

## Tackling barriers to treatment access: The need for stakeholders dialogue

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### 1. Introduction

Rare diseases, which are often complex genetic conditions that are either life threatening or chronic and debilitating, are rightly seen as a growing public health priority in the European Union.

The European Union considers a disease to be “rare” if it does not affect more than “1 per 2,000 persons”. It is estimated, that there are between six to seven thousand identified rare diseases to date, with approximately five new diseases described every week in the medical literature [1].

Both the European Commission and several EU Council Presidencies have identified Rare Diseases as a key area in healthcare policy. The recently published European Commission proposals outline the necessary steps for an efficient policy addressing the issue of rare diseases in Europe. [http://ec.europa.eu/health/ph\\_threats/non\\_com/rare\\_10\\_en.htm](http://ec.europa.eu/health/ph_threats/non_com/rare_10_en.htm).

It is within this context that increased attention is being given by the EU to rare plasma related disorders.

### 2. Rare plasma related disorders

Rare plasma related disorders fall under the rare diseases threshold and comprise over 200 life-long and life-threatening conditions including among others:

- Alpha1-antitrypsin deficiency
- B-cell chronic lymphocytic leukemia
- Chronic inflammatory demyelinating polyneuropathy
- Guillain-Barré syndrome

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- Haemophilia A
- Haemophilia B
- Hereditary angioedema
- Idiopathic thrombocytopenic purpura
- Kawasaki syndrome
- Primary immunodeficiencies
- von Willebrand disease

Whilst many rare diseases cannot be diagnosed or appropriately treated, most rare plasma related disorders which often are chronic and congenital disorders fortunately can be. Many of them are treatable with life-saving and life-enhancing plasma protein therapies. Plasma protein therapies are unique therapies including plasma-based and recombinant biological therapeutics. However discrepancies in patient access to plasma protein therapies are being observed between EU Member States due to poor diagnosis rates and cost-containment measures.

### 3. Plasma protein therapies: Orphan or not orphan?

Orphan drugs are correctly referred to as an important category of rare diseases therapies. However not all rare diseases are treated with medicinal products that are considered ‘orphan’ or at least have an orphan drug status.

Plasma protein therapies represent such a category of life-saving therapies. Although most plasma protein therapies do not have an ‘orphan drug’ status, they nevertheless often are confronted to similar barriers that hinder patient access to treatment and one could rightly ask oneself why they should not be considered on a similar level than orphan drugs in national healthcare policies in many instances. The rarity or ‘orphan nature’ of the conditions they treat, the consequently small size of the patient populations, the difficulties to conduct large clinical trials and the need to differentiate them from traditional, chemically-based pharmaceuticals when it comes to reimbursement or taxation policies indeed are, similarly to orphan drugs, some of the barriers that threaten patient access to plasma protein therapies.

Plasma protein therapies are intrinsically a unique class of medicinal products. Their unique nature mainly lies in the biological origin of the raw material from which they are produced – human plasma. Human plasma is the yellow liquid portion of blood that remains after red blood cells, white blood cells (leukocytes) and platelets have been removed. It contains mostly water and a wide range of *plasma proteins*, some of which are used for therapeutic purposes. Examples of such plasma protein therapies and some of the rare plasma related disorders they treat are provided in Table 1.

Several plasma protein therapies are defined by the World Health Organisation as Essential Medicines [2]. There are several specificities resulting from their biological origin that make these essential therapies a special case.

