Challenges and Opportunities for Orphan Medicinal Products under the European Regulatory Framework

BioBridges 2018
Institute of Pharmacology, First Faculty of Medicine, Charles University Prague
Czech Republic

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Chair of the Committee of Orphan Medicinal Products (COMP)
Human medicines

In 2017, EMA recommended 92 medicines for marketing authorisation. Of these, 35 had a new active substance, i.e. one which had never previously been authorised in EU.

Many of these medicines represent a significant improvement in their therapeutic areas; they include medicines for children, for rare diseases and advanced therapies.

Medicines for children:

- **Brineura** for the treatment of a very rare, fatal neurodegenerative condition in children called neuronal ceroid lipofuscinosis type 2 (CLN2) disease. This is the first medicine approved in the EU for the treatment of CLN2.

- **Spinraza** to treat spinal muscular atrophy (SMA), an inherited disease that affects the motor neurons and is usually diagnosed in the first year of life. This is the first medicine approved in the EU for the treatment of SMA.

- **Alkindi** for the treatment of primary adrenal insufficiency, a rare hormonal disorder in infants, children and adolescents.

Advanced therapy medicinal products:

- **Spherox** to treat adult patients who have symptomatic cartilage defects in the knee joint.

- **Alofisel** for the treatment of complex perianal fistulas in patients with Crohn’s disease. Perianal fistulas occur when an abnormal passegeway develops between the rectum and the outside of the body.

Rare diseases:

- **Oxervate** for the treatment of neurotrophic keratitis, a rare eye disease.

- **Qarziba** (previously Dinutuximab beta Apeiron) for the treatment of high-risk neuroblastoma (a cancer of nerve cells).

- **Xermelo** for the treatment of carcinoid syndrome (a rare cancer-related condition leading to diarrhoea and flushing).
What is a rare disease?

**EU definition:**
- Medical condition affecting **not more than** 5 in 10,000 persons in the European Community (close to 252,000 people)

**US definition:**
- The disease or condition for which the drug is intended affects fewer than 200,000 people in the US (close to 6.4 in 10,000)
What is different about rare diseases?

- Diseases are usually **poorly** or **incompletely understood**
  
  *Generally, the lower the prevalence, the less well we tend to understand them*

- **Small populations**
  
  *Limited opportunity for study and replication*

- Highly **heterogeneous** group of disorders
  
  *Some references point to ~6000-7000 different diseases*  
  
  *Often high phenotypic diversity within individual disorders*

- Usually little **precedent** for **drug development** within individual disorders

- Development often requires **more** (and more careful) **planning** than non-Orphan
  
  *Need a solid scientific base upon which to build an overall program*
How did we get from Oliver Twist ... to the orphans everyone wants to adopt?
Patients with rare diseases without cures in the EU.

Pharma industry not willing to develop OMP under normal market conditions.

Only a few MS developed measures for rare diseases.

Regulation (EC) 141/2000

EU procedure for orphan designation

Protocol assistance

EU authorisation

EMA Committee

Aid for R&D

EMA fee waiver

Involvement of patients groups

10-year market exclusivity +2 PIP
A TIMELINE of ORPHAN DRUGS

1970 - 1980
- 1973-1983: 10 orphan drugs are introduced.
- 1983: The U.S. passes the Orphan Drug Act, becoming the first country to enact legislation to support orphan drug development.

1980 - 1990
- 1983-1990: 45 orphan drugs are approved for sale.
- 1983-2012: Approximately 400 orphan drugs come to market.

1990 - 2000
- 1993: Japan passes orphan drug legislation.

2000 - 2010
- 2000: The EU passes orphan drug legislation.
- 2000-2010: Mean present value of an orphan drug increased from $351 million to $637 million. Mean present value of a non-orphan drug remained constant at $600 million.
- 2001-2010: Revenue from orphan drugs grows 25.8 percent annually, compared to revenue growth for non-orphan drugs of 20.1 percent.

2010 - 2020
- 2010: Orphan drugs represent 22 percent of total drug sales.
- 2012: There are 7,000 rare diseases in the U.S., affecting 25 million people.

