Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2014), **20**, 455–458 DOI: 10.1111/hae.12462

EDITORIAL

Does the orphan medicinal product regulation assist or hinder access to innovative haemophilia treatment in Europe?

Introduction

The first longer acting factor IX treatment product was granted marketing authorization in Canada and the United States in March 2014 and the first longer acting factor VIII treatment product is expected to be granted marketing authorization in North America later this year. In Europe, the first of these products is not expected to be granted marketing authorization until 2015–2016. Unfortunately, in Europe, we are faced by a uniquely difficult delay due to the current regulations in Europe requiring paediatric clinical trials [1] and sequential testing of certain haemophilia drugs *before* products are approved for adults.

However, a matter of *much greater concern* to the European haemophilia community is a potential barrier to patient access of these new products due to the European Union's Orphan Medicinal Product Regulation (OMPR). The European Haemophilia Consortium (EHC), together with the European Association for Haemophilia and Allied Disorders (EAHAD) and the World Federation of Hemophilia (WFH), has recently communicated our joint position outlined below, both to the European Commission and to the European Medicines Agency (EMA).

About haemophilia

Haemophilia is a congenital rare disorder characterized by spontaneous haemorrhage or prolonged bleeding. There are two types of haemophilia: haemophilia A and haemophilia B. Patients with haemophilia A have clotting FVIII deficiency and patients with haemophilia B have clotting FIX deficiency [2]. Patients with haemophilia are at risk of prolonged bleeding, which can be particularly damaging when it occurs in joints (haemarthroses), leading to joint damage, destruction and disability. Another concern is intracranial bleeds, which, if left untreated, can be fatal. The incidence of haemophilia A and B is of 1 in 10 000 and 1 in 50 000 people respectively [2]. Haemophilia occurs primarily in males and rarely in females.

Haemophilia treatment consists of replacement therapy of FVIII or FIX concentrates, produced either from donated plasma (plasma-derived) or engineered (recombinant). Current state-of-the-art treatment consists of regular intravenous injections of factor concentrates, which treat bleeding episodes 'on-demand' or prevent spontaneous bleeding if injected prophylactically. However, neither of the current treatment regimens associated with prophylaxis or on-demand therapy achieves sufficient trough levels to prevent many bleeds or long-term joint damage. Also, frequent infusions compromise venous access especially in children and ageing adults. Currently, many pharmaceutical companies are developing longer acting factor concentrates. These would mean less frequent infusions for patients, therefore resulting in greater protection of veins, but would also mean achieving higher trough levels and for longer duration than under current regimes. In short, the new longer acting products being developed at the moment could well revolutionize haemophilia treatment by better preventing bleeds and therefore minimizing long-term consequences as well as achieving a significantly better quality of life for patients today and into the future.

About the OMPR

The European Union (EU) Orphan Medicinal Product Regulation (141/2000) came into effect in 2000 in response to an important public health concern regarding the lack of treatment for patients with rare diseases. At the time in the 1990s, pharmaceutical companies were not attracted to niche products and instead concentrated their investments on 'blockbuster pharmaceutical products' for more prevalent conditions. As a result, most European patients affected by rare diseases were either not receiving any treatment, relying on off-label use of existing products or relying on imported products, which meant that there was little transparency and also a lack of control of these products.

From the perspective of pharmaceutical companies, an important obstacle to investing in rare diseases was the lack of return on those investments. The OMPR changed this by offering several incentives to encourage the pharmaceutical industry to invest in rare diseases including protocol assistance, assistance with centralized-EU marketing authorization and waiving of specific fees, as well as access to further incentives

provided by EU Member States. The biggest and most important incentive, however, was and continues to be the promise of 10-year EU-wide marketing exclusivity.

The OMPR has now been in place for 15 years. It has resulted in orphan drug designation being granted to 1247 therapies and marketing exclusivity being granted to 85 therapies [3]. It has benefited patients who suffer from serious, rare conditions for which there has been no satisfactory treatment. The current estimate of number of rare disorders is 6000 to 8000, many of which are of genetic origin, and affect children at a very early age. The EHC, EAHAD and the WFH believe in the importance and utility of the OMPR particularly for rare bleeding disorders such as FII, FV, FX and FXIII deficiencies, which completely lack or have very limited access to factor-specific treatment products. However, the case is completely different for haemophilia.

