



European Haemophilia Consortium

EHC Round Table of Stakeholders

Rare Bleeding Disorders and Orphan Drugs

Meeting Report

European Parliament, Brussels, 3 March 2014



Executive Summary

The European Haemophilia Consortium (EHC) Round Table of Stakeholders is an event that takes place three times a year and that addresses issues related to the comprehensive care of haemophilia. Each event aims to explore a different aspect of comprehensive haemophilia care while bridging the gap between European health policy and treatment of haemophilia, tackling common issues faced by patients as well as spotlighting the latest scientific developments.

On March 3, 2014, nearly 50 representatives from the patient and scientific community, the industry as well as health policy specialists gathered in the European Parliament in Brussels to discuss the impact of the Orphan Medicinal Product Regulation (141/2000) on Rare Bleeding Disorders. This was the 21st EHC Round Table and it was chaired by Members of the European Parliament (MEP) Dr Miroslav Mikolášik and Dr Paul Rübig, both from the European People's Party.

Regulation 141/2000 was implemented by EU Member States in 2000 and was originally written in order to respond to a public health concern, which was the lack of treatment for patients suffering from rare diseases. Through this legislation, regulators encouraged the pharmaceutical industry to invest in the orphan drug sector. With this in mind, the Regulation provides a series of incentives to pharmaceutical companies, such as protocol assistance and ten-year marketing exclusivity, to compensate for the reduced return on investment for this type of pharmaceutical product. To this day, European regulators believe that this legislation has proved highly successful with over 1,000 orphan drug designations since its inception.

Nonetheless, during the Round Table discussions representatives from the medical community, patients and pharmaceutical industry all felt that some aspects of the legislation could be improved through a more pragmatic interpretation by regulators. In particular, both patients and physicians pointed out that there should be a clear distinction between rare conditions that are well-known and characterised and those that are rarer and for which there is a lack of treatment and diagnostics. However, this differentiation should not reduce the extensive efforts by research and development organisations to provide treatments for both types of conditions. This event was also the opportunity for patients' representatives to voice their concerns with regard to the potential barriers that a ten-year marketing exclusivity period could raise for accessing a wider array of therapies for their conditions.

As for the pharmaceutical industry, speakers at the event gave an overview of the hurdles faced in developing orphan medicinal products and they also provided some suggestions on how to improve the situation in the future: for instance, by having greater harmonisation between the EU and US legislative environments and by having a more pragmatic approach in the interpretation of the regulation for treatments that are better understood versus for completely new molecules.

Finally, during the event the payers' representative also explained that the EU reimbursement landscape is very diverse and that currently there are a number of EU initiatives to try to harmonise reimbursement assessments.



To conclude, the following recommendations emerged from the discussions:

- A distinction should be made between rarer bleeding disorders and more common bleeding disorders that are well-characterised and better understood and for which there is more treatment and expertise available. However, this differentiation should not reduce research efforts for both types of conditions.
- The EHC believes that the longer-acting products coming to the market have different mechanisms of action and that they would all suit patients differently.
- Pharmaceutical companies should increase their efforts to market older-generation products in a wider array of markets.
- Pharmaceutical companies should consider making novel treatments more affordable; marketing products that cannot be reimbursed due to their high price benefits neither patients nor companies.
- Patients should be included in the reimbursement discussions as they provide a unique expertise on the use of products.

Speakers at the Round Table included:

- Prof Flora Peyvandi, Director of Internal Medicine Department RCCS Maggiore Hospital, University of Milan, member of the EHC Medical Advisory Group.
- Ms Agnès Mathieu, Legal Officer at the European Commission.
- Mr Brian O'Mahony, President, EHC.
- Dr Peter Feldman, Unit Manager, Coagulation Factors Development, Bio Products Laboratory (BPL).
- Dr Claudia Nardini, Product Development Director, Kedrion Biopharma.
- Assoc. Prof. Cristina Solomon, Medical Affairs Director, CSL Behring.
- Dr Stephanie Seremetis, CMO and CVP Haemophilia R&D Portfolio, Novo Nordisk.
- Philippe Van Wilder, Director Studies & Strategy, Independent Health Insurance Funds of Belgium.

