level setting for epidemiological data of the donor population to be established by the marketing authorization holder.

  The reporting and trending of epidemiological data under this guideline does not add value to finished plasma protein products' safety. The PPTA's Viral Maker Standard is congruent with the needs of finished therapy safety profiles. Today, each donation is subjected to multiple viral testing with highly sensitive Nucleic Acid Test (NAT) and Enzyme-linked immunosorbent assay (ELISA) methods. The window period of infection for HIV, Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) has thus been reduced dramatically over the past decade, and with it the residual risk of potentially contaminated plasma units entering a production pool. In addition, plasma pool testing with sensitive NAT and Elisa methods further mitigates the small residual risk of contaminated manufacturing pools, and validated viral inactivation and removal processes ensure that there is basically no risk for the finished product, or the patient with regard to these antigens. This is also supported by solid pharmacovigilance data of the plasma industry for the past decades. The monitoring and trending of epidemiological data should be the responsibility of the health authorities, and should be focused especially on transfusion products (e.g. red blood cells) that are not subjected to virus reduction treatment. The last HCV transmission was reported in 1994[225]

- Provisions of GMP Annex 14 on contract manufactures: Contract fractionation is an opportunity for all countries with no or insufficient plasma fractionation capacity to use plasma suitable for fractionation collected in their countries. There are necessary prerequisite for a successful contract fractionation agreement:
  - Epidemiological control of the donor population
  - Donor screening and management
  - Information system (donor information, national donor registry, traceability of donors and units
  - Validated collection procedures and transport conditions.

  Contract fractionation is a well-established procedure performed by PPTA member companies located in the EU. The current GMP Annex 14 PPTA imposes unnecessarily stringent conditions for contract manufacturers by not accepting plasma collected under equal, but not identical conditions to plasma intended for products marketed in the EU. PPTA believes that plasma is suitable for contract manufacture if it fulfils comparable, but not

[225] E. Tabor, "The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1", TRANSFUSION, V. 39, November/December 1999

identical criteria as EU plasma. It is in the interest of any fractionator to ensure that plasma entering their facilities is of appropriate quality and safety.

GMP Annex 14 is too restrictive and prevents EU based manufacturers from providing contract manufacturing services to non EU countries, thus wasting precious starting material for manufacturing of plasma protein therapies

Capacities for contract fractionation may be factored in routinely or used in case of free capacity of the fractionation plant. In both cases contract manufacturers may contribute to ensuring a sustained utilisation of the facility and to securing jobs.

- Physicians' presence in blood and plasma collection centres in Germany: In some EU Member States, for example in Germany, national law requires that a physician is always present in a blood or plasma collection centre. In other EU Member States it is sufficient that specifically trained nurses are responsible for routine plasmaphaeresis, while a trained physician needs to be available, but not permanently present. In 2005, Diekamp et al. conducted a study (unpublished) showing that screening of qualified frequent plasmaphaeresis donors by a qualified health professional effectively detects 99.986% of ineligible donors without any physician's input. The authors concluded that it seems appropriate to relieve physicians of the obligation to see every qualified frequent plasmaphaeresis donor prior to his/her release for each donation. This task can be delegated safely to qualified health professionals.
  The permanent presence of a physician in a plasmaphaeresis centre adds significant costs to the centre, without adding any substantial benefit. The tasks and responsibilities of the centre physician are very limited and can be fulfilled by qualified health professionals. When the presence of the physicians is required by national law, a plasma collection centre cannot operate without the presence of qualified physicians, which may impair the supply of plasma for fractionation[226].

