

Do orphan medicines benefit patients?

More and more governments are providing incentives to companies to develop treatments for rare diseases. However, although many of these initiatives have been a success, the treatments do not always reach those who need them. Jackie Holding reports

Some diseases are so rare that no pharmaceutical company would consider it financially viable to develop a treatment or cure without special support or incentives. An estimated 30 million EU citizens and 20 to 25 million US citizens have one of these 6,000 "orphan" diseases so although each disease affects a tiny number of people, collectively they represent a significant health problem. Although some of these conditions are untreatable, others are not and where governments have acted to provide incentives to industry research and development of orphan medicines have been stimulated, albeit with varying degrees of success.

Incentive schemes have contributed to the development of a variety of new treatments, but these — especially in the UK — do not always reach the patient. Access may be barred or slow if the local health funding body refuses to pay what is often a premium for medicines to treat rare diseases.

Many countries have their own definition of orphan disease. In the US, for example, the term refers to conditions with a prevalence of seven cases per 10,000 population whereas in Japan the definition is narrower, at 2.5 cases per 10,000 population. The EU definition is a prevalence of five cases or fewer per 10,000 population.¹

In the US, the incentive scheme introduced under the 1983 Orphan Drugs Act helped increase the number of medicines and biologic products that came to market exponentially: 282 have come on stream in the past 24 years, compared with 10 approved by the Food and Drug Administration in the eight to 10 years preceding the Act.

Under the Act all designated orphan products are eligible for a federal tax credit up to 50 per cent of the clinical research expenditure. Orphan products are exempt from the application fee for FDA approval and the first product authorised for a specific indication gets a seven-year marketing exclusivity period. Congress assigns about \$20m for FDA for orphan product grants.

The considerable success of US efforts to provide incentives for companies to develop orphan medicinal products have led other countries to follow suit and similar schemes were introduced in Japan in 1995, in Singapore in 1997 and in Australia in 1998.

Orphan medicines in Europe

EU legislation on orphan medicines (regulations EC141/2000 and 847/2000) came into force in 2000. The legislation, which applies to the UK and other member states, intro-



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duced a procedure for the designation of medicinal products as orphan medicines. Developers are now eligible for incentives for developing orphan medicines and placing them on the market.² Incentives include exclusive marketing rights for 10 years, assistance with clinical trial protocols and reduced regulatory fees. The owner of an orphan medicine may be an individual or a company but must be established in the EU.

To achieve orphan designation in Europe a medicine must be intended to treat diseases that are life-threatening or chronically debilitating, with a prevalence of fewer than five per 10,000 population, or to treat a life-threatening, seriously debilitating or serious and chronic condition where, without incentives, there would be no justification for investing in the development of a treatment. In addition, no satisfactory treatment of the condition should exist or the product must be of significant benefit to those with the condition. Incentives are more limited in Europe than in the US (see Panel 1).

The European regulations are implemented and monitored by the Committee for Orphan Medicinal Products (COMP), which was set up by the European Agency for the Evaluation of Medicinal Products (EMA). The COMP has established a database of 350 experts who can be called on to help evaluate specific products or provide scientific advice.

In 2005, the committee reported to the European Commission that between April 2000 and April 2005, 458 applications for orphan designation were submitted to the EMA. By April 2005, more than 260 products were so designated, relating to more than 200 rare conditions. Ninety per cent of the conditions for which a medicinal product has received an orphan designation, have a prevalence of less than three in 10,000. Most designations were granted in the area of cancer (36 per cent), followed by metabolism (11 per cent), immunology (11 per cent), and cardiovascular and respiratory (10 per cent).

Once the EU legislation came into force, 22 products went on to receive a marketing authorisation for 20 different diseases. For eight out of these diseases there were no satisfactory treatment options before authorisation of the new medicines, so new hope was offered to patients who previously had no alternatives. For the other 12 diseases, the new authorised orphan medicines are expected to bring benefits on the basis of improved efficacy of existing treatment (29 per cent), improved safety (14 per cent), a major contribution to patient care (7 per cent) and the remaining 50 per cent on a combination of two of these factors.

