Rare diseases, orphan drugs and their regulation: questions and misconceptions

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Abstract | Sustained advocacy efforts driven by patients’ organizations to make rare diseases a health priority have led to regulatory and economic incentives for industry to develop drugs for these diseases, known as orphan drugs. These incentives, enacted in regulations first introduced in the United States in 1983 and later in Japan, Europe and elsewhere, have resulted in substantial improvements in the treatment for patients with a range of rare diseases. However, the advent of orphan drug development has also triggered several questions, from the definition of rarity to the pricing of orphan drugs and their impact on health-care systems. This article provides an industry perspective on some of the common questions and misconceptions related to orphan drug development and its regulation, with the aim of facilitating future progress in the field.

Historically, health-care systems and medicine development did not address the needs of patients with rare diseases. In the early 1980s, the National Organization for Rare Disorders (NORD), a patient organization based in the United States, advocated for the installation of special incentives to change that situation. In 1983, the Orphan Drug Act (ODA) was passed in the United States to promote the development of drugs for rare diseases, which amount to more than 6,000 identified diseases at present.

This landmark legislation, recognized as one of the most successful legislative actions of the United States in recent history, generally acknowledged the medical needs of patients with rare diseases. It also recognized that a fundamental obstacle to the introduction of rare disease therapies was the reluctance of industry to invest in research and development with little prospect of return on that investment. The ODA, which defined rare diseases as those affecting fewer than 200,000 people in the United States, therefore introduced economic incentives for drug development for such diseases. These economic incentives include 7 years of US Food and Drug Administration (FDA)-enforced market exclusivity for approved products, exemptions from FDA fees for regulatory submissions, regulatory advice and tax credits.

In the 27 years since the ODA was introduced, more than 350 orphan drugs have been approved in the United States, compared with only 10 such drugs in the decade preceding the ODA. Legislation to promote the development of orphan drugs has also been successfully introduced elsewhere in the world, including in Japan in 1993, in Australia in 1998 and in the European Union in 2000. Nevertheless, even in countries with existing legislation, many patients with rare diseases are still faced with many challenges in receiving appropriate care, owing to low disease awareness and limited access to medical expertise, diagnostic testing and therapies.

These challenges, coupled with the medical and commercial success of some orphan drugs and their growing number, have increased societal scrutiny of the field. Questions are being raised over several issues, from the validity of incentives for orphan drug development to the value of long-term patient outcomes and the appropriate pricing of orphan drugs. However, the debate around these questions has sometimes been hindered by misconceptions that might slow down efforts to advance the field or to provide access to the treatments. With this in mind, this Perspective provides an industry view on some of these questions and misconceptions, with the aim of improving understanding of the field (see also REF. 3).

Rare disease characteristics

Knowledge of rare disease pathology and the patient population. A commonly encountered misconception is that patients with a particular rare disease are readily identified before the development of a potential orphan drug starts and that ample information about the disease and its epidemiology is available. Currently, there are ~6,000–8,000 rare diseases described in the literature, of which 80% have a genetic basis. The Orphanet database (see Further information) also provides valuable insights on the issue of identified and confirmed rare diseases versus the estimated number. These diseases are thought to affect about 6% of the population in the European Union alone (30 million out of 500 million inhabitants in the 27 European Union countries), suggesting that a relatively high percentage of the population would need treatment for a rare disease.

However, not only is the prevalence of most rare diseases ill-researched, not all of the affected individuals will need treatment and even those that do are not necessarily already identified. Indeed, although some rare diseases, such as Duchenne’s muscular dystrophy, have clear and identifiable clinical symptoms, this is not the case for most rare diseases, which may have symptoms that resemble those of other diseases or which are unfamiliar to most general practitioners. Increased knowledge of the disease mechanisms is now potentially allowing better diagnosis but this does not automatically lead to the identification of patients suffering from a rare disease before
Should rare cancers be classified as rare diseases? A second view encountered related to orphan disease characteristics is that rare cancers should not be part of the systems for rare diseases because they are covered by systems for oncolgy, which has its own set of treatment centres and rules. However, patients with rare cancers, just like those affected by other rare diseases, suffer from lack of information, difficulties in diagnosis and lack of available treatment. So, even if these patients could be treated in an oncolgy setting, the rare disease systems would provide additional access to information, awareness, diagnosis and incentives for treatment development.