Haemophilia and the OMPR

The OMPR defines orphan drugs as treatments for patient populations having an incidence of less than five in 10 000 people affected by life-threatening or seriously debilitating conditions. Certainly, this is the case for both haemophilia A and haemophilia B. However, the OMPR also specifically targets '*...conditions [that] occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions*' [4].

Haemophilia A has a total of 40 plasma-derived and recombinant treatment products available worldwide (of which 22 are available in Europe) and haemophilia B has a total of 30 plasma-derived and recombinant treatment products available worldwide (of which 13 are available in Europe). The current global market for haemophilia products is worth in excess of US $ 7 billion and the market is expected to be worth US $11 billion by 2016 [5]. Clearly, haemophilia does not require the OMPR to be profitable. On the contrary, and in an ironic twist of fate, the OMPR may in fact create a barrier to patients accessing longer acting treatment products by giving 10-year marketing exclusivity to the first product that receives marketing authorization.

The dangers of marketing exclusivity for haemophilia

The OMPR automatically grants an orphan designated product 10-year marketing exclusivity once it has received marketing authorization in the EU. Under the terms of the legislation, this means that no subsequent *similar* product for the same indication can be accepted for marketing authorization in the EU for a period of 10 years unless it meets one of three derogation criteria, namely: (i) the holder of the marketing authorization for the original orphan medicinal product has given his consent to the second applicant; (ii) the holder of the marketing authorization for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product; or (iii) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior. Frankly, all of these criteria would be unlikely to be met in the area of haemophilia.

Marketing exclusivity, while beneficial for the above-mentioned rare disease areas where no or little diagnosis and treatment is available, would be of great detriment in haemophilia. It could potentially create a monopoly rather than market competition to ensure the widest possible access at the most affordable price. In addition, the potential for better products based on different mechanism's of action may never be realized. Patients would be deprived of potentially better clinical options for their individual clinical needs. There would be no competition and therefore higher prices – thereby potentially hindering or severely limiting patient access to these products around Europe. Finally, there would be no cascading effect on lowering prices for current recombinant or plasma-derived treatment products or broadening market access into European countries where patients have limited or severely limited access to treatment products.

The joint position of the EHC, EAHAD and WFH

For the above-mentioned reasons, the EHC has been advocating on these issues for more than 2 years and is supported both by EAHAD as well as WFH. We are aware that the EMA and the Commission are currently considering the 'similarity' of these different longer acting products under the orphan drug designation that each of these products has received in Europe. The joint position of the EHC, EAHAD and WFH is that the new longer acting products are *not similar* and that each protein modification should be treated as distinct and therefore be granted marketing authorization.

To help guide the legal interpretation of 'similarity' and how to assess it, the European Commission published a Communication [6] in 2008, which interprets 'similar active substance' as one that has '*the same*

principal molecular structural features and acting via the same mechanism of action' and also interprets 'same mechanism of action' as meaning that both products share '*the same pharmacological target and the same pharmacodynamic effect*.'

The bioengineering strategies used for the manufacturing of the longer acting FVIII and FIX products employ three main and dissimilar approaches. PEGylation, the covalent attachment of PEG polymers to a protein-, peptide- or small molecule drug, is one of the most promising techniques to improve pharmacokinetic and pharmacodynamic properties of therapeutic proteins by increasing their molecular size, making them less susceptible to proteolytic cleavage and degradation and changing their surface charge properties to interfere with receptor-mediated clearance processes [7]. Fc- and albumin fusion consist of the union of an immunoglobulin Fc domain or albumin to recombinant protein through a linker sequence. The neonatal Fc receptor (FcRn) mediates longevity of both albumin and immunoglobulins by preventing degradation. Proteins fused to Fc- or albumin are internalized by endothelial cells and bind to the FcRn present in the acidified endosome in a pH-dependent manner and are then recycled back to the cell surface, avoiding catabolism in the lysosome, and they are subsequently released back into plasma at physiological pH [8,9].

