Key findings

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

Objectives

The purpose of this Creative Ceutical report was to provide an economic perspective on the European blood sector. Such perspective is important to understand and improve safety, quality and availability of the therapies delivered by this sector. While safety and quality are the direct mandate of the European Commission, availability is a recurrent concern for national authorities, healthcare professionals and patients in the European Union.

These therapies result from a multi-step process. To start, the collection of all blood and blood components depends entirely on the awareness and willingness of EU citizens to make donations. However, not every citizen willing to donate is fit to do so. A number of health-related criteria, laid down in EU and national legislation, have to be verified in order to ensure safety for the donor and the eventual recipient. Consequently, a collection can take place, either of a unit of whole blood (WB) or of just one of the blood components (plasma, platelets, red blood cells or white blood cells).

Following collection, the units of WB are usually separated into units of blood components. These units of blood components are further processed, stored and distributed following EU legal requirements in order to be transfused in the clinic. Plasma, one of the blood components, can be further processed in an industrial setting into plasma derivatives (PD), subject to a separate EU legislation for pharmaceuticals.

This Creative Ceutical report has collected quantitative data, in particular on volumes, and, where possible, prices in the EU. In addition, the report offers qualitative perspectives, including views from different stakeholders on factors that affect the economics of the sector like payment of donors, shortages and self-sufficiency.

The findings of the report cannot be taken to reflect the views of the European Commission and/or the Executive Agency for Health and Consumers (EAHC), now renamed CHAFEA.

Working Methods

The report is based on desk research and the collection of stakeholder views through surveys and interviews. The fact that many of the economic issues relate to the diverging interests of the public and private actors active in this sector proved challenging for the work. Also few reliable data sources could be found, and it proved difficult to find coherent data sets across all Member States.

In order to help mitigate these concerns the study relied primarily on data from the Council of Europe (EDQM/CoE) and Market Research Bureau (MRB), even if also these data sets do not cover all aspects (e.g. on prices).

Key data

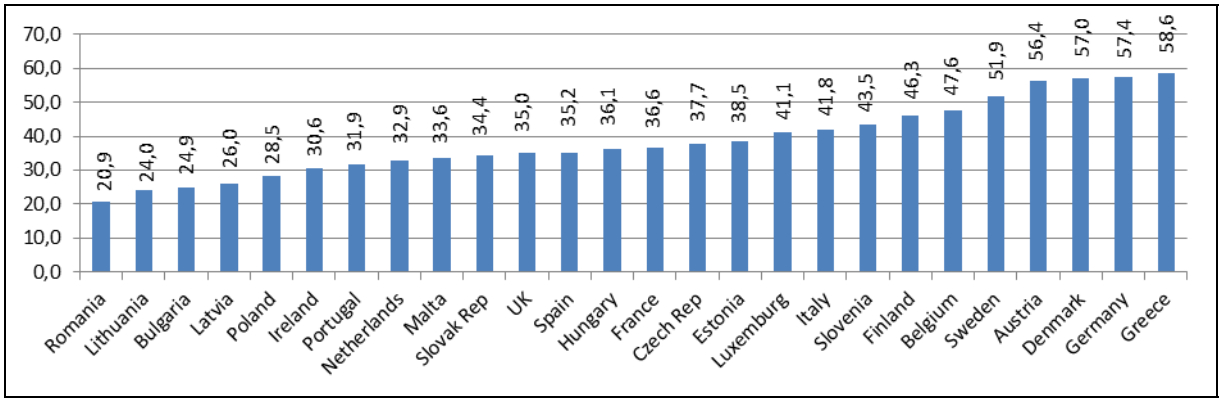
Whole Blood (WB) and blood components

Between 2005 and 2010 the total number of donors in the EU increased by 19% (annual growth of 3.5 %), leading to a total of 14.1 million donors in the EU Member States. On average 25% of these 2010 donors were first time donors, indicating a significant turn-over rate and the need for continuous recruitment efforts. Member States are therefore obliged to invest in donor recruitment and donor retention strategies. One related recruitment aspect that has been highlighted by certain stakeholders is the potential competition between paid and unpaid donation systems. This ratio of first time donors varied however significantly between Member States from 10% of all donors (HR, NL, PT) to more than 30% (LT, PL, SK).