Orphan drugs for rare cancers make up 30–40% of the orphan drugs developed or designated in Europe or in the United States. Oncological diseases also have the highest chance to have a related orphan drug designation. Orphan drugs developed for cancer indications include imatinib (Novartis), dasatinib (Bristol–Myers Squibb) and nilotinib (Novartis) for chronic myeloid leukaemia; clofarabine (Genzyme) for acute lymphocytic leukaemia; and bortezomib (Millennium Pharmaceuticals) and thalidomide (Celgene) for multiple myeloma.

An additional complexity for rare cancers is that orphan drugs developed for one therapeutic indication may be also used for other indications. For example, imatinib has been approved for several cancer indications. It is not well understood by society that for each therapeutic indication, the clinical trials for that indication have to be carried out independently from the previously approved indication(s). Also, different indications have different disease prevalences. Taking again the example of imatinib, the first approved indication encompasses about 90% of all patients treated with the drug, whereas the remaining indications account for about 10% of the patients.

Orphan drug research and development
Public funding of orphan drug research and development. Outside of industry, a commonly encountered view is that research on rare diseases and orphan drugs is done in academic institutions and so society is paying twice for orphan drugs; once by providing public funds for research and again by paying for approved orphan drugs. Indeed, this view is also often expressed about drug research and development in general.

Basic research in almost any sector is carried out by academic researchers and this is also true in the biomedical field. With regard to orphan drugs, research suggests that the likelihood that a drug development programme for a rare disease will be started is more than two times higher if more than 600 scientific papers were published for that disease. Basic research therefore has an important role in orphan drug development.

However, these researchers focus on discovering new scientific knowledge and exploring new avenues, not on making products. Once biomedical research becomes more translational — for example, identifying suitable drug candidates and conducting clinical trials — it is nearly exclusively pursued by industry. The translational stages in the development of new drugs demand high standards for quality control and reproducibility, which entail large amounts of capital investment and the need for highly trained personnel. In addition, most clinical trials, even for very small patient populations, can be very expensive. Highly controlled and regulated manufacturing processes are necessary to provide a safe and efficacious final product that consistently meets regulatory marketing authorization requirements.

For biotechnology-derived drugs in particular, the development of such a manufacturing process and the construction of manufacturing facilities that meet regulatory standards is costly and time-intensive.

Relative costs and regulation of orphan drug development. A common misconception is that orphan drugs are cheaper to develop than other drugs because smaller clinical trials are required and they are subject to different regulatory standards.

Researching, developing, manufacturing and bringing to market any medicine is a long, complex process and recent data indicate that approximately 30% of all drugs still fail in Phase III trials, although others claim that this number could be as high as 50%. With regard to orphan drugs, each stage of the development process is further complicated by disease rarity. Challenges for
Enzyme replacement therapy

Lysosomal storage disorders, such as Gaucher’s disease and Pompe’s disease, are a life-threatening or seriously debilitating group of very rare genetic diseases that are caused by the lack or dysfunction of an enzyme in the lysosome. They have a published prevalence that is 50–100 (or more) times lower than the cut-off point defined for a rare disease in the existing orphan drug regulations, and so treatments for these diseases may be granted an orphan drug designation.

Enzyme replacement therapies (ERTs)—in which a replacement enzyme is injected regularly throughout the patient’s life—have been used to treat lysosomal storage disorders since the early 1990s. Gaucher’s disease, which is caused by a deficiency in the enzyme glucocerebrosidase, was the first such disorder for which an ERT was developed, initially using glucocerebrosidase purified from human placenta. The original work on this project was done in the United States by the National Institutes of Health and then transferred to the Tufts University Enzyme Centre, Boston, Massachusetts. However, production of sufficient quantities of the enzyme was a major barrier to project progression, as more than 20,000 placenta were needed to provide enough of the enzyme to treat one patient for 1 year. Genzyme took over the project in the 1980s and developed a viable production method. In 1991, the product alglucerase (Genzyme) was approved by the US Food and Drug Administration as an orphan drug. To address the sustainability of supply and other challenges, Genzyme developed a recombinant version, imiglucerase, which required the company to build a US$200 million manufacturing plant, although its annual revenues were ~$120 million at the time. The recombinant product was approved by the US Food and Drug Administration in 1994 and subsequently elsewhere.

