Orphan designation and market exclusivity

Flora Peyvandi MD, PhD
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center,
Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and
University of Milan
Italy

8th Global Forum – Montreal, September 26-27, 2013
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<th>Disclosure - if conflict of interest exists</th>
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<td>Research Support</td>
<td>NovoNordisk, Biotest</td>
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<td>Director, Officer, Employee</td>
<td>No conflict of interest to disclose</td>
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<td>Shareholder</td>
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<td>Speakers fee</td>
<td>Novo Nordisk, CSL Behring, Bayer, Baxter</td>
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<td>Advisory Committee</td>
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Rare disorders

- Are a group of diseases, of very different aetiologies, whose common denominator is that they are low-prevalence diseases.
- The current estimate of rare disorders is 6000 to 8000 and 80% have a genetic origin and affect children at a very early age.
- In US a disease that affects less than 200,000 inhabitants.
- In the EU, besides affecting fewer than 5 per 10,000 inhabitants, a rare disease needs to be life threatening or chronically debilitating.
Orphan Drugs

- Because of the rarity, the cost of developing and marketing a medicinal product to diagnose, treat or prevent a rare condition would not be recovered by the expected sales of the medicinal product under normal market conditions.

- Therefore, in several jurisdictions specific legislation has been introduced to stimulate the development of drugs for a rare diseases, so-called “orphan drugs”.
Regulation of Orphan drug was adopted:

- **USA** (Introduction of the US Orphan Drug Act) in 1983
- **Japan** (Orphan Drug Regulation) in 1993
- **Australia** (Orphan Drug Policy) in 1998
- **European Union** (Regulation Number 141/2000 of the European Parliament and the Council) in 2000
Orphan drug designation in Europe

The European Medicines Agency (EMA), through its Committee for Orphan Medicinal Products (COMP), is responsible for reviewing designation applications from persons or companies who intend to develop medicines for rare diseases, known as ‘orphan medicines’
Annual number of orphan drug designation and marketing (2000-2010)

European Union:
- 684 designated orphan drugs
- 63 received marketing approval
Orphan drugs designation and obtaining marketing approval

• The EU Orphan Drug regulation is highly appreciated for its role in creating a favorable orphan drug development environment

• However, this apparent success of the legislations has also been questioned
Orphan drugs

• The development of orphan drugs is stimulated through a number of regulatory and economic incentives

• These incentive measures can be broken down into three types:
  
  ➢ Marketing exclusivity of the orphan drug, whereby sponsors of this drug are granted a given period of marketing exclusivity during which no other drug will be approved for the disease in question
  
  ➢ the setting up of tax credits and research aids
  
  ➢ simplification of and advantages in the drugs authorization procedure
Marketing exclusivity

- USA: 7 years
- European Community: 10 years
- Japan: 10 years
- Australia: 5 years
Orphan Medicinal Products
EC regulation 141/2000

Article 8(1) - 10 years market exclusivity:

for 10 years after granting of a marketing authorization (approval for sale), orphan medicinal products benefit from market exclusivity in the EU. During this period, directly competitive similar products cannot normally be placed on the market.
EC regulation 141/2000 on Orphan Medicinal Products

**Article 8(3)** describes three types of derogations from the market exclusivity provided under Article 8(1) of that Regulation:

(a) consent of the original marketing authorisation holder

(b) inability of the original marketing authorisation holder to supply sufficient quantities

(c) the second medicinal product is safer, more effective or otherwise clinically superior
Market exclusivity and Hemophilia
Orphan designation

A medicine must meet a number of criteria to qualify for orphan designation:

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Applications for orphan designation are examined by the European Medicines Agency’s Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation.