Regarding PPTA concerns over GMP Annex 14, the European Commission has provided some clarification on its implementation[227], which states: "the legal requirements on traceability and serious adverse events and reactions reporting (Directive 2005/61/EC) and quality systems for blood establishments (Directive 2005/62/EC) have to be applied only when products are intended for distribution in the EU." IPFA considered that further clarifications are needed as the minutes also state that "… also for third countries fractionation programmes, consideration should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Commission Directive 2005/62/EC, the traceability requirements and notification of serious adverse reactions and events set out in Commission Directive 2005/61/EC and the relevant WHO

[226] German Transfusion law. (Transfusionsgesetz, paragraph 4)

[227] Meeting of the Competent Authorities on Blood and Blood Components 16-17 May 2011 Summary Report, http://ec.europa.eu/health/blood_tissues_organs/docs/blood_mi_20110516_en.pdf

guidelines and recommendations." Also some Member States reiterated the importance of traceability for third country fractionation programmes.

5.4.10.3 Policies to safeguard the supply of plasma derived products to patients:

IPFA commented that the European Blood Directive promotes and encourages the development and achievement of a secure blood and plasma product supply from voluntary non remunerated donors. The EU and its Member States provide a free and open competitive environment which facilitates the supply of products from within the EU and elsewhere (e.g. US).

IPFA stated that specific EU policies do not exist to protect the supply of plasma products to EU countries in the event of a global shortage or commercial preference to supply in higher price regions. However, a range of policies exist in some EU MS to safeguard their national supply. These include:

- The operation of national fractionation facilities such as LFB, Sanquin, BPL, CAF-DCF using locally collected plasma as their main (though not exclusive) source of raw material.
- Contract manufacturing arrangements with commercial or not for profit organisations in which locally collected plasma is manufactured into plasma products, which are returned for use in the country of origin. In the absence of such arrangements EU countries would require to compete in a global market for product supply.

6. Appendices

6.1 Appendix 1a. Pre-questionnaire to stakeholders

Dear Sir/Madam,

Creativ-Ceutical is contacting you on behalf of the European Commission.

Creativ-Ceutical has been contracted by the European Commission to provide an overview of the landscape of blood, blood components and plasma derivatives with a particular focus on their availability for patients in the 27 member states.

The main objective is to gather information that will provide insight on the following aspects:

A. <u>Characteristics of the blood, blood components and plasma derivatives landscape</u>

a. Volumes of collected, processed, stored and distributed products
b. Volumes of demand of these products: whole blood, red cells, plasma, immunoglobulins, clotting factors, etc.
c. Cost of obtaining these products with EU Member States for the different phases of the supply chain (collection, processing, storage and distribution).
d. Information about reimbursement of medicinal products, as well as their price
e. Description and volumes of imported and exported products for each member state

B. <u>Identification of the main actors involved in the supply chain</u>

a. Public authorities establishing regulations in this field
b. Process of recruitment of donors
c. Blood and plasma collecting establishments
d. Public fractionation plants and for-profit and not-for-profit private fractionation plants as well as pharmaceutical industries involved in the supply chain
e. Fractionation plants that import and export products to other EU countries and outside Europe.
f. Distributors and suppliers of fragile and stable blood, blood components and plasma derivatives. Towards hospitals and ambulant/retail sector, as well as in the hospitals.

In order to gather the required information for the European Commission we are collecting all the publicly available information that has been produced at national and international level.

Furthermore we proceeded by identifying the main stakeholders and address to them this pre-questionnaire that will help us recover any additional data that we have not been able to obtain through public sources or that we might have missed. We remind that this is a pure collection of data and that we do not ask you to produce any new data.

In addition we will ask for the inputs and perspectives of the Member States' Competent Authorities, as well as from some academics.

Please indicate the topic and the name of the file that you would like to share with us in the different boxes below and please send back the file along with the pre-questionnaire filled in.

1. Based on the description of the scope as indicated in the letter from the European Commission as well as in abovementioned study objectives, do you have any **published material** that you are willing to share with us and would help cover any of those topics?

2. Based on the description of the scope as indicated in the letter from the European Commission as well as in abovementioned study objective, do you have any **confidential material** that you nevertheless believe to be important for reasons of clarification and are willing to share with us? These materials will be treated in a confidential way by Creativ-Ceutical and the Commission. Where Creativ-Ceutical or the Commission believes the inclusion of these data would be desirable within a public report, you will first be asked for your approval.