The medical and commercial success of ERTs for Gaucher’s disease also generated interest in the industry by demonstrating that a viable market for innovative orphan drugs to treat very rare diseases existed. Examples of other approved ERTs for different diseases are: agalsidase β (Genzyme) and agalsidase α (Shire) for Fabry’s disease; laronidase (BioMarin/Genzyme) for Hurler–Scheie syndrome (also known as mucopolysaccharidosis type 1 (MPS-II)); idursulphase (Shire) for Hunter’s disease (also known as MPS-II); alglucosidase α (Genzyme) for Pompe’s disease; and galsulphase (BioMarin) for Maroteaux–Lamy syndrome (also known as MPS-VII). In addition, alternative treatments continue to be developed. For Gaucher’s disease, miglulstat (Actelion Pharmaceuticals), an oral small-molecule drug, was approved in 2002. In addition, another recombinant version of glucocerebrosidase, velaglucerase α (Shire), was approved in 2010 and yet another, taliglucerase α (developed by Protalix Biotherapeutics), is in advanced stages of development and received temporary authorization for use in France. Development programmes for alternative treatments have also been started for some of the other above-mentioned diseases.

The price per patient of newer ERTs is similar to the pricing model originally used by Genzyme for its Gaucher’s disease treatment, presumably reflecting similar risk, high development and manufacturing costs and challenges in the clinical trial programmes (see main text for discussion). The annual treatment prices for ERTs are high—starting at ~€30,000 for infants to potentially over €400,000 per patient per year, as dosage depends on the patients’ weight. However, the market for the discussed orphan drugs is not by definition lucrative because the patients are not all identified and their numbers remain small. There are no published data on price-setting for orphan drugs and the industry is highly heterogeneous, with the only common factor being that increasing rarity and price are linked (see main text). Generally speaking, the price of an orphan drug is based on costs and on profit needs, and most companies developing orphan drugs do so as part of a strategic portfolio, especially after the first product has made it to market and is profitable. Owing to the nature of the development process, it may be difficult, if not impossible, to isolate the direct costs related to one product and to measure these direct costs against any return made from that product. Product-specific pricing details are also considered commercially sensitive information, but if societal agreement could be reached on what data should be made publicly available and according to what financial standards, more transparency in the price-setting of orphan drugs could be possible.

Orphan drug development typically include lack of data on the natural course of the disease, poor or late diagnosis, lack of validated clinical end points, major logistical difficulties in the organization of clinical trials and low expertise in the medical community. Given this complexity, a recently cited success rate of 62.9% in the orphan field compared with 70.7% for non-orphan drugs should be considered a success for orphan drug development.

Randomized placebo-controlled clinical trials involving several hundreds of patients, which are typically part of drug development programmes for more common diseases, are often not possible for rare diseases because of rarity, ethical considerations and medical need. Nevertheless, although our knowledge on the safety of orphan drugs is still incomplete and is based on mostly modest patient numbers, to our knowledge, no orphan drugs have been withdrawn from the market in Europe for safety reasons. Certainly, the literature information supports the conclusion that orphan drugs are relatively safe drugs, even compared with those for other diseases.

The additional challenges in finding patients, as mentioned above, and the organization of clinical trials can both contribute considerably to the cost of orphan drug development. An example is the clinical trial for the development of alglucosidase α (Genzyme)—a therapy which obtained regulatory approval in the European Union and in the United States in 2006—for the treatment of infants with Pompe’s disease. Pompe’s disease or acid maltase deficiency, also known as glycogen storage disease type II, is an extremely rare, life-threatening lysosomal storage disorder that affects the muscles. The incidence of Pompe’s disease may vary according to ethnicity and clinical form. Infantile or early onset Pompe’s disease has a prevalence of 1 in 100,000 to 1 in 200,000 in Caucasians, 1 in 37,000 among individuals of Dutch descent but 1 in 14,000 in African Americans and 1 in 40,000 to 1 in 50,000 among Chinese. The frequency of late-onset disease in Caucasians may be as high as 1 in 60,000 individuals.