These 14.1 million donors accounted for 21.2 million whole blood (WB) donations in 2010, i.e. on average every donor donated about 1.5 times per year. This was a 6% increase compared to the 2005 exercise of CoE, or an annual growth of 1.1%.

Collected units of WB are then separated, further processed, stored, distributed and eventually ready for transfusion. The CoE data mention transfusion numbers, within the EU-28 Member States, of 19.9 million units for RBC, 4.4 million units for plasma and 2.2 million units for platelets in 2010. RBC are mainly needed for invasive surgery, haemato-oncology, intensive care and emergency care. Transfusion of platelets and plasma is often used for treating bleeding disorders.

The utilisation levels of RBC vary significantly between EU Member States, from below 25 units transfused per 1000 inhabitants to more than 50 *(figure, adapted from* EDQM report). This variation reflects differences in clinical practice as well as in organisation of supply and resulting availability.



Blood components are rarely exchanged between Member States. Besides some sporadic exchanges of very specific blood units for specific needs, the report only mentions 2 import agreements for blood components (RBC into EL, and plasma into UK).

The collection and supply of WB and blood components is usually undertaken by public actors. Prices per unit are often set by national authorities and some 2008 MRB data suggest a variation e.g., from 100€ or less per unit RBC (DE, BE) to close to 200€ (FR, NL, IT). A comprehensive list of prices, and therefore of market values, is however not available.

Plasma derivatives (PD)

Plasma, one of the components of WB, can also be recovered by companies who manufacture plasma derivatives (immunoglobulines, albumin and clothing factors like factor VIII or factor IX). Besides recovering plasma from WB donations, these companies obtain plasma mainly from plasma-only donations (so-called plasmapheresis or collection of source plasma). The report shows that plasmapheresis is mainly organised in HR, DE, BE and NL (precise data for AT and HU are missing, but it is widely known in the sector that plasmapheresis takes place in these countries). Plasmapheresis is not organised in IE and UK, due to the history of Creutzfeld-Jacob disease.

Plasma collection in the EU for manufacturing PD is growing much faster than WB collection and has almost doubled between 1993 and 2010, from 8.5 to 16.6 million litres (an average annual growth rate of 4 %). The growth in PD is therefore also mainly driven by plasma from plasmapheresis (source plasma annual growth of 6 %) and less from recovered plasma (annual growth of 1 %). With 11.7 million litres, source plasma supplies about 70 % of processed plasma.

In 2010, there was a global manufacturing capacity in 2010 for fractionation of 48 million litres, while 34 million litres were manufactured, meaning there was significant overcapacity. Of this volume, commercial actors manufactured 29 million litres of plasma (87%), while (semi-)public organisations manufactured 4.5 million litres (13%). Within the last decennia the sector has also migrated to fewer but larger manufacturing plants. As these plants do not exist in each EU Member State, plasma (the starting material) and PD (the end product) are frequently exchanged across borders, both within the EU and to/from third countries (no exact data on the extent of the movements exist). Also the steadily increasing demand generates significant import flows of PD from third countries into the EU.

While data on the utilisation of PD are not available for all countries, MRB data indicate a steady global growth of 6% per year and a significant variation between EU Member States. A good example is immunoglobuline, for which the 2011 utilisation rates range from above 110 grams per 1000 inhabitants in SE, FR and BE to below 20 grams in the Baltics, HR and HU. [NOTE: the Creative Ceutical study used 2007 data]. Immunoglobulines are mainly used to treat patients with neurological, immunological and/or hemato/oncological conditions. The growth is mainly driven by pharmaceutical companies who study and obtain authorisations for new clinical applications and increased levels of treatment for existing applications. Also off-label use is mentioned as a driver for growth.