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the

3. Did your organization recently conducted any **questionnaires** and are you willing to share the questionnaire and the results with us?

4. Do you have any materials (publications, studies, reports, etc.) describing the different system structures that regulate the management and collection of blood, blood components and plasma derivatives in (all or some) EU Member State(s)?

Beside the general information that we have requested above, we have identified a number of issues and concerns related to the blood, blood components and plasma derivatives landscape that we would like to get your view on in order to analyze them further.

5.

6. **Shortages in supply** of blood, blood components or plasma derivatives.

   Do you know of such shortages, with which products, in which countries/parts of the EU?

   What is your view on the drivers for these shortages and on the potential solutions?

   Do you have any data/materials that would help shed some light on this topic?

7. Shift, evolutions and conflicts within **donor populations.** How do donors for full blood compare to donors for plasma and what is the impact of having both within one system/country?

   What is the role of voluntary unpaid donation, of compensation, payment or other incentives?

   What is the impact if the regulatory set-up changes (e.g. when regulation is changes allowing (or not) payments)?

   Do you have any data/materials that would help shed some light on this topic?

8. The availability of **recombinant Factors**, like Factor VIII. What is their impact on the need for and use of plasma derivates, blood and blood component?

   Do you see differences in different Member states?

   Do you have any/materials data that would help shed some light on this topic?

9. The development of **new clinical indications for the use of intravenous immunoglobulins** (e.g. for Alzheimer disease). What is their (expected) impact on the demand for plasmas derivatives, blood and blood components?

   What is their (expected) impact on self-sufficiency?

   Do you see differences in different Member states?

   Do you have any data that would help shed some light on this topic?

10. The need for and importance of **import/export** of blood, blood components and plasma derivatives between the different Member States and from/to non EU countries.

    Do you have any data that would help shed some light on this topic?

11. Do you see any **other particular topic that raises particular concerns** - on the landscape of blood, blood components and plasma derivatives – that you believe should be covered in this overview study? Please highlight them here and they will be potentially included in our study.

    Do you have any data that would help shed some light on this topic?

Appendix 1b. Questionnaire to IPFA and PPTA

An EU-wide overview of the market of plasma and plasma derived medicinal products focusing on their availability for patients.
Data to be Correct as at 2011

This survey is conducted by Creativ-Ceutical on behalf of the European Commission.

The scope of the survey is to have an overview of the main concerns related to the plasma and plasma derivative supply across the European countries and from the perspective of fractionators in the EU.

Participant Information

1. Name of the institution/organisation/association	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
2. Please indicate which companies your institution/organisation/association is representing	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
3. Please indicate which EU Countries your institution/organisation/association is covering	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Part I. Plasma Collection [on the top of each page in this section]

This part aims at identifying plasma collection sources.

We assume that there are three main sources of plasma for the production of plasma derived medicinal products to be supplied in EU countries:

- A **self collection system**: where your organization directly owns collection centres and holds donor registries
- **Agreement(s) with organisations:** where third party groups collect plasma in EU countries and your organization is responsible for the fractionation and for the production of plasma derived medicinal products to be supplied in EU countries.
- **Purchase system:** where your organisation purchases plasma from third party groups centres, blood establishments and/or blood collection centres for the purpose of supplying plasma derived medicinal products to EU countries.

4. Do you collect your own plasma?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
5. Please name the countries where you collect plasma	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
6. Do you provide financial incentives to plasma donors for the supply of plasma to be used for the preparation of plasma products to be supplied in the EU?	☐ Yes ☐ No

7. Which type of financial incentives you provide to plasma donors?	☐ Remuneration i.e. fixed allowances ☐ Reimbursement of medical costs ☐ Reimbursement of travel costs ☐ Compensation linked to loss of earnings ☐ Food vouchers ☐ Other, please specify **Add also an open comment box at the end of this question** [MORE THAN ONE ANSWER CAN BE SELECTED]
8. Do you provide non-financial incentives to plasma donors for the supply of plasma to be used for the preparation of plasma products to be supplied in the EU?	☐ Yes ☐ No