More than half of the products that have been the subject of a designation application between 2000 and 2004, are new or innovative — there are 92 biotech products and emerging therapies, such as antisense, gene and cell therapies.⁴

At the beginning of 2008, over 520 products were listed on the register of designated

Panel 1: Differences between the EU and US regulations

	Europe	US
Prevalence	< 5 per 10,000	< 7.5 per 10,000
Tax incentives	Tax credits developed by member states	A tax deduction of up to 50 per cent of clinical trial costs
Designation criteria	Epidemiological or financial and no other satisfactory treatment exists	Epidemiological or financial
Market exclusivity	10 years (or six years if criteria no longer met)	Seven years (but no reduction even if prevalence changes)

Panel 2: Orphan medicines approved in 2006 and 2007

Brand name	Disease
Atriance (nelarabine)	Acute lymphoblastic leukaemia
Cystadane (betaine anhydrous)	Homocystinuria
Diacomit (stiripentol)	Severe myoclonic epilepsy in infancy
Elaprased (idursulfase)	Hunter syndrome
Evoltra (clofarabine)	Acute lymphoblastic leukaemia
Exjade (deferasirox)	Chronic iron overload
Increlex (mecasermin)	Primary insulin-like growth factor deficiency
Inovelon (rufinamide)	Lennox-Gestaut syndrome
Naglazyme (galsulfase)	Maroteaux-Lamy syndrome
Nexavar (sorafenib)	Renal cell carcinoma
Onsenel (celecoxib)	Familial adenomatous polyposis
Revlimid (lenolinamide)	Multiple myeloma
Savene (dexrazoxane)	Anthracycline extravasation
Siklos (hydroxycarbamide)	Sickle cell syndrome
Soliris (eculizumab)	Paroxysmal nocturnal haemoglobinuria
Sprycel (dasatinib)	Chronic myeloid leukaemia and acute lymphoblastic leukaemia
Sutent (sunitinib)	Gastrointestinal stromal tumours and renal cell carcinoma
Theelin (sitaxentan sodium)	Pulmonary arterial and chronic thromboembolic pulmonary hypertension

orphan medicinal products, of which more than 40 have been granted marketing authorisations.

Between 2006 and September 2007, 18 orphan medicines were granted marketing authorisations (see Panel 2). By adopting EU orphan legislation, the European Parliament and Council have created the opportunity for more than a million patients suffering from rare conditions to benefit from new medicines. The EMA expects the number of authorised medicinal products to increase in years to come.

Access

A major problem affecting ease of access is that member states lack expertise in terms of the number of clinicians who are educated about the rare disease. Prescribing physicians lack experience of the medical benefits of these medicines, which means that access to orphan medicines is worse than to other medicines.

In addition, marketing authorisation does not guarantee that products will be accessible to patients because each member state determines whether or not to fund the medicine. Orphan medicines may seem expensive, but costs need to be looked at in the context of

research and development. Clinical development costs are high, partly because patients are more difficult to recruit and a larger number of centres may be needed. Costs of research, pharmacovigilance, medical information and manufacturing are at least as high as for other medicines because there are fewer economies of scale and the small number of patients makes it more difficult for companies to earn a return on investment.

The European Commission was so concerned about equality of access to orphan medicines that it commissioned a survey from Alcimed in 2004.¹ This revealed that all 10 orphan medicines on the market were only available in nine of the 25 EU member states. Moreover, only one of the member states had them on a national reimbursement list.

There was also a lack of homogeneity in time between obtaining the marketing authorisation and commercialisation of these drugs through funding (reimbursement) of the products by each member state. The EU orphan medicine regulation requires member states to bring orphan medicines to market within 180 days of approval, but the average delay is 189 days and has taken up to 700 days, according to the European Organization for Rare Diseases.

