



Contribution to the treatment of rare diseases: Orphan drugs

by *Christiane Breithaupt*

Usually the elapsed time from discovering a new molecule until its marketing is lengthy (10 years on average) and expensive (several million to billions of euros). Generally it is also true that for every ten molecules tested, only one is found to show some therapeutic effect. Taking this into consideration and knowing that a number of conditions occur very rarely, it becomes obvious that the cost of developing a therapeutic compound for a rare condition could not be recovered by projected sales. Consequently, pharmaceutical companies are often unwilling to develop such medicinal products for the treatment of rare diseases. Approximately 25% of these occur at birth or during childhood and include infantile spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus, familial adenomatous polyposis and cystic fibrosis. Half of the concerned diseases affect both children and adults. Typical rare diseases in adulthood include renal cell carcinoma, glioma and acute myeloid leukaemia. Approximately 5,000 to 8,000 distinct rare diseases have been discovered to date, affecting between 27 and 36 million patients in the European Union (EU).

It became apparent more than 30 years ago that incentives are necessary to encourage the development of medicines for rare conditions. The first country to develop a specific legislation in order to promote the registration of orphan drugs was the USA with its Orphan Drug Act (<http://www.fda.gov/orphan/oda.htm>) in 1983. It was followed 10 years later by Japan's Orphan Drug Regulation. In 1998 Australia released its Orphan Drug Policy and in 1999 the European Union followed with the Regulations (EC) 141/2000 and 847/2000 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm).

The European Medicines Agency (EMA) defines an orphan medicinal product as a medicinal product which is:

- Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting more than 10,000 persons in the EU at the time of submission of the designation application (prevalence criterion), or
- 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 a method exists, the medicinal product will be of significant benefit to those affected by the condition.¹

Prevalence of a disease justifying orphan drug status is defined as follows:

EU: 5 per 10,000 individuals
(<246,000 patients per year in 2007)

USA: 7.5 per 10,000 individuals
(<200,000 patients per year)

Japan: 4 per 10,000 individuals
(<50,000 patients per year)

Australia: 1 per 10,000 individuals
(<2,000 patients per year)

It is important to know that this prevalence only relates to the country/region in which the application is made, and is not representative of world-wide prevalence. Malaria, for example, is endemic in most tropical countries. Nonetheless, it is seldom seen in Europe and makes an orphan drug designation possible in the EU (3/10,000 inhabitants).

As it is considered that patients with rare conditions deserve the same quality, safety and efficacy in medicinal products as any other patients, it was decided that orphan medicinal products should be submitted and reviewed according to the normal evaluation process. To facilitate marketing of these drugs throughout Europe, sponsors of these products should have the opportunity of obtaining a Community Authorisation; the 'centralised' marketing authorisation procedure was therefore made mandatory. The experience gained in the USA and Japan showed that the strongest incentive for the pharmaceutical industry to invest in the development and marketing of orphan medicinal products is the prospect of obtaining market exclusivity for a specified number of years during which time a significant part of the investment might be recovered. Based on this, the EU decided on a number of different possible incentives:

- **Protocol assistance** (scientific advice) during the product development phase: "The sponsor of an

¹ Regulation (EC) 141/2000.

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orphan medicinal product may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, in accordance with Article 510 of Regulation (EEC) 2309/93.²¹ This advice is free of charge.

- **Marketing exclusivity** is granted for 10 years. “The member states shall not accept another application for a marketing authorisation (MA), or grant an MA or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.”²¹ Exceptions are
 - consent of the Marketing Authorisation Holder (MAH) to the second application
 - inability of the sponsor to supply sufficient quantities of the medicinal product
 - a second medicinal product is safer, more effective or otherwise clinically superior.
- **Fee reductions** (100% for pre-authorisation inspections, 50% for new applications for MAs and 50% for post-authorisation activities including annual fees in the first year after granting the MA)
- **EU incentives** (grants)
- **National incentives** (grants, tax reductions).

In 2007, the fund for fee exemptions by the EU amounted up to €6,000,000. In order to benefit from these incentives, the products in question must be registered as orphan medicinal products by the EMEA. This is done by submitting an application requesting orphan designation for the product.

For the purpose of evaluating requests for orphan drug status, the EMEA implemented a Committee for Orphan Medicinal Products (COMP). It consists of representatives from the member states and from the EMEA as well as patients’ organisations and (non-voting) European Free Trade Association (EFTA) state and EU Commission representatives as well as general observers. The tasks of the COMP are to advise the Commission on the establishment and development of a policy on orphan medicinal products for the EU; to examine any application to decide if the medicinal product qualifies as an orphan medicinal product; to assist the Commission in liaising internationally on matters relating to orphan medicinal products and liaising with patient support groups; and finally to assist the Commission in creating detailed guidelines.

Before applying for orphan drug status, the sponsor must submit a letter of intent to the Agency. A pre-submission meeting is strongly encouraged. The application is then submitted to the EMEA, validated and forwarded to the COMP. The final opinion of the COMP is forwarded to the EU Commission, who then adopts a decision (for details please refer to <http://www.emea.europa.eu/pdfs/human/comp/1422200en.pdf>). The application may be submitted in parallel in the EU and the United States using the common application form for submissions to the EMEA and the FDA.