In contrast to WB and blood components, PD are considered to be pharmaceuticals and market value data are available. The worldwide market of PD was estimated at 11.8 billion USD in 2009, of which almost half for immunoglobulines. MRB estimated the total EU market value of PD to be close to 3 billion Euro in 2011. For the sake of completeness it needs to be mentioned that some clothing factors (VIII and IX) can be manufactured entirely within a factory setting, without the need for human donations. These so-called recombinant products are characterised by a perception of higher safety and by a higher price. They are not available in all EU Member States and their EU market value is estimated to be worth another 1.3 billion Euro in 2011.

Market data also show that there is usually one leading plasma manufacturer, public or private, who supplies the major part of each national EU-28 markets, complemented by a few international

private actors supplying each smaller parts in multiple national markets. The markets ins UK, FR, BE and NL are led by (semi-) public local manufacturers, each focused on their own national market. CSL-Behring, Octapharma, Baxter and Grifols are the main private-sector companies manufacturing and marketing PD in multiple countries (inside and outside the EU), following a significant consolidation process over the last 20 years. Some (semi-)public-sector manufacturers also work on a contract basis for the private-sector actors.

Key challenges

The diverse activities and diverging interests of the stakeholders, some with a public-sector background and others with a private-sector one, are the underlying reason for diverging views, in particular on how the sector should be organised. The report aims at capturing these different views.

Several key issues relate to the interpretation of the principle of voluntary and unpaid donation, which is strongly encouraged in EU legislation, though not mandatory, and the related principle of self-sufficiency.

In particular what is given in return for a donation, is classified differently by different stakeholders. It can vary from refreshments and tokens, to time off work, to medical checks and cash amounts. In general compensation strictly limited to making good the expenses and inconveniences related to the donation is considered to be compatible with the principle of voluntary unpaid donation. Where the value of such supposed compensation goes beyond this, it is considered to be an incentive.

There are a number of factors that should be considered:

- In practice it often is difficult to draw a clear/precise line to determine where compensation ends and incentives begin;
- The expenses/inconveniences incurred by each individual donor might vary significantly, which raises the question whether – in order to limit administrative burden – lump sum compensations are allowed. In this respect it is also important to underline that for donors there are significant differences between WB and source plasma donations, the later requiring more time per session, but also being possible on a more frequent basis;
- The large difference in purchasing power between Member States raises the question whether, what is considered to be a suitable level of compensation in one Member State, could be considered as an incentive to potential donors living in another Member State. This has led e.g. to countries reporting cross-border donations;
- The term "unpaid" is sometimes interpreted as meaning that no exchange of cash is involved. But in some cases cash is considered to be a legitimate compensation e.g. to reimburse travel costs for donors.

It has also proven hard to come to a common understanding of the term 'self-sufficiency'. While this concept is in general understood as 'fulfilling the needs' for medical applications within a population, geographic scope needs to be considered. Defining self-sufficiency at national, regional or at EU level leads to different interpretations and views on whether exchanges of substances across Member States are to be encouraged or discouraged. The ideal geographic scope for self-sufficiency is considered by some stakeholders to be broader for PD, which often need to be shipped cross-border

from/to manufacturing plants, compared with WB and blood components, which are usually processed and provided within national borders.

While the report does not provide comprehensive data on self-sufficiency, in general it seems to be agreed that self-sufficiency can be achieved within each Member State for WB and blood components. This seems to be more contested for PD. IPFA, the International Plasma Fractionation Association representing (semi-)public plasma manufacturers, mentions that the needs in the EU-15 can be covered with locally collected plasma. PPTA, the Plasma Protein Therapeutics Association, representing the private plasma manufacturers, mentions that more than 50 % of PD used in the EU has been collected outside the EU (mainly in the US). All parties, brought together within the Dublin Consensus Statement on optimized supply of PD, and joint by patient associations, agree on the need for both recovered and source plasma and on the need to avoid wastage of recovered plasma.

