Are rare diseases still orphans or happily adopted?

DOI:10.1111/j.1365-2125.2006.02654.x

Are rare diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products

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Keywords
orphan disease, orphan medicinal product, rare disease, ultra orphan disease

Received
7 January 2006
Accepted
31 January 2006
Published *OnlineEarly*
28 April 2006

Orphan medicinal products (OMPs) are targeted at the diagnosis, prevention or treatment of rare diseases and have a special status in European law. This status brings incentives for pharmaceutical companies to invest in OMP development. The goal of the legislation is to encourage the development of more treatments for life-threatening rare disorders, but increased availability of OMPs raises important issues surrounding the public funding of very expensive treatments by national health services. In this article we review OMPs and the incentives for their development and discuss the challenges presented by funding these treatments.

Introduction

Orphan medicinal products (OMPs) are those medicines intended for the diagnosis, prevention or treatment of rare disorders. The label 'orphan' arose largely because such drugs yield little financial return on investment because of the limited size of the rare disease drug market and therefore pharmaceutical companies have shown little interest in 'adopting' treatments for rare diseases. Although individually rare, collectively these diseases affect about 30 million Europeans and 25 million North Americans [1]. Many of these diseases have no effective treatments and therefore rare diseases pose a substantial public health concern.

Over the last 23 years legislation has been created in the USA (1983), Japan (1993), Australia (1998) and Europe (2000) to provide incentives for the development

of OMPs. In this review article we discuss the European and American definitions of orphan disease, the incentives available to encourage product development and the challenges of funding the clinical use of OMPs.

Definitions

A rare disease or 'orphan' disease is defined as one that affects a restricted number of people. Definitions use prevalence of disease as the main criterion (Table 1). In the USA, the Orphan Drug Act (1983) defines orphan disease as a disease or condition which affects <200 000 people in the USA or has a prevalence of <7.5 per 10 000 Americans [2]. The definition for orphan disease agreed by the European Committee for Orphan Medicinal Products (COMP) [3] is a life-threatening or very serious disease affecting not more than five per 10 000 Europeans (the USA definition does not specify disease severity) [4]. A diagnostic assay, preventative or therapeutic agent with a rationale for use in a specific orphan disease can apply to have the status of an OMP. If proper scientific justification of the intended use is submitted, orphan designation may be obtained at any stage of development (preclinical or clinical). However, designation as an OMP is not approval for the use of the drug in the orphan condition. It does not indicate that the product has the amount of data regarding efficacy, safety and quality required for marketing authorization. Similar to the requirements for any other medicinal product, these criteria can only be assessed once the application for marketing authorization has been submitted. The European designation process for orphan medicines is determined by COMP and takes a maximum of 90 days from submission of the application to receipt of an opinion. The European Commission's (EC's) decision then follows in a maximum of 30 days.

OMP status provides valuable benefits to the drug producer but is defined by an 'all or nothing' arbitrary cut-off in disease prevalence. Therefore, a product to treat a disease with a prevalence of five per 10 000 Europeans can benefit from a number of incentives but if the disease prevalence were six per 10 000 these incentives would not be available. While the disease may be rare in Europe, it may be common elsewhere; for example, drugs to treat tropical diseases can benefit from orphan status in Europe, which may be reasonable given the differences in resources available in Europe compared with countries affected by tropical disease. A disease which is more common in one European member state may also qualify for orphan status if the overall prevalence across Europe is less than five per 10 000 (e.g. Balkan nephropathy). Disease redefinition in the postgenomic era may create many new diseases that meet the criteria for orphan status [5]. For example, sepsis is a relatively common disease, accounting for a

Table 1
Definitions

Orphan disease – A disease which has not been 'adopted' by the pharmaceutical industry because the small market provides little financial incentive for the private sector to make and market new medications to treat or prevent it. The definition is based on disease prevalence and differs between Europe and the USA

European definition. Life-threatening or very serious disease affecting not more than five in 10 000 people in the European Community. This includes tropical diseases which are uncommon in Europe but common elsewhere