All medicinal products for which an orphan drug designation application has been made, are entered into the Community register for orphan medicinal products for human use (<http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm>). The register lists all products for which orphan drug designation has been applied for regardless of outcome. In July 2008 this register contained 831 applications including 552 medicinal products with orphan drug status of which 42 had obtained an MA. Sponsors of designated orphan medicinal products are required to submit an annual development report to the EMEA (for the respective guideline see <http://www.emea.europa.eu/pdfs/human/comp/018901een.pdf>).

Applying for orphan drug status is possible at any stage during the development of the medicinal product, however this must be prior to the application for marketing authorisation. In case a marketing authorisation application for the same medicinal product (in respect of the same therapeutic indication and submitted by the same sponsor) has been submitted in any Member State within the Community, then this medicinal product is no longer eligible for an orphan drug designation independent of whether the marketing authorisation has been granted or not.

A sponsor may however apply for the designation of a medicinal product as an orphan medicinal product for an already approved medicinal product provided the orphan drug designation concerns an unapproved therapeutic indication. In this case a separate MA covering only the orphan indication must be applied for. Ibuprofen is a good example of a well-known drug which has obtained an MA in 2004 as an orphan drug for the treatment of a congenital heart malformation (patent ductus arteriosus) in infants—a condition affecting approximately 97,900 patients in the EU. Further examples are tabulated below.

Examples of orphan medicinal products:

Indication	Active substance	Patients (EU)
Treatment of patent ductus arteriosus (congenital malformation of the heart)	Ibuprofen (Pedea®)	97,900
Treatment of Mucopolysaccharidosis type II (Hunter-Syndrom)	Idursulfase (Elaprase®)	400
Treatment of N-acetylglutamate synthetase deficiency	N-carbamyl-L-glutamic acid (Carbaglu®)	46
Treatment of acute lymphoblastic leukaemia (most common form of leukaemia in children)	Nelarabine (Atriance®)	51,000
Treatment of renal cell carcinoma	Temsirolimus (Torisel®)	115,500
Treatment of anthracycline extravasations (accidental extravasal application of anthracycline)	Dexrazoxane (Savene®)	152

A source for obtaining additional information both on orphan medicinal products as well as on rare diseases is Orphanet: <http://www.orpha.net>. Orphanet was established

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in 1997 by the French Ministry of Health and the INSERM (Institut National de la Santé et de la Recherche Médicale). Both agencies are still funding the core project. Its aim is to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases. Orphanet includes a:

- Professional Encyclopaedia, which is expert-authored and peer-reviewed
- Patient Encyclopaedia and
- Directory of expert services. This Directory includes information on relevant clinics, clinical laboratories, research activities and patient organisations.

The European Commission is actually funding the encyclopaedia and the collection of data in European countries.

More information on rare diseases is provided by the European Organisation for Rare Diseases (Eurordis): <http://www.eurordis.org>.

As the procedure of development and submission of orphan drugs should follow that of “normal” drugs as close as possible, the same guidelines apply when developing the respective documents (e.g. ICH E3, E6). The EU application form, general information, as well as multiple COMP guidelines (e.g. on calculating prevalence, on significant benefits or on Protocol Assistance) can be found at <http://www.emea.europa.eu/htms/human/orphans/guidance.htm>.

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photo: Marlies Kari Neuner

Just in case you didn't know! Butter pack discovered by James Visanji at the EMWA conference (20-22 November 2008) in the Holiday Inn Hotel, London.

More information should be given with 'adapted' figures and tables

The data contained in a figure or table is not protected by copyright. It is only the artwork of the presentation in the figure or table that is protected.

A question posed on the WAME listserver [<http://www.wame.org/resources/wame-listserve-discussion/>] asked to whom you should apply for copyright permission if you want to reproduce an 'adapted figure'. The answer to this question depends on many things you might not know, e.g. who holds the original copyright, who adapted the figure/table, and the extent of the rights that were granted for the adaptation. Copyright might be held by the author, journal or art designer who drew the figure of the original or adapted figure/table. There is also the possibility that the permission granted for the 'adaptation' had in fact never been needed. An example given was when data from a table are used to create a pie graph.

What the discussion really brought out was that the phrase 'figure adapted from' is insufficient and can be misleading when no substantive change has been made.

Doug Altman added an important contribution to the discussion which is reproduced below with his kind permission:

“The terms “adapted” or “modified” are used frequently in journal articles. These adjectives are not just used for figures but more often to scales and checklists (e.g. modified SF-36) and also within text (e.g. “modified intent to treat analysis”). In all these cases there is often no clue as to the extent or nature of the modification. In the case of a figure, for example, the adaptation might be to the formatting (probably unimportant) or to the information content (potentially critical)—one surely needs to know which.

The terms “adapted” or “modified” alone are never adequate. When I see a “modified” checklist or a “modified” quality of life instrument I need to know exactly how (and why) the modification was made; I need to judge whether this modification was legitimate.

Journals should require authors to be specific about the way(s) in which the material was altered from the source, or give a reference to where this information can be found. Authors should not be allowed to hide behind such undefined terms.”