Opening Remarks



Dr Mikolášik addressing the opening remarks

Dr Mikolášik welcomed participants and stressed his long standing collaboration with the EHC for the past eight years. He committed to renewed support and collaboration in the new Parliamentary term, pending election results.

Dr Mikolášik introduced the topic of the event with a quick overview of the Orphan Medicinal Product Regulation, which was created in the year 2000 to encourage pharmaceutical companies to develop treatments for patients' populations with an incidence of less than five individuals in 10,000. The Regulation does so by providing pharmaceutical companies with a series of incentives to increase return on investment, such as marketing exclusivity and protocol assistance.

Finally, Dr Mikolášik introduced the speakers and suggested that for upcoming meetings on this topic, the EHC should also invite representatives from the Member States' Ministries of Finance, in order for them to better understand patients' needs and provide more funds for the treatment of rare diseases.

Clinical Perspective on Rare Bleeding Disorders

Prof Flora Peyvandi from the Centro Emofilia e Trombosi Angelo Bianchi Bonomi in Milan gave an overview of rare bleeding disorders (RBDs).

She explained that currently there is a difference in definition between Europe and the US of what a rare disease is. When combining both definitions, a rare disease is defined as a condition that has an incidence of one person in 1,500 or 2,000 people. She stated that, in her opinion, a distinction should be made between rare and very rare disorders. In fact, of approximately 90,000 patients affected by bleeding disorders in Europe, only three to five percent are affected by a very rare bleeding disorders such as FXIII deficiency and FV, which are in fact amongst the rarest.



Prof Flora Peyvandi (far right) presenting on rare bleeding disorders



This distinction is necessary because it would more accurately represent the current diagnosis and treatment reality of these rarer conditions; namely a widespread lack of laboratory equipment to conduct diagnosis and a lack of treatment. As a result, there is a real standardisation problem and great variability in the quality of diagnoses provided across Europe, which in turn leads to under-diagnosis of these conditions.

“More accurate and standardised tests may help to define a safe and minimum residual coagulant level to ensure a normal haemostatic process and to adopt the appropriate treatment.”

Prof Flora Peyvandi

Prof Peyvandi then pointed out that some very RBDs still do not have any type of treatment at all. Non-specific types of treatment such as Fresh Frozen Plasma (FFP) are therefore used as alternatives. In contrast, patients with haemophilia A and B have a great variety of products to choose from. For instance, in 2012, there were approximately 30 types of clotting factors for FVIII deficiency on the market while there were still no treatments for FV deficiency and other rarer bleeding disorders only had one or two treatments available. For this reason Prof Peyvandi underscored the urgent need for a distinction between well-characterised and well-understood disorders with sufficient diagnostic methods and treatment, and rarer bleeding disorders for which there is a lack of diagnosis and treatment.

Prof Peyvandi also gave a brief description of the Orphan Medicinal Product Regulation, noting that of the 686 orphan drug designations granted between 2000 and 2010 only 63 drugs were approved. This is less than ten percent. It is estimated that 50% of the patient population affected by RBDs around the world still uses FFP. More shockingly, 30% of RBD patients in Europe also use FFP. This is because the product is inexpensive and widely available. Prof Peyvandi questioned whether the complete orphan drug designation and authorisation process should be reviewed to allow a greater number of therapies to enter the market and ultimately to reach patients.

Prof Peyvandi also noted some dangers in the heterogeneity of available products and pricing in Europe. This is mainly due to the different types of marketing authorisations in place:

- Centralised authorisation procedure
- National authorisation procedure
- Decentralised procedure
- Mutual recognition procedure

As a result of these different authorisation tracks, ‘older’ treatments such as plasma-derived products do not necessarily get EU-wide authorisation but are only available in a handful of countries. As a consequence, there is a lack information on such (and other) products, because they do not need to produce European Public Assessments Reports (EPAR), which are only required of centrally-licensed medicinal products.