USA definition. The term 'rare disease or condition' means any disease or condition which (a) affects <200 000 persons in the USA, or (b) affects >200 000 persons in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug

Ultra-orphan disease – A very rare disease. There is no formal definition but the National Institute of Clinical Excellence uses the term for diseases affecting <1000 people in England and Wales

Orphan medicinal product (OMP) – Products for the diagnosis, prevention or treatment of orphan diseases. For OMP designation in Europe there needs to be no satisfactory method of diagnosis, prevention or treatment of the orphan disease in the European Community. Alternatively, the medicinal product must confer a significant benefit compared with the existing diagnostic, preventative or therapeutic products available for the orphan disease

USA Orphan Drug Act (1983) and EU Orphan Drug Regulation (2000) – Legislation designed to encourage the development of OMPs. In both territories there is marketing exclusivity which prevents any competitor gaining market access unless superiority is demonstrated. In both territories the regulatory authorities offer assistance in the design of clinical trials; and they waive their normal licensing fees. In the USA (but not the EU) there is also tax relief and the possibility of access to ear-marked research grants.

ICER (incremental cost-effectiveness ratio) – The financial cost for each extra unit of health improvement gained by using the intervention

QALY (quality-adjusted life year) – A measure of the quantity and quality of life generated by a healthcare intervention. Provides a unit which can be used to compare different interventions

similar number of deaths to myocardial infarction in the USA [6]. Considerable efforts are underway to define subgroups of septic patients by investigating host susceptibility factors (e.g. single nucleotide polymorphisms) [7], biomarkers of host response pathways [8] and pathogen virulence factors [9]. These studies may lead to subgroups of sepsis which will be sufficiently rare to apply for the benefits of orphan status. Whether such disease subgroups should be considered as orphans remains unclear, but sponsors applying for orphan status will have to produce convincing evidence that their product is subgroup specific [10].

Orphan diseases are defined by their rarity. However, if a disease has a prevalence of five per 10 000 then in a country of 60 million (UK) there may be 30 000 cases and across the EC there may be over 200 000 people affected. These patient numbers should provide a large enough pool from which to draw subjects for adequately powered clinical trials, an issue we will return to later. This size of OMP market may also allow a pharmaceutical company to make a substantial return on investment while still benefiting from the incentives given to orphan drug status. The terms 'ultra-orphan' disease and 'ultra-orphan' medicinal product (uOMP) have recently been coined to describe very rare diseases and their treatments, and draw a distinction with the 'commoner' orphan diseases. The definition used by National Institute of Clinical Excellence (NICE) is less than 1000 cases in England and Wales.

Incentives for the development of orphan medicinal products

The process for approval of a new drug is complex and expensive, requiring an average of 10–15 years for completion. By definition, the OMP market is small and this makes orphan diseases potentially unprofitable for pharmaceutical and biotechnology companies. The USA Orphan Drug Act and European legislation provide incentives intended to stimulate research and development on, and approval of, products with orphan status. The European and US legislations are compared in Table 2. Since 2000, 295 products have been granted orphan status in Europe and 21 have progressed to market approval (Table 3). For comparison, between 1995 and 2000 only 12 medicines for rare diseases came to market in Europe. Although not an exact comparison, because the USA Orphan Drug Act predates European law, 473 products have been given orphan designation in the USA since 2000 and, of these, 23 have market approval. By contrast, in the 10 years before the USA Orphan Drug Act, only 10 products were approved for treatment of rare disease [10]. The diseases with the most products designated orphan status in Europe are cystic fibrosis and renal cell carcinoma, each having 10 OMPs (although none yet with European market approval).

The incentives for OMP development are market exclusivity, protocol assistance, fee reduction, tax credits (in the USA) and specific grants for OMP trials.