Our joint position is that products based on PEGylation, Fc fusion and albumin fusion are three *separate* and *distinct* approaches and are non-similar to each other due to the use of *different* pharmacological targets. All of these products are welcome and the haemophilia patient community requires access to all of these choices. Orphan drug designation should not be used to hinder the development, licensing and marketing of other products for the same condition, which have demonstrably different protein modification or enhancement. This position is also supported by recent recommendations issued by the European Directorate for the Quality of Medicines and Healthcare [10].

Conclusion

The original and noble intention of the landmark orphan drug regulation was to ensure the development of orphan medicinal products for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10 000 persons in the EU. The EHC, EAHAD and the WFH fully support the spirit and purpose of this regulation, which continues to stimulate investment into research and production of products for very rare diseases – including rare bleeding disorders such as FII, FV, FX and FXIII deficiencies – which completely lack or have very limited access to a factor-specific treatment products. However, as argued above, the number of available clotting factor concentrates for haemophilia A and haemophilia B are significantly higher than for other rare bleeding disorders and haemophilia is not a low-income market that struggles for investments and investment returns. The orphan drug designation and marketing exclusivity should be reserved *only* for very rare bleeding disorders such as FII, FV, FX and FXIII deficiencies [11]. Granting marketing exclusivity to *any* new haemophilia treatment product would not only be an aberration of the spirit of the orphan drug regulation, but also would result in a gross misapplication of the legislation, set a dangerous precedent and gravely damage patients' rights to access.

B. O'Mahony
European Haemophilia Consortium, Brussels, Belgium
Irish Haemophilia Society, Haemophilia Product Selection Monitoring and Advisory Board, Ireland
F. Peyvandi
Angelo Bianchi Bonomi Haemophilia and Thrombosis Center, IRCCS Ca'Granda Foundation Maggiore Policlinico Hospital,
Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
A. Bok
European Haemophilia Consortium, Brussels, Belgium

References

1 European Medicine Agency: EMA/CHMP/BPWP/144552/2009 - Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (2011). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109691.pdf. Accessed March 26, 2014.

2 Orpha.net: Haemophilia. http://www.orpha.net/consor/cgibin/Disease_Search.php?lng=EN&data_id=646&Disease_Disease_Search_diseaseGroup=haemophilia&Disease_Disease_Search_diseaseType=Pat&Disease%28s%29/group%20of%20diseases=Hemophilia&title=Hemophilia&search=Disease_Search_Simple Accessed 18 March 2014.

3 Mathieu Agnès(March, 2014). Regulator's perspective on the legislation. Speech presented at the European Haemophilia Consortium Round Table on Orphan Drugs and Rare Bleeding Disorders, Brussels, Belgium. http://www.ehc.eu/fileadmin/Round_table/21-2014-03-03/02-Agnes_mathieu_Rare_Bleeding_Disorders_and_Orphan_Drugs_regulators_perspective.pdf Accessed March 26, 2014.

4 Regulation of the European Parliament and of the Council 141/2000 of 16 December 1999 on orphan medicinal products [2000] OJ L 18/1. Preambule

5 http://uk.reuters.com/article/2014/03/07/us-hemophilia-idUKBREA2600T20140307. Accessed March 09, 2014.

6 Communication from the Commission. Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity. C(2008) 4077 final.

7 Jevševar S, Kunstelj M, Porekar VG. PEGylation of therapeutic proteins. *Biotechnol J* 2010; **5**: 113–28.

8 Huang C. Receptor-Fc fusion therapeutics, traps, and MIMETIBODY technology. *Curr Opin Biotechnol* 2009; **20**: 692–9.

9 Kratz F. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. *J Control Release* 2008; **132**: 171–83.

10 Schramm W, Seitz R, Buchheit K.-H. (2013). Optimal use of Clotting Factors and Immunoglobulins. Proceedings of the 2013 Kreuth Symposium. Available from the website of the European Directorate for Quality of Medicines and Healthcare (EDQM). Accessed March 26, 2014.
11 O'Mahony B, de Moerloose P, Weill A. Letter to Sabine Jülicher [European Commission]. Concern regarding market exclusivity for longer- acting factor VIII and longer-acting factor IX concentrates. Letter to the European Commission. Available on www.ehc.eu. Accessed March 14, 2014.