In conclusion, Prof Peyvandi underlined that there is a need to ensure that the orphan drug regulation helps – and does not hinder – products from reaching the market. She also emphasised that the marketing exclusivity granted by the Regulation should only be applied to treatments aimed at very rare RBDs. Finally, she stressed the need to further discuss how these novel therapies can be sustainable and more easily accessed by patients.

Regulators' Perspective on the Orphan Medicinal Product Regulation

Ms Agnès Mathieu, Legal Officer at the European Commission with the Unit for Medicinal Products – Authorisations, and the European Medicines Agency presented on the Orphan Medicinal Product Regulation (141/2000).

Ms Mathieu started by giving background information on the Regulation, which was developed in response to an important health concern regarding the lack of treatment for patients with rare diseases. Contrary to the current trend, when the Regulation was implemented in 2000, pharmaceutical companies were not as interested in niche products as they are today and



*Ms Agnès Mathieu, legal officer
European Commission*

instead concentrated their investments on so-called blockbuster products. Indeed, at the time, most European patients affected by a rare disease were either relying on off-label use or on imported products, which meant that there was little transparency and also a lack of control of these products.

Ms Mathieu went on to say that one of the primary obstacles for pharmaceutical investment in rare diseases' treatments was the lack of investment returns. She said that Regulation 141/2000 offers a ten-year marketing exclusivity, protocol assistance, EU marketing authorisation and access to further incentives provided by the Member States. The Regulation defines orphan drugs as a treatment aimed at a patient population with an incidence of less than five in 10,000 people affected by life-threatening or seriously debilitating conditions. Orphan drugs have to provide treatment where there is no treatment available or provide new treatment

that is significantly better than the existing one. Finally, orphan drugs are also defined as medicinal products that would not generate enough return on investment without the incentives provided by the Regulation.

The Regulation established the European Medicines Agency's (EMA) Committee for Orphan Medicinal Products (COMP) that reviews the applications from companies and gives either a positive or negative opinion. This opinion is then transferred to the European Commission (EC), which takes it into consideration. The EC Standing Committee reviews the application and publishes either a positive or negative decision.

Once the product is authorised, it automatically benefits from a ten-year marketing exclusivity. This is regarded as the most significant incentive for orphan medicinal products because it concretely means that no other similar active substance for the same indication can be accepted for authorisation in the EU. However, there are derogations that can be applied if, for example, there is another product coming on the market that has a significant benefit or if the marketing exclusivity holder consents to share the market with another company. The marketing exclusivity can also be derogated if there is a supply shortage or if a new product is safer or clinically superior.

In terms of development, it is estimated that after 15 years of orphan drug designation it will now be possible to amend current designations whose ten-year market exclusivity has ended.

In terms of results, the Regulation is considered to have delivered on its promises as it has attracted pharmaceutical investments in the area of rare diseases. Since 2001, 85 medicines have



been authorised and more than 1,000 products under research and development have been given orphan drug designation.

Furthermore, the revised version of the Clinical Trials Directive which will get voted in April, will have in its preamble a paragraph on rare and ultra-rare diseases and it will facilitate the implementation of cross-border clinical trials.

Finally, another challenge for orphan medicinal products is their access and financial sustainability. Member States are currently cooperating on Health Technology Assessments and there may be an emphasis on orphan drugs. The EU has developed a new programme “Shaping European Early Dialogue” (SEED) which allows medicinal products manufacturers to ask for cooperation on HTAs from about ten different payers. These will gather and define the requirements they want to see for the reimbursement of medicinal products.

EHC Perspective on Rare Bleeding Disorders

Mr Brian O’Mahony, President of the EHC, gave an overview of the EHC perspective on the impact of the legislation on bleeding disorders. Mr O’Mahony explained that a difference should be made between more common and well-characterised conditions such as haemophilia A and B and rarer bleeding disorders. He reiterated the point made by Prof Peyvandi that patients affected by haemophilia have access to far better diagnosis and treatment options compared to those affected by RBDs.