Table 1

Plasma protein therapies	Conditions
Immunoglobulins (intravenous, subcutaneous and intramuscular)	<ul style="list-style-type: none"> <li>– Primary Immunodeficiencies</li> <li>– Guillain-Barré Syndrome</li> <li>– Idiopathic thrombocytopenic purpura</li> <li>– Chronic inflammatory demyelinating polyneuropathy</li> <li>– Kawasaki Syndrome</li> </ul>
Coagulation factor VIII – Plasmatic and Recombinant	– Haemophilia A
Coagulation factor IX – Plasmatic and Recombinant	– Haemophilia B
Alpha-1 antitrypsin	– Alpha-1 Antitrypsin Deficiency
C1 Esterase Inhibitor	– Hereditary Angioedema

To start with, the supply of the raw material, human plasma, is entirely depending upon the good will of plasma donors. Whereas this problem never occurs in the traditional pharmaceutical industry, the availability of plasma protein therapies rests entirely on the altruistic motivations of plasma donors without whom it would not be possible to make these life-saving therapies. In short, without these plasma donors it would simply not be possible to produce plasma protein therapies which would have devastating effects for the patients whose lives and well-being depend on them. A striking example are haemophilia patients whose life-expectancy in the 1950's before the introduction of coagulation factor therapies was not over their teenage years. The World Federation of Haemophilia points out that “without adequate treatment, many people with hemophilia die before they reach adulthood. However, with proper treatment, life expectancy for people with hemophilia is about 10 years less than that of males without hemophilia, and children can look forward to a normal life expectancy” [3].

Another unique aspect is the long and complex production process that is necessary to produce safe and effective plasma protein therapies. Once the plasma has been collected and screened, it is pooled and used as raw material from which the various plasma protein therapies will be produced. Through the process of fractionation which was first developed in the 1940s by Professor Edwin J. Cohn the plasma is separated into different proteins, each of which holds specific therapeutic properties. Purification stages and viral inactivation / removal techniques ensure the optimal safety and efficacy of plasma protein therapies. This complex production process takes approximately 6 months from the moment the plasma is pooled until the finished products are ready to be distributed.

The cost and scarcity of the raw material and the complexity of the lengthy production process make the entire cost-structure of plasma protein therapies entirely different in comparison to the traditional pharmaceutical industry. Direct manufacturing costs including those of the raw material can account for up to 70% of the

## Comparative cost structure of plasma protein therapies and chemical-based pharmaceuticals

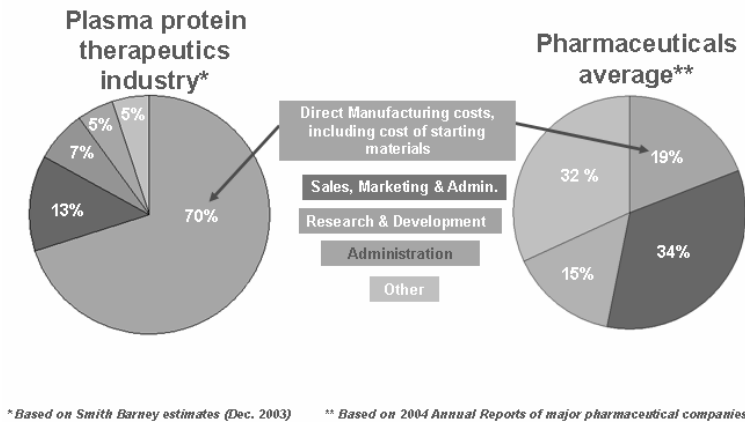


Fig. 1.

purchase price compared to less than 20% for chemically based pharmaceuticals [4] as shown in Fig. 1.

The interdependence of the whole range of plasma protein therapies is another key difference with traditional pharmaceuticals. One of the principles in plasma economics is to find the right balance between the production of the different plasma protein therapies which all are produced from the same raw material, human plasma. One liter of plasma will yield a certain quantity of each therapeutic protein, and it is a constant challenge for plasma protein manufacturers to allocate proportional costs to each protein to ensure the sustainability of the industry. One conclusion that seems quite evident is that because the costs of the raw material and production process are so important, to be economically viable the manufacturers have to sell as many of the proteins as possible. Ideally all plasma proteins should therefore be distributed to ensure an appropriate cost-absorption. However this is rarely the case as historically the demand for each plasma protein therapy changes over time. This situation is made even more complicated when taking into account the diverging policies enforced in different countries and their potential impact on supply of plasma protein therapies. The interdependence of plasma protein therapies therefore is another unique challenge for the plasma protein industry.