Marketing exclusivity

This is the main factor encouraging pharmaceutical companies to develop specific OMPs. The Regulation (EC) no. 141/2000 of the European Parliament and of the Council of 16 December 1999 grants OMPs market exclusivity for 10 years after approval, whilst sponsors are granted exclusivity for 7 years in the USA [2, 4]. During that authorized period, no similar competitive

Table 2
Comparison of European and US orphan medicinal product (OMP) development

	Europe	USA
Date of legislation creating incentives for OMP development	2000	1983
To date, number of products given OMP status	Total number 295 59 per year since creation of legislation	Total number 1494 68 per year since creation of legislation
To date, number of OMPs with market approval	Total number 21 4 per year since creation of legislation	Total number 268 12 per year since creation of legislation
Incentives available for OMP development	Market exclusivity for 10 years (reviewed after 5 years) Protocol assistance and fee reductions	Market exclusivity for 7 years (not reviewed) 50% tax credit for clinical trials Protocol assistance and fee reductions Research grants ear-marked for orphan disease

Table 3
Orphan medicinal products with market approval in Europe

Date of designation as OMP	Drug name	Orphan disease indication	Trade name	Date of market authorization
12/12/2003	Sildenafil citrate	Treament of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Revatio	4/11/2005
9/7/2001	Ziconotide (intraspinal use)	Treatment of chronic pain requiring intraspinal analgesia	Prialt	24/2/2005
29/12/2000	Nitisinone	Treatment of tyrosinaemia type I	Orfadin	21/2/2005
29/12/2000	Anagrelide hydrochloride	Treatment of essential thrombocythaemia	Xagrid	16/11/2004
31/7/2001	Zinc acetate dihydrate	Treatment of Wilson's disease	Wilzin	18/10/2004
14/2/2001	Ibuprofen	Treatment of patent ductus arteriosus	Pedea	29/7/2004
12/6/2002	Mitotane	Treatment of adrenal cortical carcinoma	Lysodren	30/4/2004
18/9/2001	Cladribine (subcutaneous use)	Treatment of indolent non-Hodgkin's lymphoma	Litak	14/4/2004
6/3/2002	Porfimer sodium (for use with photodynamic therapy)	Treatment of high-grade dysplasia in Barrett's oesphagus	PhotoBarr	25/3/2004
20/11/2001	Celecoxib	Treatment of familial adenomatous polyposis	Onsenal	17/10/2003
29/12/2000	Iloprost	Treatment of pulmonary hypertension	Ventavis	16/9/2003
29/12/2000	Busulfan (intravenous use)	Conditioning treatment prior to haematopoietic progenitor cell transplantation	Busilvex	9/7/2003
14/2/2001	Laronidase	Treatment of mucopolysaccharoidosis, type I	Aldurazyme	10/6/2003
18/10/2000	N-carbamyl-L-glutamic acid	Treatment of N-acetylglutamate synthetase (NAGS) deficiency	Carbaglu	24/1/2003
18/10/2000	Miglustat	Treatment of Gaucher disease	Zavesca	20/11/2002
14/2/2001	Pegvisamant	Treatment of acromegaly	Somavert	13/11/2002
14/2/2001	Bosentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Tracleer	15/5/2002
18/10/2000	Arsenic trioxide	Treatment of acute promyelocytic leukaemia	Trisenox	5/3/2002
14/2/2001	Imatinib mesylate	Treatment of chronic myeloid leukaemia and treatment of gastrointestinal stromal tumours	Glivec	27/8/2001
8/8/2000	Alpha-galactosidase A	Treatment of Fabry disease	Replagal	4/5/2001
8/8/2000	Alpha-galactosidase A	Treatment of Fabry disease	Fabrazyme	4/5/2001

products can be placed on the market unless superiority is demonstrated. In a few cases this has produced confusion and legal challenge regarding the amount of evidence needed to prove superiority [11], but market exclusivity is still a powerful incentive for OMP development. In Europe (not the USA), the period of market exclusivity may be reduced to 6 years if, after 5 years, the drug is deemed 'sufficiently profitable'. The profits of the first OMPs with European market approval will be reviewed in 2006 [Replagal and Fabrazyme]. Certainly, the OMP market can be very profitable. Indeed, in 2004, a total of nine OMPs each generated sales revenues in excess of US$1 billion [12]. However, the definition of 'sufficiently profitable' in the context of European Orphan Drug law is unclear. The EC has commissioned a fact-finding study [13] and is currently defining the procedure which will be used to review an OMP's orphan status 5 years after marketing. This decision may have considerable impact on future OMP development [14]. Market exclusivity is the main incentive for OMP development in Europe because tax credits cannot be legislated at the European level (unlike the USA, where tax credits are a considerable incentive). Any loss of years with market exclusivity will potentially deter future OMP development.