Source: PAMPLIN, College of Business Magazine, Virginia Tech, 2013
Team players
Elosulfase alfa
MS Type IV A
Morquio A syndrome

CHMP
B/R assessment

COMP
Orphan designation

PDCO
PIP Decision

COMP
Review of designation
The Committee of Orphan Medicinal Products

- 1 elected Chair
- 1 elected Vice chair
- 1 Member per MS (28)
- 3 Patients Reps
- 3 Members by EC on proposal from EMA
- 1 Member for Norway, 1 for Iceland
Current EMA/COMP activities in the orphan landscape

**COMP mission and responsibilities**

- Give opinions on designation and orphan drug status maintenance
- Actively contribute to *Protocol Assistance* for Significant Benefit
- Advise the European Commission on establishment and development of a policy on orphan medicinal products
- Assist on guidelines
- Assist the European Commission in international liaison
Main characteristics orphan designation

- Applications for treatment, prevention or diagnosis of rare diseases
- Procedure free of charge
- Designation can be requested at any stage of development before the application for MAA is made
- Sponsor can be either company or individual [Established in the EEA (EU, Ice, Liech, Nor)]
- European Commission decision gives access to incentives such as protocol assistance and centralised procedure
- Designated products are entered into the Community Register of OMPs by the EC
Incentives after Initial Orphan Designation

**Economic / marketing**
- Fee reduction / exemption

**Product development**
- Protocol assistance
- Benefits for SMEs

**Community marketing authorisation**
- Centralised procedure and Conditional Licencing

**National incentives (EC inventory)**
Designation criteria

RARITY (prevalence) / NO RETURN OF INVESTMENT (Art 3.1 (a) of 141/2000)
• Medical condition affecting not more than 5 in 10,000 in the Community (around 250,000 people)
• Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

SERIOUSNESS
• Life-threatening or chronically debilitating

ALTERNATIVE METHODS AUTHORISED (Art 3.1(b) of 141/2000)
• If satisfactory method exist the sponsor should establish that the product will be of significant benefit

EXCLUSIVE for EU
The designation process in the EU

- **Submission**
  - Intention to submit letter

- **Validation**
  - Day 1

- **Evaluation**
  - Day 60
    - COMP Meeting
  - Opinion
    - List of Questions / Oral Explanation
    - Decision by the European Commission

- **Decision**
  - Day 90
    - COMP Meeting
    - Opinion

Publication of a Public Summary of Opinion at the EMA website
Areas of growing interest and trends in OMP development

**Eye diseases:** e.g. Retinitis pigmentosa, Non-infectious uveitis, Leber’s congenital amaurosis, Choroideremia, Stargardt’s disease

**Skin diseases:** e.g. Epidermolysis bullosa, Congenital ichthyosis, Dyskeratosis congenita, Pemphigus;

**Genetic a/o Metabolic disorders** – continuing and rising

**Conditions in prematurely born infants** (e.g. Bronchopulmonary dysplasia, Respiratory Distress Syndrome, Retinopathy of prematurity)

**Tropical diseases:** Malaria, Leishmaniasis

‘The first orphan designation sparks the interest’ – clusters of applications for e.g. pulmonary arterial hypertension, hemophilia (A and B), amyloidosis, epidermolysis bullosa, Fragile X syndrome

**New types of therapies** - Gene therapies / Stem cell therapies (mesenchymal etc.), cancer ‘vaccines’

**Oncology:** glioma, pancreatic cancer and ovarian cancer
Drug Repurposing and orphan drugs

- ‘De-risking’ therapeutic development
- Aprox. 20% of Orphan Drugs
- CNS diseases with high potential
- Reduced development costs (1/20)
- Time to market is reduced
- Safety profile in general well-known
- Manufacturing process in place
- PK / PD known in humans

- Medical plausibility needs to be established
- PK / PD particularities relevant for the new orphan condition need to be fully substantiated
- SB needs to be demonstrated (when applicable)
- Bibliographic data needs to be fully supportive of the claims
- New data might still need to be generated
COMP responsibilities

"Dreamworks"

- Idea
- Hypothesis
- Assumption or viable hypothesis

COMP

- IDEA

CHMP

- Proof / Evidence
“Maintenance of Orphan Status” is not an easy walk

Philippe Petit high-wire walk between the Twin Towers of the World Trade Center (7th of August of 1974)
Review of the orphan criteria at the time of MAA

• At the time of submission for MAA, the sponsor is requested to submit a report on the maintenance of ODD criteria.

• Guidance on the submission of this report in the pre-submission mtg for MAA.

• The COMP re-evaluates the criteria based on data generated by the sponsor (not assumption) in parallel to the MA assessment, if doubt the sponsor will be invited for an oral hearing.