So, whilst plasma protein therapies encounter similar hurdles to orphan drugs when it comes to the rarity of the conditions they treat, the small patient populations, the difficulties to conduct clinical trials, to get new indications, and the need to be treated separately in reimbursement and taxation policies, they are also 'orphan' in the sense that they are the product of an industry faced with unique challenges. These unique challenges need to be better understood by healthcare policy makers and recognized

in healthcare policies to ensure that the patients who need them can appropriately access them.

#### **4. Stakeholder dialogue and joint actions: The way forward**

The specific issues that the plasma related disorders stakeholder community is faced with are increasingly being put under the spotlight by the EU Institutions. The growing number of joint actions by concerned stakeholders is paving the way forward for a better recognition of these disorders and a better life for the affected patients.

Primary Immunodeficiencies for example have been addressed both at the EU PID Consensus Conference sponsored by the European Commission held in Langen, Germany on 19–20 June 2006 and at the European Parliament's Scientific and Technological Options Assessment Panel (STOA) meeting on Primary Immunodeficiencies held in Brussels on 17 March 2004. Both meetings which brought together various stakeholders in the field called for action at EU level in order to improve awareness, screening, diagnosis of PIDs and access to treatment within the EU. For more information, [www.eupidconference.com](http://www.eupidconference.com).

Haemophilia is another example where the EU Institutions have taken an active role. On 12 January 2006 the European Parliament held a meeting entitled 'Haemophilia Awareness and Disparity of Care within the EU' and more recently on 27 January 2009, the Launch of the European Principles of Haemophilia Care. More information can be found on [www.ehc.eu](http://www.ehc.eu).

Importantly and in addition to specific diseases-related action such as these ones, the European Union has recently started to look at rare plasma related disorders as a whole, specific category of rare diseases that deserve specific attention and tailored actions.

Two meetings were held at the European Parliament in Brussels in 2008, which were attended by numerous stakeholders in the field of rare plasma related disorders including patient, physician and plasma protein industry representatives as well as several Members of the European Parliament (MEPs), the European Commission, and the Council of the EU. This wide range of stakeholders had the opportunity to discuss the latest European Commission proposals on rare diseases and other specific developments.

The first meeting chaired by MEP Miroslav Mikolasik in January 2008 focused on 'plasma proteins in the treatment of rare diseases'. A second meeting chaired by MEPs Jorgo Chatzimarkakis and Miroslav Mikolasik on "improving care for rare plasma disorders" saw the decision to issue a European Parliament Call for Action. This Call for Action is currently being circulated at the European Parliament and will propose key actions to improve care for rare plasma related disorders

Several conclusions were drawn and recommendations were agreed during these two meetings. These are broadly summarized below:

- **Diagnosis Rates of Plasma Related Disorders**  
More effective and widely available diagnosis for chronic, rare plasma related disorders are needed and inequalities of diagnosis levels between EU Member States must be reduced
- **Better access to and more equal treatment.**  
Patients have the right to better information about their conditions and the treatment options available to them. Treatment levels for plasma related disorders vary greatly depending on the Member State. Member States should take measures to ensure optimal access to treatment.
- **Recognition of the Unique Nature of Plasma protein therapies**  
Plasma protein therapies are unique therapies which differ from traditional pharmaceuticals. Recognition of their unique nature needs to be taken into account in national health policies to ensure appropriate and sustainable access to treatment for patients whose life and quality of life depend on these important therapies.
- **Coordination between Member States**  
A more effective co-ordination of Member State activities on rare diseases is essential, so that patients, healthcare professionals and healthcare providers know where they stand.
- **National Rare Diseases Plans**  
National Rare Diseases plans are vital to success in tackling rare diseases. Many EU Member States do not have a national action plan on rare diseases, which suggests that not enough emphasis is being given to helping those with rare disorders. Each EU Member State should have a dedicated plan, using tools such as professionally run national patient registries and networks of reference centres for diagnosis and treatment, as proposed by the European Commission in their proposals.
- **Equal Treatment Levels**  
European patients have the right to access the treatment that they need. In the case of life-threatening plasma protein disorders, this requires the widest possible access for patients to plasma protein therapies and the implementation of appropriate treatment levels of care, especially in EU Member States where access to treatment is restricted and/or not optimal.
- **Supply of Human Plasma**  
The need for an adequate supply of safe and high quality human plasma for further manufacturing into therapeutic products.
- **Differences between Blood and Plasma**  
In future communications, legislation and discussions in the European Union, the intrinsic differences between the collection of whole blood and the collection of plasma and respectively between labile blood-derived medicinal products for transfusion and plasma-derived medicinal products (plasma protein therapies) should be considered carefully. The logical separation of whole blood and plasma will lead to a better understanding of the unique nature of the therapies for rare plasma related disorders, and ultimately better care and treatment for patients.