For patients with infantile Pompe’s disease, treatment initiation after 6 months of age is considered to be too late. For the pivotal trial of alglucosidase α in infants, 18 patients aged 6 months or less were identified all over the world and then flown in with their families to one of two trial sites to participate in the clinical studies. In addition to the actual clinical trial costs, transport, accommodation and language translation services had to be provided for the family members of the patients for the duration of the trial, which lasted for 52 weeks.

Once clinical proof of principle has been established for an orphan drug for which there is no alternative, the manufacturer may be under enormous pressure from patients, physicians and/or politicians to provide the therapy in development to patients, especially children, under a compassionate use programme. Apart from any financial aspects, this pressure may undermine the ability of a sponsor to perform controlled clinical trials.

In addition to the clinical trial expense, the investment needed in production methods and facilities for safe and effective medicines is high, especially for biologic therapies, which may be the preferred therapeutic modality for a number of rare disorders. As an example, the development
costs for alglucosidase α for Pompe’s disease were greater than US$500 million by the end of 2004, without including any costs related to academic research\textsuperscript{15}. The cost of post-marketing authorization studies, creation and maintenance of patient registries and other activities required for regulatory approval — aimed at collecting more information on the value of the treatment once it is on the market — should also not be overlooked.

Additionally, for biologics, the proof of biological equivalence in scaling up production to different levels and fulfilling the requirements of regulatory agencies in proving such equivalence can be a daunting task. The cost for developing alglucosidase α as a treatment for Pompe’s disease, as mentioned above, grew to greater than $900 million by the beginning of 2010 because of these additional requirements. The $900 million included investment capital (for manufacturing plants in Allston, USA, and Geel, Belgium), costs of regulatory obligations and out-of-pocket expenses, including the alglucosidase Alfa Temporary Access Program (ATAP) in the United States (Genzyme, unpublished observations).

**Incentives for industry**

*Does market exclusivity provided by orphan drug regulations create long-term, lucrative monopolies for the developing companies?* A recent paper proposed that companies are increasingly interested in rare diseases because of the market exclusivity provided for orphan drugs\textsuperscript{8}. However, although some approved orphan drug products have demonstrated substantial commercial success, we claim that no company would be motivated to develop a product by the prospect of market exclusivity alone if a market does not exist. Indeed, the clinical and the commercial success of some orphan products, and the consequent increase in interest in the development of such products by both biotechnology companies, and most recently several large pharmaceutical companies, could be viewed as a success of the incentives for companies to make the risky investments required. It is important to note that the value of orphan drug incentives is only realized if market authorization and reimbursement are both gained. Indeed, patients will mostly not be able to afford to pay for orphan drugs from their own funds. If no reimbursement approval is obtained, the company has lost its investment and has usually no way to recoup it. A small company may actually go bankrupt as a result.

Furthermore, the perception that 7–10 years market exclusivity is equivalent to allowing a company to create a monopoly is incorrect. First, the market exclusivity is provided as an incentive by the orphan drug regulations because there is no treatment available for that particular disease. Second, it is granted to prevent a ‘similar’ (in the United States ODA ‘same’) product from entering the market during the exclusivity period. Therefore, exclusivity does not prevent a ‘non-similar’ product — for example, a small molecule versus a biologic — from receiving orphan drug designation for the same therapeutic indication as an existing product or prevent that product from reaching the market. Third, a clinically superior product, even if it is similar, can break the market exclusivity of a marketed orphan drug. This is stipulated in the orphan drug regulations of the United States and of the European Union.

In fact, in the United States in the 1990s, three interferon-β products to treat multiple sclerosis, from three different companies, were all granted orphan drug status and subsequent marketing authorization, and although all three were protected by their respective market exclusivities, they had to share the market. Similarly, in the European Union, several orphan drugs have been approved for the same indications. Sildenaﬁl (Pﬁzer), bosentan (Actelion Pharmaceuticals), sitaxentan sodium (Pﬁzer), iloprost (Bay Schering Pharma) and ambrisentan (Gilead/GlaxoSmithKline) have all been approved for pulmonary arterial hypertension. Agalsidase β (Genzyme) and agalsidase a (Shire) have both been approved for Fabry’s disease. In the ﬁeld of oncology, imatinib, dasatinib and nilotinib have been approved for chronic myeloid leukaemia, and lenalidomide (Celgene) and thalidomide (Celgene) have been approved for multiple myeloma. Finally, rilonacept (Regeneron) and canakinumab (Novartis) are both approved for cryopyrin-associated periodic syndromes.

