Orphan drugs and rare diseases

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Orphan drugs and rare diseases

• Orphan drugs in Europe
  EMEA : Orphan drugs at a glance (July 2007)

• Orphan drugs in USA
  Orphan drug act January 1983

• Evaluation of orphan drug programs
  Registration, indications, access to the drugs,…
### Distinction between Essential medicines and Orphan drugs

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Essential medicines</th>
<th>Orphan drugs</th>
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<tr>
<td>Concrete policies in place since:</td>
<td>1977 worldwide</td>
<td>1983 in USA, 2000 in EU</td>
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<td>Primary focus:</td>
<td>Public health: bringing effective medicines to as many patients as possible</td>
<td>Individual patient: even a single patient warrants all possible treatment</td>
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<tr>
<td>Initiated and developed by:</td>
<td>WHO, and Member States</td>
<td>Governments of Australia, EU, Japan, and USA; patient groups</td>
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<td>Criteria:</td>
<td>Drug driven (i.e. drug to be listed on EML is efficacious, safe, cost-effective, based on evidence based data, etc.)</td>
<td>Disease driven (i.e. disease to be classified as an orphan drug has low prevalence &lt; 5-7.5 : 10000, is life-threatening, etc.)</td>
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<td>Policies aim to:</td>
<td>Provide established medicines to patients</td>
<td>Provide new medicines to as yet untreatable patients</td>
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<tr>
<td>Target populations:</td>
<td>Initially low-income countries, now all countries</td>
<td>High-income countries, developed countries</td>
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<tr>
<td>Economics:</td>
<td>Cost-effectiveness, sustainable and affordable access</td>
<td>Relatively high prices per individual patient, cost-maximization per population</td>
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## Features of orphan drug incentive systems in the USA and EU

<table>
<thead>
<tr>
<th>Feature</th>
<th>USA</th>
<th>EU</th>
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<td><strong>Program established</strong></td>
<td>1983 – the Orphan Drug Act modified the Federal Food, Drug and Cosmetic Act</td>
<td>2000 – Orphan, Medicinal Products Regulation</td>
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<td><strong>Prevalence criterion for rare disease</strong></td>
<td>&lt; 200,000 patients in the USA (&lt; 7.5 : 10,000)</td>
<td>Life-threatening or chronically debilitating disorder that affects &lt;5 : 10,000 in the EU</td>
</tr>
<tr>
<td><strong>Requirements for orphan drug designation</strong></td>
<td>Rare disease, or research and development costs cannot be recovered in 7 years</td>
<td>Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit</td>
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<tr>
<td><strong>Products eligible for orphan drug designation</strong></td>
<td>Drugs and biologicals (including vaccines and in-vivo diagnostics)</td>
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</tr>
<tr>
<td><strong>Market exclusivity</strong></td>
<td>7 years; prevents same product being approved for the same indication unless clinical superiority is shown</td>
<td>10 years; can be reduced to 6 years if orphan drug criteria no longer met</td>
</tr>
<tr>
<td><strong>Other benefits</strong></td>
<td>Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharmaceutical companies and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food</td>
<td>Regulatory fees can be reduced or waived; access to centralized procedure; protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products.</td>
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Orphan drugs and rare diseases at a glance
1. Orphan drugs at a glance

A medicinal product is designated as an orphan medicinal product if:

- it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the European Union at the time of submission of the designation application (prevalence criterion), or;

- it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that expected sales of the medicinal product would cover the investment in its development, and;

- no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such method exists, the medicinal product will be of significant benefit to those affected by the condition.
Companies with an orphan designation for a medicinal product benefit from incentives such as:

- protocol assistance (scientific advice during the product-development phase);
- marketing authorisation (10-year marketing exclusivity);
- financial incentives (fee reductions or exemptions);
- national incentives detailed in an inventory made available by the European Commission.
Since 1 January 2007, orphan medicinal products are eligible for the following level of fee reductions:

- 100% reduction for protocol assistance and follow-up;
- 100% reduction for pre-authorisation inspections;
- 50% reduction for new applications for marketing authorisation;
- 50% reduction for post-authorisation activities, including annual fees (applies only to small and medium-sized enterprises), in the first year after granting of a marketing authorisation.