*Mr Brian O'Mahony,
EHC President*

He explained that companies should seek marketing exclusivity only for products for which there are virtually no treatment options and not for conditions for which an array of clinical options are available. He explained in fact that several new longer-acting products were about to come to the market in Europe and that all of these products should be allowed to be marketed, as they are different and may suit different patients better. The EHC has communicated this position to the EMA and discussions are ongoing.

Industry perspective

The event continued with a series of presentations from the pharmaceutical industry on the development of treatments for RBDs. Speakers included:

- Dr Peter Feldman from Bio Products Laboratory with a presentation on Factor X concentrate
- Dr Claudia Nardini from Kedrion with a presentation on Factor V and Plasminogen
- Dr Cristina Solomon from CSL Behring with a presentation on plasmatic Factor XIII
- Dr Stephanie Seremetis from Novo Nordisk with a presentation on recombinant Factor XIII

The main point that came out of the presentations is that product development for rarer bleeding disorders is extremely difficult, time and resource-intensive and this is due to different factors.

First of all, the patient population is small and geographically dispersed which may lead, for example, to single patient research sites or to research sites that do not have the appropriate equipment or knowledge for dealing with these types of patients. Furthermore, the research and development phase for developing new products is extremely long. Some of the presenters showed the example of products that had been in development for 14 years. Speakers pointed out that investment costs are always high regardless of the patient population.

For many of the RBDs, there is a lack of suitability tests and characterisation and therefore new tests need to be developed for validation of clinical assays.

In the case of plasma-derived products, it is important that the fractionation of new therapies does not have an impact on existing therapies as the supply has to be continuous.

In terms of regulatory procedures for marketing authorisations, there are differences between the EU and the US, which increases the complexity of trials. Also, the advice provided by regulatory agencies is often not targeted to the orphan niche.



Dr Peter Feldman spoke about the development of Factor X



Dr Claudia Nardini presented on the development of Factor V



Dr Cristina Solomon presented on plasmatic FXIII



Dr Stephanie Seremetis presented on recombinant FXIII

All presenters stressed that in general when conducting a clinical trial for RBDs, pharmaceutical companies often provide treatment to a good portion of the patient population. In the case of RBDs, some presenters mentioned products that were covering up to 40% of the treated patient population.

Furthermore, drugs that have a well-understood mechanism of action such as plasmatic proteins are treated similarly to new therapies, despite the fact that they are better understood than novel components. This stricter approach delays patient access to treatment. Also, a more pragmatic approach is needed in terms of clinical data collection and the industry would welcome a switch to a risk/benefit analysis.

Finally, it was stressed that patient advocates should be included in the licensing process.

Payers' perspective

Mr Philippe Van Wilder from the Independent Health Insurance Funds of Belgium gave an overview on the access to orphan medicinal products from a payers' point of view. The Belgian Independent Health Insurance Funds are a member of the International Association of the Mutuality (AIM), which represents over 40 insurance groups that are active on harmonisation activities for the evaluation of medicines.

Mr Van Wilder started his presentation by pointing out that in Europe there are different procedures for marketing authorisation and reimbursement and in particular reimbursement is a Member State competence. Typically, payers will look at the additional benefits of new products compared to alternative treatments. Although, in the case of orphan medicinal products this is already done through the orphan designation.

In practice, it is also very difficult to find out about the technical methods used to assess these products and there is a lack of transparency. In general, national legislations will provide more information on how the reimbursement application procedure is conducted but will give little to no information on how the assessment is carried out in practice.



As a result, the composition of each assessment is different in every country. Also, it is noted that the official reimbursement policy can deviate from the outcome of the product assessment. This is because the ministry in charge of approving the reimbursement can deviate from the official assessment. Inevitably, this leads to a varied landscape of product reimbursements in Europe. To this, one needs to add the fact that at the moment there is neither a harmonised definition of 'value' nor a common assessment practice. Various initiatives have tried to bring payers together to look at these issues and to find common ground.