A drug developed with the benefits of orphan status may subsequently develop an indication for a common condition. Bosentan was developed with orphan status as a therapy for pulmonary hypertension but it might subsequently have also had a role in the treatment of heart failure, an area in which large clinical trials were undertaken [15]. This would have presented the opportunity of larger profits for the OMP producer or the possibility of a reduction in drug price for patients with orphan diseases. In reverse, a drug for a common condition might gain orphan status to treat a rare disease. An example would be sildenafil, currently licensed for erectile dysfunction, which has orphan status and recent

Table 4
Examples of ultra-orphan medicinal products (uOMPs) nearing market approval

uOMP name	Disease	Stage of development
α_1-glucosidase alfa	Pompe's disease	Applied for approval
Galsulfase	MPS VI	Applied for approval
Iduronate-2-sulfatase	Hunter's syndrome	Late clinical trials
OGT 923	Sandhoff's disease	Early clinical trials
Miglustat	Nieman–Pick disease	Early clinical trials

market approval for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Should a drug which is commonly prescribed be more expensive when it is being used to treat an orphan disease? In some cases, the cost of OMP development would be substantially reduced as some elements of safety would already be established, and might provide a rationale for expecting a reduced price compared with existing OMPs without mainstream indications.

The market exclusivity granted to OMPs is a superior incentive to patent protection [10]. To receive patent protection the drug producer needs to demonstrate novelty, whereas for market exclusivity the producer needs only orphan status. Therefore, drugs that would be ineligible for patent protection may be attractive targets for orphan diseases (e.g. ibuprofen has orphan status for the prevention of patent ductus arteriosus in premature neonates). Another advantage of orphan status is that market exclusivity commences with drug approval. In comparison, patents are commonly applied for and awarded early in product development so that many years of patent protection can be lost before the drug is available on the market.

Protocol assistance and fee reductions

The COMP has highlighted the importance of protocol assistance in guiding orphan products towards a successful application for marketing authorization with good quality safety and efficacy data. Orphan drugs are also eligible for reductions in the fees incurred during development. In Europe this includes fees for preauthorization activities, such as protocol assistance, the application fee for marketing authorization, and postauthorization fees. Since 2002, subject to the availability of funds, 100% fee reduction for protocol assistance and 50% fee reduction for all other fees have been agreed. Accordingly, €3.7 million (UK £2.5 million) was available in 2005 for fee exemptions.

Tax credits and grants

An important difference between the incentives for OMP development in Europe and the USA is the presence of tax credits and ear-marked grants in the latter. The nature of taxation in Europe (being controlled by individual member states) means that Europe-wide tax incentives are not possible. Funding set aside specifically for research in orphan disease is also lacking in Europe. Tax credits and grants may explain the higher number of OMPs with market approval in the USA compared with Europe (Table 2).

Marketing approval for orphan medicinal products

Before an OMP can be made available for widespread clinical use it must have marketing approval. Patients with orphan diseases have a right to be treated with drugs which are both safe and effective [4]. However, the evidence base for market approval of OMPs may be poorer than that for non-orphans, given that the rare-disease patient population will, by definition, be small. These limitations may compromise clinical trial design, although sometimes rare disease populations will be large enough for double-blind, randomized, controlled studies. As mentioned earlier, an orphan disease with a prevalence of five per 10 000 may have 30 000 cases in the UK – a population large enough for well-designed clinical trials. Nevertheless, for very rare diseases multiple geographically distinct sites may be needed and this will increase the cost of the study considerably.