The funds made available by the Community for fee exemptions for orphan medicinal products amount to €6,000,000 in 2007.
2. Rare diseases at a glance

- Rare diseases are life-threatening or chronically debilitating conditions affecting no more than five in 10,000 people in European Union. While this number may seem small, it translates into approximately 246,000 persons in the 27 EU Member States. Most of the people represented by these statistics suffer from less frequently occurring diseases affecting one in 100,000 people or fewer.

- It is estimated that between 5,000 and 8,000 distinct rare diseases exist today, affecting between 6% and 8% of the population in total – in other words, between 27 million and 36 million people in the European Union. Five new diseases are described every week in the medical literature.

- Symptoms of some rare diseases may appear at birth or in childhood, including infantile spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis. However, more than 50% of rare diseases appear during adulthood, such as renal cell carcinoma, glioma and acute myeloid leukaemia.
80% of rare diseases have identified genetic origins. They concern between 3% and 4% of births. Other rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes.

Medical and scientific knowledge about rare diseases is lacking. While the number of scientific publications about rare diseases continues to increase – particularly those identifying new syndromes – fewer than 1,000 diseases – essentially those that occur most frequently – benefit from a minimum of scientific knowledge.

The European Union’s Seventh Framework Programme for Research and Technological Development (FP7, 2007-2013) will boost research into rare diseases. Its first phase focuses on innovative and multidisciplinary projects investigating (on an EU-wide scale) the natural course and pathophysiology of non-infectious, non-malignant rare diseases in the areas of: endocrine, immune and metabolic diseases; genito-urinary tract diseases; diseases affecting the digestive and respiratory system. The acquired knowledge will provide the basis for future development of diagnostic, therapeutic and potentially preventive approaches. The FP7 will also include research into rare Mendelian phenotypes (human phenotypes) of common diseases.
Orphan Drug Act (FDA)
USA, January 4, 1983

The Orphan Drug Act (P.L. 97-414) was signed into law on January 4, 1983. The Act provides incentives for pharmaceutical manufacturers to develop drugs, biotechnology products, and medical devices for the treatment of rare diseases and conditions. These products are commonly referred to as orphan products. Incentives for orphan product development include marketing exclusivity for orphan drug sponsors, tax incentives, and research grants.
FOCUS ON RESEARCH

Adopting Orphan Drugs — Two Dozen Years of Treating Rare Diseases

Marlene E. Haffner, M.D., M.P.H.

In 1982, when the Orphan Drug Act was passed as an amendment to the Federal Food, Drug, and Cosmetic Act, few suspected the extent to which this law would alleviate the plight of patients with rare diseases. The law defines an orphan drug as one with efficacy against a disease affecting fewer than 200,000 people in the United States or one that scientists and economists at the Food and Drug Administration (FDA) determine will not be profitable for seven years after FDA approval. In the 24 years since this law was passed, 282 such drugs and biologic products, providing treatment for more than 14 million patients in the United States, have come to market under its aegis. In the 8 to 10 years before 1982, by contrast, only 10 treatments for rare diseases had been approved by the FDA and brought to market.

Many rare diseases have a genetic component, and the patients who have them require treatment throughout their lives. Many cancers are also quite rare, and a substantial proportion of the drugs in development are for use in children; for example, somatrem for injection (Proterpin) has been developed to treat congenital growth hormone deficiency. Although most rare diseases are chronic, a number — such as infant botulism, discussed by Amon et al. in this issue of the Journal (pages 462–471) — are acute.

Whether a disease is rare or common, however, the discovery, development, and clinical testing of a drug that can treat it represent a long, arduous, and expensive process. Drug companies are therefore loath to invest in a product for a disease that affects relatively a few people unless they can be assured of a return on their investment. The Orphan Drug Act created government incentives to encourage academic researchers to participate in research on drugs for the treatment of rare diseases.
Drugs Approved by the FDA for the Top Seven Types of Rare Diseases Addressed by Orphan Drugs.
The indication for a rare disease leads to orphan drug status, not the drug by itself! Revatio® (sildenafil for pulmonary arterial hypertension) is an orphan drug, but not Viagra® (sildenafil).
COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 20.6.2006
SEC(2006) 832

COMMISSION STAFF WORKING DOCUMENT

on the experience acquired as a result of the application of Regulation (EC) No 141/2000
on orphan medicinal products and account of the public health benefits obtained

Document on the basis of Article 10 of Regulation (EC) No 141/2000
5 years of Orphan Designation

Between April 2000 and April 2005, 458 applications for orphan designation were submitted to the EMEA. By April 2005, more than 260 products were designated, relating to over 200 different rare conditions. Twenty-two products have gone on to receive a marketing authorisation (20 of those through the centralised procedure).