Panel 3: Access to orphan medicines across 15 EU member states

	Early access	Access
Austria	UC/NP	Slow
Belgium	UC/NP	Slow
Denmark	UC/NP	Complex
Finland	UC/NP	Complex
France	TUA	Rapid
Germany	No	Easy
Greece	UC/NP	Classic
Ireland	UC/NP	Classic
Italy	TUA	Classic
Luxembourg	UC/NP	Classic
Netherlands	UC/NP	Classic
Portugal	Case dependent	Case dependent
Spain	UC/NP	Classic
Sweden	UC/NP	Easy
UK	UC/NP	Slow

(UC = Compassionate use; NP = Named patients; TUA = Temporary use authorisation)

EMEA, London 2004

do badly under current procedures involving an assessment of the incremental cost-effectiveness of the new therapy compared with existing treatments for the disease.

The incremental cost-effectiveness ratio (ICER) is usually judged against a threshold of around £20,000–£30,000 per quality-adjusted life-year (QALY). Since prices for orphan medicines are usually high, the corresponding ICER will be high and there may not be the same breadth and quality of clinical evidence compared with more prevalent diseases to make the figures robust. The authors conclude: “The current situation, where companies are given incentives to develop orphan drugs, yet access to the drugs is limited by financial constraints, is inefficient for society at large and unsatisfactory both to patients and to industry.” There is, therefore, a need to review the HTA processes for orphan medicines.

Incentives and commissioning

An inventory of incentive measures to aid the research, marketing, development and availability of orphan medicinal products was published by the European Commission in 2001 and revised in 2006.³

Priority measures exist to ensure availability to patients in Belgium, France, Hungary, Italy, Lithuania, Poland and the Netherlands. For example, in France there is an accelerated pricing process (15 days) as well as a widespread “compassionate-use” programme. In the Netherlands, orphan medicines are exempt from the need to show pharmacoeconomic data and special funding is available to ensure hospitals are reimbursed for costs. Patients in the UK are poor relations in terms of funding — special funding arrangements are available through the National Specialist Commissioning Group, but for treatment of extremely rare cases only.

An article in *The Pharmaceutical Journal* (5 November 2005, p569) reviewed the issues surrounding the funding of orphan medicines, which generally requires the NHS to pay a premium for medicines to treat patients with rare diseases. It discussed whether or not society wishes to pay for the treatment of rare diseases if that means denying treatment to patients with more common illnesses and conditions. Most UK taxpayers would be willing to pay more for treatment of rare diseases provided certain criteria are met, as recommended by the NICE Citizens’ Council in 2004.

Specialist treatments in the UK pose funding difficulties at a local level, particularly where there are no national recommendations from NICE because the treatment has not been referred for assessment due to low total budget impact, or there is a delay in the recommendation (often up to two years). Local decisions may prevent patients getting the treatment they need, or delay treatment beyond the ideal timescale.

Only treatment for selected very rare diseases may be commissioned nationally by the National Specialist Commissioning Group.



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The budget is held centrally by the Department of Health and specific providers are designated to provide these services for a national caseload.

In these cases, the drugs may not be funded because the arrangements are, primarily, about service and infrastructure provision. Most orphan medicines are subject to the same commissioning mechanisms as other medicines.

A review report (May 2006) was commissioned by the Department of Health of commissioning arrangements for specialised services. This made recommendations aimed at improving commissioning arrangements in England, which are now being implemented. These include the development of 10 regional Specialist Commissioning Groups which are made up of joint primary care trust representatives. This will enable commissioning for specialised services (which includes orphan diseases) to be done more efficiently. If these recommendations are implemented effectively they may provide a better framework for commissioning of specialist treatments such as orphan medicines.

At European level, excellent progress has been made in the past few years to encourage the development of medicines for rare diseases, often where there is low commercial viability. Despite this, patients in Europe and particularly in the UK may have delayed or no access to the innovative treatments being developed. This position is likely to worsen, particularly where more targeted treatments are being developed (eg, in cancer and immunology) and where there is a large increase in numbers of orphan medicines being developed.

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