OMP development was recently assessed by Joppi *et al.* [16, 17]. Their study [16] critically appraised the quality of drug dossiers for OMPs with market approval in Europe. A common weakness of market applications for OMPs was small patient numbers in clinical trials. While this may be understandable for very rare diseases, it is perhaps not for diseases such as cystic fibrosis (which has 10 European OMPs, none approved) with a patient population of approximately 20 000 in Europe. The studies were also commonly placebo controlled, when it might have been expected that an existing treatment should have been the active comparator. The authors also found that trials were too short in relation to the natural history of the disease and surrogate end-points were often used without strong evidence of validity.

The incentives offered to OMPs aim to compensate for the small disease market. Therefore, orphan status should not necessarily allow a reduction in the quality

of evidence presented for market approval. Some conditions will be very rare and the evidence base will be reduced (ultra-orphan conditions) but often patient numbers will be sufficient for well-designed clinical studies.

The ultra-orphan medicinal products and public funding

There is no EU definition of ultra-orphan disease but the UK NICE recently used a prevalence of <1000 people in England and Wales to define ultra-orphan status. As these diseases are very rare, the evidence base for a new treatment's efficacy and safety is likely to be small and the treatment expensive, giving a high and relatively imprecise incremental cost–effectiveness ratio (ICER). As an example, Cerezyme (imiglucerase) is an ultra-orphan medicinal product (uOMP) for the treatment of Gaucher disease. The cost of treatment with this drug is approximately €580 000 (UK £400 000) per adult per year (personal communication). The high financial cost of certain OMPs creates a conflict between the rights of the individual and the health of society as a whole. Should the priority for a nation's finite health budget be the greatest health gain for the greatest number, or is this less important than the right of every individual to treatment even if that treatment does not offer the largest health gain for its financial cost? This will remain an important issue as several drugs of this type are currently awaiting approval (Table 4).

As already discussed, the EU provides legislation regarding incentives for OMP/uOMP development. However, there is no EU legislation to guide the use of OMP/uOMPs in member states once the products have market approval. In fact, there are considerable differences in the availability and price of OMPs when European countries are compared [18]. Different countries have different bodies that produce recommendations on the use of treatments. For example, in Scotland, the Scottish Medicines Consortium (SMC) has reviewed six OMPs and recommended the use of four, even though the ICER was one of the guides to acceptance. As more OMPs and uOMPs gain market approval, a challenge for agencies such as NICE and SMC is to develop protocols and criteria so that products can be objectively evaluated and consistent decisions made.

There are ethical arguments for and against the public funding of ultra-orphan drug use. A utilitarian viewpoint (greatest benefit for the greatest number) might favour a limit on spending as each ultra-orphan disease represents few individuals so it is not maximizing the benefit of that spending to society [19]. When the cost effectiveness of health interventions is compared then the ICER is often expressed as a cost per QALY (see Table 1). In chronic myeloid leukaemia, imatinib (Glivec), for instance, has an estimated ICER of €21 000–€75 000 (UK £15 000–£52, 000) per QALY [20]. This can be compared with general practice-based advice to stop smoking costing €390 (UK £270) per QALY [21]. Thus, when health spending is restricted, spending on uOMPs does not bring the greatest benefit to the greatest number of people. In a cash-limited health system there are likely to be opportunity costs incurred by funding high cost per QALY treatments, which serve to restrict the availability of therapies which offer better value for money and limit the funding available for health service priorities such as computed tomographic scanning after stroke, reduction of cancer treatment waiting times and recruitment of health service staff. In fact, the utilitarian could argue that by funding expensive uOMPs, patients with more common conditions are being deemed less worthy of treatment ('why should a patient with a very rare disease receive treatment at the expense of 10 with common equally serious conditions?') [22]. Many ultra-orphan diseases produce chronic disability and significantly reduce quality of life and this is a strong argument to support public funding for treatments. However, it must not be forgotten that common conditions such as lung cancer and heart failure can also produce pain and disability, but their treatments may be more cost effective. The evidence base supporting the clinical efficacy of treatments for ultra-orphan disease will commonly be based on trials with only a small number of patients. Therefore, in addition to incurring a high cost there may be large uncertainty about the clinical effectiveness.