9. Which type of non-financial incentives you provide to plasma donors?	☐ Free physical check-up ☐ Time off work, private sector; ☐ Time off work, public sector; ☐ Small tokens ☐ Refreshments ☐ Other, please specify **Add also an open comment box at the end of this question** [MORE THAN ONE ANSWER CAN BE SELECTED]
10. Do you have in place agreements with third party groups for plasma supply?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
11. Could you please describe the terms of these agreements?	[OPEN ANSWER IN THE TEXT BOX]
12. Do you buy/obtain plasma?	☐ Yes ☐ No **Add also an open comment box at the end of this question**

13. From which organisations/countries do you buy/obtain plasma for the preparation and supply of plasma derivatives to EU countries? (Please specify the quantity in kg)	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
14. If your plasma supply is obtained from more than one source (self collection, specific agreements and/or purchase), please indicate the contribution (in percentage) of each source for your organization's total plasma provisions	Self Collection Specific agreements Purchase [OPEN ENDED QUESTION, NUMERIC ANSWER IN THE TEXT BOX] [IF TOTAL ≠ 100, A MESSAGE "**THE TOTAL MUST BE 100**" APPEARS]

Part II. Plasma Export [on the top of each page in this section]

15. Do you export plasma derived medicinal products?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
16. Could you please list products derived from European plasma which you export to non European Member States and/or other countries and specify the quantities for each exported product? **17. (e.g.: Product (Factor VIII) ; Countries ; Quantities unit/g)**	1. 2. 3. 4. 5. 6. 7. 8. 9. 10. [OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Part III. Supply tensions [on the top of each page in this section]

Regular and sufficient supply of blood, blood components and plasma derivatives is by far the major concern for all actors involved in the blood and plasma supply chain. To fully appreciate the extent of this topic, it is important to work with common definitions of e.g. 'sufficiency of supply' and 'product shortage'

18. Are you aware if a country in the EU (including the one where you are located) has experienced over the last years any difficulties in fulfilling the demand from health care providers for any plasma derivatives?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
19. Could you please specify for which product there has been difficulties in fulfilling the demand, in which year(s) and in which country(ies)? Please provide references when available **(e.g.: Product (Factor VIII); Years (2004, 2007); Countries (IT, FR); reference)**	1. 2. 3. 4. 5. 6. 7. 8. 9. 10. [OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

20. Could you indicate the main reasons behind the difficulties mentioned above in fulfilling the demand for any plasma derivatives?

NB: the numbers correspond to your previous classification in Q19.

	Hospital health policies	Regional health policies	National health policies	Country budget restrictions	Collection resources and capacities	Fractionation related issues	Storage and distribution related issues	Other
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								

[MORE THAN ONE ANSWER CAN BE SELECTED]

21. Please provide details and reference on the reason(s) mentioned above (Which policies? Which hurdles? What other reasons?)

NB: the numbers correspond to your previous classification in Q15 and Q16.

1.
2.
3.
4.
5.
6.
7.
8.
9.

	10. [redacted] [OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Part IV. Increasing demand and need for Immunoglobulins (IG) [on the top of each page in this section]

Demand for immunoglobulins (IG) is the highest among all derivatives when considering the amount of plasma required producing it. Its use continues to grow as the number of clinical indications for IG keeps increasing.

One of the most promising indications for IG therapy may be Alzheimer's disease (AD).

An increase in overall IG consumption worldwide is to be expected in the upcoming years, especially if AD indication will be approved.