Ninety percent (90%) of rare conditions, for which a medicinal product has received an orphan designation, have a low prevalence of less than 3 in 10,000. Of these, 43% occur in less than 1 in 10,000. Only 10% have a prevalence of 3-5 in 10,000. Sixty-nine percent (69%) of positive COMP Opinions recommending designation have been based on the criterion of significant benefit. A substantial proportion (54%) is intended for paediatric use; 11% solely for paediatric use and 43% for adult & paediatric use.

More than half (53%) of the products, which have been the subject of a designation application between 2000-2004, are novel/innovative products, including 92 (21%) biotech products and emerging therapies such as anti-sense, gene therapy and cell therapy.
Figure 1: Overview of Orphan Designation Procedures - Outcomes April 2005
Figure 2: Prevalence Range of Designated Orphan Conditions - April 2005
Figure 3: Distribution of Orphan Designations by ATC code (April 2005)
Figure 4: Paediatric Use of Orphan Medicinal Products (April 2005)

Orphan Medicinal Products in adult or paediatric use
Figure 7: Overview of Fee Reductions Granted to Orphan Medicinal Products – Status (April 2005)
3. **CONCLUSIONS**

The response to the orphan legislation in the EU has far exceeded initial expectations: more than 450 applications for orphan designation have been submitted in the period between April 2000 and April 2005. Of those, more than 260 have been designated and 22 have gone on to receive a marketing authorisation.

Although more than 5 years of experience with the Regulation has now been gained, the true impact of the EU orphan initiative on public health will only be revealed progressively as longer term experience is accumulated. Already, more than 1 million patients suffering from orphan diseases in the Community may potentially benefit from these new 22 orphan medicines authorised during the first five years of application of Regulation (EC) No 141/2000. In addition, there is good ground to assume that the legislation has stimulated industrial activity leading to company creation with promising high-tech potential.

The full benefits of the EU orphan regulations require optimal synergies between action on Community and on Member States level. Incentives at the European Union level need to be translated into rapid access of patients to the new products throughout the entire Community and they need to be supplemented by incentives at Member States level. In this regard, the past experience was not entirely satisfactory.
Expensive drug gives hope to rare disease sufferer

Family wonders who will pay bill

Trevor Pare, 16, suffers from a rare form of muscular dystrophy. He and his mother, Linda, worry his condition will worsen if the province doesn’t pay for a drug that costs up to $400,000 a year.

Photograph by : Mikael Kjellstrom, Calgary Herald
Genzyme: WHO WILL PAY?

WHEN YOU MAKE THE WORLD’S MOST EXPENSIVE DRUGS, YOU HAVE TO WONDER...

CEO Henri Termeer

Rising Profits
Genzyme has tripled revenue in five years.

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<th>Year</th>
<th>Revenue</th>
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<tbody>
<tr>
<td>2000</td>
<td>$903 M</td>
</tr>
<tr>
<td>2001</td>
<td>$1.2 B</td>
</tr>
<tr>
<td>2002</td>
<td>$1.3 B</td>
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<tr>
<td>2003</td>
<td>$1.7 B</td>
</tr>
<tr>
<td>2004</td>
<td>$2.2 B</td>
</tr>
<tr>
<td>2005</td>
<td>$2.7 B</td>
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Source: Genzyme annual report
Ethics: Equity in drug distribution and resource application

A major problem is that some pricing authorities believe that all new drugs should reach minimum standards of cost effectiveness. Some economists say that despite their clinical efficacy, equity in resource application should also be valued and that the funding of orphan drugs is not efficient in that it does not maximise health gains when compared to other conditions.

Companies developing orphan drugs must take into account that they will have to provide some economic justification for the price of the product. More countries are likely to make this a requirement in the future. To ignore this may mean that fewer patients will get access to these often life-saving drugs.
Information sources

European Commission Directorate-General for Health and Consumer Protection:

European Organisation for Rare Diseases (Eurordis):
http://www.eurordis.org

Orphanet:
http://www.orpha.net/

Community Register of orphan medicinal products for human use (Provides access to European Commission decisions on designation of orphan medicinal products.):
http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm

Seventh Framework Programme for Research and Technological Development (FP7):
http://ec.europa.eu/research/fp7/index_en.cfm