• The opinion by the COMP on if the product should be removed or not from the Community Register
Maintenance Designation Criteria

Key criteria that must be met:

- Confirm that the condition/disease is a distinct medical entity.
- Confirm that the prevalence calculation which meets the criteria of being below 5 in 10,000
- Where there are authorised medicines the sponsor will need to confirm that their product offers a significant benefit over authorised medicinal products in Europe.

Incentives After MAA and Review of ODD

- Reduced licencing fees for SMEs.
- 10-year market exclusivity protection against
  - similar products (structure/mechanism of action)
  - same indication
- 2yr extension if PIP has been complied with specific per indication.
Prevalence criteria

Prevalence (≤ 5 / 10,000)
OR
Insufficient return on investment (costs > expected revenues)

Seriousness criteria

Life-threatening or chronically debilitating

Life-threatening, seriously debilitating or serious and chronic

Existing methods criteria

Available methods for diagnosis / prevention / treatment

NO

YES Significant benefit / non satisfactory
Significant benefit in the context of the orphan regulation is ADDED VALUE to patients.

The orphan status of a product in Europe is not easy to maintain ...

**Orphan Designation**

"Assumptions of potential benefit(s) should be plausible"

**Market Authorisation**

"demonstration of significant benefit over currently authorised methods in order to maintain orphan status"

The COMP will require a higher level of data/evidence for the orphan status at the time of Market Authorisation.

It's very easy to be different, but very difficult to be better.

Jonathan Ive
The orphan status of a product in Europe is not easy to maintain …

Significant Benefit at time of Marketing Authorisation (for 2016)

- Negative: 36%
- Positive: 68%
Orphan environment after 16 years of EU legislation

• Rising importance in PA+SB for marketing success

• Stark rise of appeal procedures on COMP SB assessment in 2016/2017

Hofer et al., *Nat Rev Drug Discov.* 2015
How Applicants [used to] see us at the time of Marketing Authorisation
The orphan status of a product in Europe **is not meant to last forever**.

**Art 8 (2):**

This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.
Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)

At the time of initial Orphan Designation (OD):
Sound pharmacological concept to support the assumption

Compelling evidence in relevant preclinical models

Unconvincing preliminary clinical data
Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009 Final)

‘...the COMP will evaluate whether there is a high probability for the patients to experience a clinically relevant benefit... it has to be concrete and based on the data contained in the application for marketing authorisation and the arguments presented by the sponsor’
"Significant benefit’ is defined in Article 3(2) of Regulation (EC) No 847/2000 as ‘a clinically relevant advantage or a major contribution to patient care’. The purpose of the legislation is to encourage and reward innovative treatments. These require investment in research and in the development of potential improved medicinal products that can bring meaningful advantages for patients. It is clear from Article 3(1)(b) of Regulation (EC) No 141/2000 and the spirit underlying the system it establishes, that the criteria for a finding of significant benefit are strict.”
“Protocol assistance is recommended to ensure an appropriate clinical development ...can also include guidance to demonstrate significant benefit...”
Scientific advice and protocol assistance requests received - total

- Protocol-assistance and follow-up requests
- Scientific-advice and follow-up requests

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Requests</th>
<th>Protocol-Assistance</th>
<th>Scientific-Advice</th>
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<td>2017</td>
<td>159</td>
<td>471</td>
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</table>
Scientific advice requests by therapeutic area (2017)

- Alimentary tract and metabolism: 53
- Anti-neoplastic and immunomodulating agents: 229
- Anti-parasitic products, insecticides, repellents: 2
- Blood and blood-forming organs: 37
- Cardiovascular system: 23
- Dermatologicals: 15
- Diagnostic agents: 5
- General anti-infectives for systemic use: 61
- Genito-urinary system and sex hormones: 10
- Musculoskeletal system: 19
- Nervous system: 81
- Respiratory system: 24
- Sensory organs: 28
- Systemic hormonal preparations, excluding sex hormones: 10
- Various: 14
Commission Notice on the application of Articles 3, 5 and 7 of regulation (EC) No 141/2000 on Orphan Medicinal Products

Decisions on the most relevant endpoints, including those capturing patients’ views, should stem from discussion and collaboration not only between regulators and industry, but also with academia and patients that have to work together to generate the data and work towards validation of new outcome measures to be used for regulatory purposes.
All progress is precarious, and the solution of one problem bring us face to face with another problem.