– MEP Interest Group on Rare Plasma Related Disorders

A proposal was made to create a European Parliament Interest Group on Rare Plasma Related Disorders that would meet regularly to ensure the unique challenges facing these patient groups are appropriately taken into account in relevant EU legislation and actions. Face-to-face consultation between EU decision makers and patients' groups facilitates a greater understanding of the challenges faced by patients and where the European Union can contribute and add value.

This last point is reflected in the recently created liaison mechanism between plasma related patient organisations and the European Commission's Directory-General for Health and Consumer Protection's Unit on Health Information. This is the first 'liaison group' created by the European Commission in the context of their rare diseases proposals to ensure the views and perspectives of patients are taken into account into all upcoming relevant EU legislative and policy actions.

## **5. Conclusions**

These initiatives at EU level are a few examples that testify to the growing interest into rare plasma related disorders and the specific challenges facing the patients who live with them. They also highlight the benefit of dialogue between stakeholders and key policy makers to ensure resources available at Member State level are used optimally and in the most efficient way to ensure that appropriate treatment is available for all patients affected by rare plasma related disorders.

Many of these disorders can be treated with effective plasma protein therapies, which is unfortunately not the case for many other rare diseases that do not yet have available treatments. However the availability of plasma protein therapies does not mean all patients have access to their treatment. It is estimated for example that 70% of hemophilia patients do not have access to treatment on a worldwide scale. Whilst such horrific numbers are still a reality for many patients in the world, thankfully this is not the case in the EU although wide disparities still exist.

The situation in the EU is not ideal; and much improvement is needed as it has been described in this article. Hugely varying treatment levels for these disorders characterize the European Union's environment where not many Member States have yet implemented healthcare policies that encourage early identification of patients with rare plasma related disorders and ensure appropriate access to the adequate treatment. The situation in the EU needs to be improved as these patients have the right to access their treatment. Patients who are suitably treated will in turn contribute back to society and unnecessary expenditure often due to misdiagnosis and subsequently inappropriate/ineffective treatment will be avoided. Interestingly, a recent survey [5], conducted by the Jeffrey Modell Foundation, a foundation active in the field of immunodeficiencies, compared the cost of treatment of undiagnosed and diagnosed people with immunodeficiencies in the United States of America. The

survey clearly indicated a much higher rate of infections and a much higher use of antibiotics, days in hospitals and school/work days missed for undiagnosed patients not receiving proper replacement therapy with immunoglobulins. Based on these outcomes, the survey estimated that once diagnosed the average savings, per patient, per year, would be around 80,000 US \$. The survey concluded that on the basis on this per patient/year figure, the impact of undiagnosed PID patients to the healthcare system in the USA totals over US\$ 40 billion annually.

Whilst such figures are not available yet for the European Union, one can easily deduce that implementing appropriate and more effective policies not only will make life better for the patients but also for the national authorities as they will avoid wasting resources unnecessarily and actually end up reducing their healthcare expenditure. But for this goal to be achieved, key decision makers and stakeholders in the EU who have recently embarked on the right way forward, will need to continue and increase their dialogue and joint actions. It is through shared expertise and experience that the best solutions will be found.

## References

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