A widely held and powerful alternative view is that society should not abandon individuals who are unfortunate enough to develop a serious condition that is rare, applying the 'rule of rescue', a term used to describe the imperative people feel to rescue identifiable individuals facing avoidable death [23]. This is enshrined in EU legislation, which states 'that patients suffering from a rare condition should be entitled to the same quality of treatment as other patients' [4]. Also, treatments may be expensive for the individual but, if the disease is very rare, the impact on a nation's overall health budget is going to be small.

The funding of uOMPs has recently been debated by a Citizens' Council organized by NICE [24]. This was a lay group educated for 3 days about the issues surrounding uOMPs and then asked to decide whether these treatments should be funded by the National Health Service (NHS). The results reflect the complexity of the issues. Around half of the 30 members of the Council thought that, with certain conditions, the NHS

should consider paying for high-cost uOMPs. This high expenditure should be conditional on the degree of disease severity, the ability of the drug to provide health gain and whether the disease was life-threatening. However, seven members thought that the NHS should not consider paying the premium prices but rather treat ultra-orphan disease with the same clinical and cost-effectiveness rules as any other disease. On the other hand, four members concluded that the NHS should pay any price required to treat a patient with a very rare disease, irrespective of disease severity.

Several possible options are available to develop criteria on which funding decisions for uOMPs can be based [22].

- Individual decisions could be made with modifying factors such as disease severity, potential of the treatment to reverse the disability rather than slow further disease progression, or the potential for a uOMP to bridge to receipt of a definitive treatment such as transplantation. However, these factors will differ with each ultra-orphan disease, which makes comparison across illnesses difficult and subjective.
- The decision to recommend public funding may be based on the cost per QALY of existing treatments.
- Ultra-orphan diseases could be weighted so that as a disease becomes less common a higher cost per QALY is accepted. This QALY weighting has the advantage that it allows threshold values of cost effectiveness to be created based on disease prevalence. These thresholds make decisions about funding transparent and can guide price negotiations with pharmaceutical companies. However, QALY weighting would be rejected if a utilitarian viewpoint is applied – 'why are rare disease QALYs more valuable, surely all QALYs are equal'?
- A country's government may enter a risk-sharing agreement such that if agreed health gains are not achieved the cost of the treatment will be paid by the treatment producer. This has been used for the treatment of multiple sclerosis [25], but whether it would be applicable to, or realistic for, all uOMPs is unclear.
- Ultra-orphan diseases could have their funding 'ring-fenced' into a dedicated health service fund, or funding could be provided from charities or research councils with the treatments being delivered through clinical trials. In England some uOMPs are commissioned 'centrally' by the National Specialist Commissioning Advisory Group [26]. An example would be enzyme replacement therapy for lysosomal storage diseases, which cost €75 million (UK £52 million) this financial year (personal communication). However, this is a cost levied from primary care trusts and has been criticized from a utilitarian viewpoint as an unacceptable opportunity cost that is centrally mandated from the budgets of local services [27].

Patients with ultra-orphan diseases receiving licensed uOMPs should be carefully monitored and the treatment should be stopped if not producing benefit. The 'stopping rules' for OMPs need to be clearly defined to prevent excessive expenditure on cost-ineffective treatments. Difficulties may arise if the treatment is deemed cost ineffective but the patient is already established on treatment with clinical benefit, e.g. after the conclusion of a clinical trial. In the future it may be necessary to specify in clinical trial protocols a risk-sharing policy such that the health service will pay for patients to continue therapy only under prespecified conditions.

Conclusion

The management of rare disease is a challenging problem for all countries. Legislation has defined rare or orphan disease by arbitrary disease prevalence, which grants incentives to OMP producers. There are over 5000 rare diseases and in Europe so far 21 OMPs have been granted marketing approval. It is hoped that for patients suffering from previously neglected orphan diseases many more OMPs will be approved. However, in addition to increasing the number of OMPs reaching the market place, society needs to debate and better understand the funding issues so that reasonable criteria can be established by which cost effectiveness can be consistently and transparently determined.

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