Haemophilia is the most frequent inherited coagulation disorders due to the deficiency of FVIII (haemophilia A) and FIX (haemophilia B)

- 1 in 5,000 is born with haemophilia type A
- 1 in 30,000 is born with haemophilia type B
Haemophilia

• is X-linked recessive blood coagulation disorder

• associated with bleeding episodes affecting soft tissue, joints and muscles

• repeated haemorrhages result in chronic arthropathy, with loss of joint movement, fixed flexion contracture, and severe muscle wasting
New drugs for hemophilia

could be qualified as “orphan drugs”

and, as orphan drugs, could benefit from economic incentives including market of exclusivity (10 years)

Could market exclusivity potentially create a monopoly rather than market competition to ensure the widest possible access at the most affordable price?
Market Exclusivity

Key Concepts

- Significant Benefit
- Definition of a similar product
Market exclusivity and Hemophilia

If satisfactory treatment exist the sponsor should establish that the product will be of significant benefit
Haemophilia care

- substantial improvements during the past 40–50 years
- advent of recombinant concentrates, has greatly improved the safety and availability of therapy
CURRENT HEMOPHILIA THERAPY
Very safe and very effective but....

Problems of hemophilia care

- Immunogenic
  Neutralizing antibodies in ~30% of severe hemophilia A and up to 3% of hemophilia B patients

- Frequent injections

- Prophylactic regimens:
  infusion 2–3 times weekly

- No available products
  Treated 30%
  Untreated 70%

Flora Peyvandi
Challenges for new hemophilia products

- Greater safety and reduced immunogenicity
- Enhanced efficacy
  - Prolongation of the half-life
- Lower cost with improved delivery
- Greater and wider coagulation factor availability
Extension of half-life

PEGylation

- Chemical coupling of polyethylene glycol (PEG), increased hydrodynamic volume to prevent clearance by kidney

Fc fusion

- Fc fragment and albumin have the same unique mode to recycling through the FcRn ligands at the endothelial cell surface to increase the half-life

Albumin fusion
Prematurely stopped due to an increased number of bleeding events.

Suspended - A multiple dose phase 1b trial has been paused in order to allow further assessment of non-clinical data prior to proceeding into higher dose cohorts.
May 2013, the FDA has accepted the marketing approval of ELOCTATE

March 2013, the FDA has accepted the marketing approval of ALPROLIX
Results of Long acting products  
- Clinical studies -  

Factor IX  3 to 5-fold  

Factor VIII  1.5 to 1.8-fold  

rFVIIa  2 to 3-fold
Market Exclusivity

- The Haemophilia community welcome all of these approaches.

- Not clear which of these will result in best clinical outcomes in the long term.

- Need different approaches and competition.
Based on the definitions set out in Article 3 of Regulation 847/2000, the assessment of similarity between two medicinal products under Article 8 of Regulation (EC) No 141/2000 takes into consideration:

1. Principal molecular structural features
2. Mechanism of action and therapeutic indication

If significant differences exist within one or more of these criteria, then the two products will be considered as not similar.
FVIII & FIX Long-acting
Are they similar products?

- Different recombinant proteins
- Different cells
- Different PEG molecules (different sizes) linked to the protein
- Different fusion proteins (Fc, Albumin)
Could Market exclusivity create a market monopoly rather than allow competition?

- Market size
- Turnover of the first OMP
- Disease class
- Disease-specific scientific output
- Age of onset

(Anne EM Birabers et al. Orphanet Journal of Rare Disorders 2011,6:59)
Follow-on OMP
(Orphan Medicinal products)

In the EU is allowed to approve a follow-on OMP next to the first OMP, if provided that significant benefit to those affected by the condition can be established and significant benefit means:

- a clinically relevant advantage or a major contribution to patient care, and is justified by “demonstration of potentially greater efficacy”, an improved safety profile and/or more favorable pharmacokinetic properties than existing methods.
EHC Position communicated to EMA:

“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.
Conclusion

- Coagulation disorders differ for diagnosis and treatment

- Haemophilia patients benefit from a large number of plasma-derived and recombinant products however further improvement is required to extend the half-life of products and reduce their immunogenicity

- These products differ in structure (cDNA, vectors, cells) and could not be considered similar
Conclusion

• Critical evaluation on missing follow-on Orphan Medicinal products is necessary:
  – Matter of time or market size
  – Or market exclusivity

• Orphan drug designation and market exclusivity should be considered for those coagulation disorders with no available products as FV deficiency