Consequently, there is no commonly agreed definition of 'shortage', which, again, can be defined at national or at Union level. The difficulties in defining shortages also relate to the impact of shortages which can vary from postponing planned surgery to, in more serious cases, being unable to treat urgent needs. For WB and PD respectively the reports highlights the following:

- The report refers to the 2nd Commission report on Voluntary Unpaid donation, mentioning five Member States (BG, CY, EE, HR and SE) with regular shortages of at least one of the blood components. The report also mentions an agreement between Greece and Switzerland for the supply of surplus RBC. The CoE survey found that three EU Member States (CY, EL and RO) report not being self-sufficient for RBC, while two (FI and IE) report surpluses. A recent initiative by certain Member States is assessing possibilities to exchange surplus supplies.

- In spite of strong growth in the PD manufacturing sector, there are no recent reports by manufacturers on significant shortages of PD to treat patients. Past national shortages were often related to Good Manufacturing Practice (GMP) issues of one supplier, taking into account that most Member States are largely dependent on one supplier. Other factors mentioned are the increase in demand like in case of off-label use or of introducing immunoglobulin (IG) as a treatment for new clinical indications. Noteworthy are recent trials on a potential new drug to treat Alzheimer's disease which, although not successful, have generated concerns on the capacity to supply sufficient additional IG to treat such a large potential patient group (MRB had estimated that a successful outcome of the trials would require a double growth rate (of 12%) to supply for additional demand).

Given that a shortage is the result of whether demand and supply match, the report also focuses on national policies to manage demand for WB/blood components and for PD:

- For WB/blood components, the report outlines different supply management practices. The majority or Member States seem to have introduced such practices, involving blood establishments (suppliers) and hospitals (users) into annual forecasting exercises as well as into weekly balancing of supply and use. In most Member States supply management includes looking at clinical practice, assessing and optimizing the patient's needs for transfusion through benchmarking, guidelines and training programmes;

- For PD, access is often limited due to cost (in particular for lower income countries). Manufacturers mention that changes in national conditions, e.g. in reimbursement, often require them to reallocate the limited supply. For immunoglobulines, some authorities, such as those in the UK and FR, have developed systems to monitor supply and, when needed, prioritise supply to those patient groups with the most dependent clinical indications.

The report also mentions barriers to trade/restricted practices in several EU Member States where national arrangements are in place to ensure that the collected plasma is exclusively manufactured by an assigned, often local, plasma manufacturer. PPTA believes these arrangements lead to price distortions and relate to cross-subsidisation of local actors who also organise collection of WB and plasma. IPFA believes such arrangements are necessary to guarantee the supply of essential medical treatments.

The field work for this report also offered an opportunity for stakeholders to provide comments on the regulatory framework. They expressed concerns and suggestions related to regulations on:

- Donation (legal status of eligibility criteria; mandatory presence of medical staff; recall/exclusion for (v)CJD; impact on cost and supply of new measures; double inspections of US centres; collection and use of epidemiology data)
- Manufacturing of PD (non-harmonisation of EU and US rules; national exclusivity arrangements for manufacturing locally collected plasma; administrative burden of the plasma master file; application of GMP Annex 14 for contract manufacturing);
- Other areas like the number of patients required for clinical trials for PD indications, the absence of supply protection measures for the EU markets and concerns on generic substitution between PD.

<u>Overall conclusion</u>

The data and issues in the Creative Ceutical report indicate a clear tension between the PD sector and the blood and blood components sector.

Both result from citizens' donation. However the industrial manufacturing of PD is undertaken mainly by private-sector companies supplying PD to a steadily growing market. The small scale processing of whole blood into blood components is undertaken by (semi-)public actors supplying a stable clinical demand.

The differences in market growth put different expectations and pressures on the required number of donations, and lead to different views on related issues like voluntary unpaid donation, self-sufficiency and shortages. The development of common definitions would allow for a clearer interpretation and more common understanding and transparency.

These differences have also triggered the need for demand management measures, in order to ensure optimal use of the limited supply from donations, both for WB/RBC and for PD.

Finally, these differences in approach lead to different views on risks, e.g. related to epidemiology or processing steps, and related safety and quality measures.