Martin Luther King
The changing world of Orphan Designations

Applications for orphan medicinal product designation
Objective 2020: 200 new therapies
Since 2000

2069 Orphan designations
166 Orphan designations included in authorised indication
151 Authorised OMPs
61 To be used in children
4 Removed from the market
45 Marketed, but no longer "orphans"

To date
106 Products with a marketing authorisation and an orphan status in the European Union

06 September 2018
Translation of regulatory experience to guidance

The scientific and regulatory experience from designations, protocol assistance and marketing authorisations gives us valuable information to identify bottle necks and research needs

Analysing the reasons why there continue to be gaps in the development of orphan medicines

• negative outcome of a Marketing Authorisation assessment procedure
• withdrawn and negative applications for designation
• rare diseases where we see no or very little development

To be used to reduce the gaps for the benefit of the public health
Regulators, HTA bodies and payers – we all perform an important task in one way or the other as gatekeepers for medicines to the healthcare systems in the EU. But we also have an increasingly important role as enablers of medicine development. Our cooperation can help medicine developers to address some of the inefficiencies in the current system of clinical research so that they become better at generating the evidence each of us needs for good decision-making.

Guido Rasi
EMA Executive Director
Reality check: from EU regulatory approval to national HTA/P&R decisions for orphan oncology products

<table>
<thead>
<tr>
<th>Orphan medicine</th>
<th>Indication</th>
<th>EU MA Approval</th>
<th>Time for HTA/P&amp;R after MA (month)</th>
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<td>bosutinib (Bosulif)</td>
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<td>cabozantinib (Cometrix)*</td>
<td>medullary thyroid cancer</td>
<td>03/2014</td>
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*first in class; MA = marketing authorisation; P&R = price and reimbursement

Differences in Time to Market Entry across EU countries

Source: www.efpia.eu
Synergy through alignment of evidence generation

• Experience shows that parallel scientific advice can help to align regulatory and HTA views on evidence needs

• There is close collaboration between EMA and EUnetHTA to continuously optimise the processes to facilitate such dialogue

• Whilst the focus so far has been on evidence needed for market entry, more engagement is needed on post-licensing evidence generation, which is particularly relevant for orphan medicines
Parallel regulatory/HTA advice for orphan medicines

Since the inception of parallel regulatory/HTA advice in 2010, there have been:

- 15 protocol assistance procedures on development of orphan medicines*
- 4 of these also covered questions related to the demonstration of significant benefit

* includes 2 follow-up requests

Parallel HTA procedures*  
- 87% (SA new)  
- 13% (PA new)  

[adapted from Michael Berntgen 2017]

Opportunities to stimulate such discussions on development plan for orphan medicines.
Beyond the scientific/clinical debate on data and requirements

An orphan product in the US is also orphan in the EU

Significant benefit equals benefit risk

Personalised medicine means every disease can be orphan

Acknowledges the positive impact of Regulation (EC) No 141/2000 on the development of orphan medicines, which has enabled a number of innovative products for patients deprived of treatment to be placed on the market; notes the concerns surrounding the possible incorrect application of orphan medicinal products designation criteria and the possible effect of this on the growing number of orphan medicines authorisations;

EP report Options for improving access to medicines, March 2017
Currently published documents:

Public Summary of Opinion (PSO)

Recommendation for maintenance of OD at the time of MA

COMP minutes
Orphan Maintenance Assessment Report
Where?

Spinraza

nusinersen

About | Authorisation details | Product information | Assessment history

= Previous tab

Changes since initial authorisation of medicine

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<tr>
<th>Name</th>
<th>Language</th>
<th>First published</th>
<th>Last updated</th>
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<tr>
<td>Initial marketing - authorisation documents</td>
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<tr>
<td>Spinraza : EPAR - Public assessment report</td>
<td>(English only)</td>
<td>21/06/2017</td>
<td></td>
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<tr>
<td>CHMP summary of positive opinion for Spinraza</td>
<td>(English only)</td>
<td>21/04/2017</td>
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</table>

Spinraza: OMAR – Orphan Maintenance Assessment report

+ what is the orphan status?
Facilitating patient access through collaboration

The dialogue on evidence generation plans and the exchange on assessment outcomes are **two crucial pillars** to enable later patient access to orphan medicines.

There are **specific topics and concepts** where regulators and down-stream decision makers can benefit from increased mutual understanding, also involving payers.

**Engagement and communication** is crucial to ensure that healthcare systems are prepared for the needs of patients with rare diseases.
Indiana Jones and the Raiders of the Lost Ark (1981)
Indiana Jones and the Raiders of the Lost Ark (1981)
End scene from Indiana Jones and the Raiders of the Lost Ark (1981)
Thank you for your attention

Further information

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