22. In your opinion, do you find that there is a need to adopt special measures to increase IG production?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
23. Which measures would you adopt to respond to the increasing request of IG?	☐ Increase the yield ☐ Increase plasma collection ☐ Other, please specify **Add also an open comment box at the end of this question**

	[MORE THAN ONE ANSWER CAN BE SELECTED]
24. According to your forecast, how much IG will be needed annually in the next 10 years? (Please provide references on which you based your forecast)	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
25. In order to understand the application of the different measures that you are willing to adopt and implement to increase IG production, we provide you an example of an increased collection: If you collect 20% more plasma, how much more produced IG will you obtain considering your current biotechnology equipment and resources?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Part V. Clotting factors

26. Since the introduction of recombinant factor VIII & IX there has been a significant uptake in different countries. Are you aware if any EU country has surplus plasma derived factor VIII & IX that are not directly used for patients within that country?	• YES • NO **Add also an open comment box at the end of this question**
27. If, yes could you please indicate which EU Countries do not use plasma derived factor VIII & IX, and support your answer with a reference?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Part VI. Cross-subsidisation [on the top of each page in this section]

28. Are you aware of any cross-subsidisation program in place in any EU country?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
29. Could you please describe the terms of cross-subsidisation agreements?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
30. Could you please indicate the countries that allow this practice?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
31. Does your organization have a cross-subsidisation program in place with any EU member states?	☐ Yes ☐ No **Add also an open comment box at the end of this question**
32. Please indicate countries/institutions involved in your agreement	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

33. Does the presence of cross-subsidisation around EU have an impact on your organization?	☐ Yes ☐ No
34. Could you please provide some examples	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Definition of Cross-Subsidisation: the practice of a Country subsidizing plasma collectors in order to allow them to sell plasma to fractionators at prices cheaper than the market

Part VII. European Regulations [on the top of each page in this section]

35. Are you aware of any EU country in which recovered plasma is collected but not used for fractionation as a result of policies/legislation/quality or regulatory constraints	☐ Yes ☐ No
36. Could you please provide examples and support your answer with a reference?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
37. Are you aware of any national legislation or financial health care policy which has denied or limited patient access to plasma derivatives in EU countries?	☐ Yes ☐ No
38. Could you please provide examples and support your answer with a reference?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
39. Are you aware of any regulations that are adding unnecessary costs to the plasma market at EU or country level?	☐ Yes ☐ No
40. Could you please provide examples and support your answer with a reference?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]
41. Could you please explain why you believe that the regulations mentioned above add unnecessary costs?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

42. Product supply in the future could potentially follow reimbursement price. Are you aware of any policy to safeguard the supply of products for patients in the EU?	☐ Yes ☐ No
43. Could you please provide examples and support your answer with a reference?	[OPEN ENDED QUESTION, ANSWER IN THE TEXT BOX]

Thank you for your time and valuable cooperation in completing the survey.

6.2 Appendix 2. Translation of section 4 of Circular N°DGS/PP/DHOS/E2/AFSSAPS/2008/92 of 14 March 2008 relative to the surveillance of supply in human normal immunoglobulins and the management of supply tension situations

4. Recommendations of prescriptions and indications of IVIG

In case of potential tensions in the supply of IVIg and SCIg, and in order to optimize the access of treatment to patients, the following prescription recommendation should be followed during the tension period:

4.1 Prioritisation of IVIG indications as approved in the MAA:

Prioritized indications:

- Antibody deficiency in primary immune deficiency
- Kawasaki syndrome
- Immune thrombocytopenic purpura in children and adults with hemorrhagic syndrome

Indications to prioritize in case of vital emergencies and/or failure of alternative therapies:

- Antibody deficiencies in secondary immune deficiency, especially chronic lymphocytic leukaemia or myeloma associated recurring infections
- Bacterial infections associated HIV infections in children
- Multifocal motor neuropathy
- Immune thrombocytopenic purpura in children and adults
- Guillain-Barre syndrome in adults

Non priority indications that could wait until the end of the shortage:

- Birdshot Retinochoroidopathy

4.2 Prioritisation of IVIG indications used off-label:

For off-label prescriptions of IVIG, reference frames of Good Use in a non-Homogenous Stay Group (GHS) available for these specialties, as well as any document of institutional information (letters to health professionals...) made available for ANSM, should be followed.