At the moment, the evidence submitted for reimbursement comes from the clinical evidence submitted for marketing authorisation, which is not necessarily appropriate for reimbursement.

*Mr Philippe van Wilder from
the Belgian Independent
Health Insurance Funds*

In practice, prices are set by looking at the prices of treatments used in similar settings, at the various drug price components, the differences across Member States and what price would allow fair access. For example, does the country have the expertise needed to administer a new treatment properly? Or, will the patient need to travel abroad in order to get that medicine? These are questions that are considered by the payers. In short, the diversity of the assessment of therapeutic value is creating great confusion for patients, payers and treating physicians alike.

Furthermore, one should keep in mind that it is often difficult for payers who are used to assessing products for common diseases, which have a lower cost, to understand why orphan medicinal products are so expensive. This creates a lot of confusion and misunderstanding amongst all stakeholders. From a payers' perspective, early dialogue with companies would be very beneficial as it would avoid any surprises or misunderstandings at a later stage of product development.

In conclusion, efficiency is a way toward sustainability. This also means taking the question of solidarity into account not only for current but also for future generations.

Discussions

Participants asked further questions with regard to the marketing exclusivity provided by the Orphan Medicinal Product Regulation. Ms Mathieu confirmed that for products to be excluded from the market they need to be both exactly the same as well as share the same indication as the orphan medicinal product already licensed. In the case of longer-acting products, if these products are in fact different then they should all be licensed. She also noted that the notion of ultra-rare diseases could prove disadvantageous for more common rare conditions. This is because it may mean less advantages and funding for treatment and research of these conditions. EHC representatives reiterated that they do not wish to see changes in the legislation but merely a more pragmatic interpretation.

The audience noted that current reimbursements and health technology assessments are very murky and difficult to navigate. They also noted that using the same clinical data for marketing authorisation and reimbursement may be problematic. Mr Philippe van Wilder noted that this is precisely why there are harmonisation efforts going on at EU level.

Finally, the audience commented on novel products that come to the market with very high prices, noting for example that prices are so high in Germany, one of the wealthiest countries in Europe, that the government cannot afford these treatments.

Company representatives replied that costs are high due to the long development process. Prof Peyvandi added that there is a real need to have discussions on how companies intend to get newer and expensive products reimbursed, as it makes no sense to have products that even the richest countries in Europe cannot afford. On the other hand, companies should make a real effort to make older-generation products that do not go through centralised marketing authorisation more widely available in Europe.



The audience during the discussions



Conclusions and recommendations

Dr Paul Rübig communicated his regrets in writing as he was not able to attend the event. Mr Brian O'Mahony concluded the meeting by making a number of recommendations.

Mr O'Mahony noted that the discussions shed increased light on the complexities and challenges of developing new products for RBDs. He also noted increased clarity around the Regulation and that there seemed to be a consensus for a pragmatic interpretation of the Regulation for more common bleeding disorders.

Finally, he noted the importance of patient involvement in the ongoing discussions on health technology assessments.

Recommendations

- A distinction should be made between rarer bleeding disorders and more common bleeding disorders that are well-characterised and better understood and for which there is more treatment and expertise available. However, this differentiation should not reduce research efforts for both types of conditions.
- The EHC believes that the longer-acting products coming to the market have different mechanisms of action and that they would all suit patients differently.
- Pharmaceutical companies should increase their efforts to market older-generation products in a wider array of markets.
- Pharmaceutical companies should consider making novel treatments more affordable; marketing products that cannot be reimbursed due to their high price benefits neither patients nor companies.
- Patients should be included in the reimbursement discussions as they provide a unique expertise on the use of products.

All presentations from the event can be found on the EHC website under: <http://www.ehc.eu/round-table-of-stake-holders/last-round-table.html>

The next EHC Round Table will be held on 16 June 2014 at the Hotel Royal Windsor in Brussels and will be chaired by EHC Medical Advisory Group Chair, Prof Paul Giangrande. The topic of this event will be: "Current Issues in von Willebrand Disease."