ANSM will propose the best course of action, case by case, according to the real state of shortage or supply tension and according the defined rules set by the steering committee.

6.3 Appendix 3. European plasma fractionation arrangements[228]

Country	Arrangement
Austria	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Belgium	Not for profit organization (CAF DCF - www.caf-dcf , which is owned: 50% by Sanquin, 25% by LFB and 25% jointly by the Flemish and French Community Red Cross Organizations) using "unpaid blood donations" and some plasmaphaeresis. Capacity of national fractionator: 750,000 (according to MRB Report 2010)
Bulgaria	One state-owned fractionation plant. "Bul Bio,"NCPD the National Center of Infectious and Parasitic Diseases Ltd Open markets to products fulfilling relevant regulatory requirements
Cyprus	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Czech Republic	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Denmark	No national state owned fractionators. Old facility closed in 2004. Open markets to products fulfilling relevant regulatory requirements
Estonia	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Finland	No national state owned fractionators.

[228] Provided by PPTA, as of July 2012

	Open markets to products fulfilling relevant regulatory requirements
France	State owned, not for profit organization (LFB - www.lfb.fr) using "unpaid blood donations" and small but increasing quantity plasmaphaeresis. Also purchased in 2010 Europlasma Holding that collects plasma from voluntary compensated donors. This plasma is used for preparation of products distributed outside of France. Owns 25% of International CAF-DCF, see Belgium. Capacity of national fractionator: 900.000 capacity (MRB report from 2010).
Germany	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Greece	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Hungary	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Ireland	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Italy	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Latvia	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Lithuania	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Luxembourg	Formerly plasma fractionated with Belgian service, but recently (2009) fractionation through private sector fractionators
Malta	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements

The Netherlands	Not for profit foundation (Sanquin - www.sanquin.nl) using VUD for whole blood and plasmaphaeresis. Owns 51% of Belgian CAF-DCF organization (see Belgium)
Poland	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Portugal	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Romania	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Slovakia	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Slovenia	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Spain	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
Sweden	No national state owned fractionator Open markets to products fulfilling relevant regulatory requirements
UK **England & Wales**	State owned fractionation organization (BPL) using USA based PPTA member plasma centres that are owned indirectly by the UK government A process of separation from Government started in 2013
UK **Scotland**	No national state owned fractionator. Open markets to products fulfilling relevant regulatory requirements

6.4 Appendix 4. Most-common off-labels indications for IVIG (example for US and Italy)

Examples of most common off-label uses for IVIG in the US[1]

Primary
• Mutlifocal motor neuropathy (MMN)
• Guillain-Barré Syndrome
• Acute panautonomic polyneuropathy
• Miller Fisher syndrome
• Crossmatch-positive solid organ transplantation
• Multiple myeloma
• Hemolytic disease of the newborn
Secondary
• Autoimmune mucocutaneous blistering diseases
• Pemphigus vulgaris
• Pemphigus foliaceus
• Mucous membrane pemphigoid (Cicatrical pemphigoid)
• Epidermolysis bullosa acquista
• Myasthenia gravis syndrome
• Lambert-Eaton syndrome
• Multiple sclerosis
• Inflammatory myopathies
• Dermatomyositis
• Polymyositis
• Idiopathic progressive polyneuropathy
• Intractable eplilepsy
• Acute cardiomyopathy
• Pure red cell aplasia
• Hemolytic anemia
• Refractory platelet transfusions
• Fetal alloimmune thrombocytopenia (FAIT)
• Stiff person syndrome
• HIV associated thrombocytopenia

Examples of main off-label uses for IVIG in Italy[2]

• Thrombocytopenia
• Hypogammaglobulinaemia in acute lymphoblastic leukemia
• Autoimmune haemolytic anaemia
• Neonatal hyperbilirubinaemia
• Rh iso-immunisation

6.5 References for Price Information

[i] http://data.worldbank.org/indicator/NY.GDP.PCAP.CD?order=wbapi_data_value_2012+wbapi_data_value+wbapi_data_value-last&sort=desc