In this context, it is important to remember that in Europe, the Orphan Medicinal Products Regulation only allows orphan drug designation if there is no existing treatment for that indication on the market, except if the new treatment proposed for designation will have signiﬁcant beneﬁt for patients. Therefore, the differences in signiﬁcant beneﬁt will in fact potentially allow multiple products for the same indication on the market. In that sense, the use of the signiﬁcant beneﬁt pathway in designating orphan drugs in Europe may be seen as a kind of extension of the use of the clinical superiority clause mentioned above.

There may also be confusion over the period of time for which orphan drug status is granted, in spite of the stipulations in the regulations that market exclusivity is limited to 7 years in the United States and to 10 years (unless reduced) in the European Union. Indeed, the market exclusivity granted to an orphan drug is not unlimited. In the United States, the majority of the approved orphan drugs have reached the end of their market exclusivity period, and market exclusivity for the ﬁrst orphan drugs approved in Europe in 2001 is also coming to an end. Once the market exclusivity period is over, the product no longer beneﬁts from the orphan drug-speciﬁc economic incentives, although it may often still be referred to as an orphan drug. There seems to be confusion between ‘orphans’ and ‘products that once received an orphan drug designation and approval’\textsuperscript{9,10}. In the same recent paper, multiple indications are said to be one of the reasons for an orphan product to achieve blockbuster status. However, it is not mentioned that a separate set of clinical trials — and their associated costs — plus a separate market authorization and a separate reimbursement approval for each indication are needed (see above).

In summary, our view is that if an orphan drug is currently the only product in its market, it is either because a company was the ﬁrst to develop a treatment for this disease and competitors have yet to enter the market or because the market is too small to attract competition, rather than because the incentives have created a monopoly.

**Criteria for orphan drug designations.**

A misconception with regard to orphan drug designation is that companies can divide diseases into small subsets (sometimes called ‘salami-slicing’) to beneﬁt from orphan drug incentives. Orphan drug designation is granted in the United States by the FDA Office for Orphan Product Development (OOPD) and in Europe by the European Commission on the recommendation of the COMP, which consists of a representative of each member state, plus three patient representatives and three representatives appointed by the European Commission on the advice of the European Medicines Agency. These qualiﬁed groups approve or deny orphan drug designation based on disease prevalence (the majority) or financial criteria (very seldom), and in Europe, on the additional criteria of absence of an alternative treatment or signiﬁcant beneﬁt to patients over existing treatments. The same drug can receive several orphan drug
designations (and approvals) for different therapeutic indications, but this is a decision of the regulators, not of the sponsors. A product can only be designated if it is shown that the indication for which the designation is sought is a distinct medical entity. In the case of almost all products designated for different indications, the sponsors themselves presented a different application for each one of the indications (each of these being a distinct medical entity). In rare cases, an application addressing a general or grouped indication was recommended by the regulators to be divided into different single independent medical entities. This remains exceptional.

To protect the value and the impact of the definition of an orphan drug, a strict application of this definition and clearly defined consequences of designating projects as orphan or not would be helpful.

**Success of orphan drug regulations**

Relative proportion of orphan products to number of designations. A common misconception is that orphan drug regulations and incentives have not been successful because a large number of orphan designations have been awarded but few of the designated products have been authorized. However, because orphan drug designation is applied for when a project is in the research phase, the ratio of orphan drug designations to the number of orphan drugs approved is not an appropriate measure of the success of orphan drug regulations.

Indeed, a sponsor can apply for orphan designation at any stage of the typical 10–12 year development period for a drug, regardless of whether the product has successfully completed the clinical development processes or not. In addition, the legislation encourages a sponsor to apply for orphan drug designation early in the development process to benefit from all potential incentives during the development phase. In a small company, management and investors may liken such designation to a stamp of approval for their work. However, most medicinal products in development in general (for common or for rare diseases) do not reach the market, owing to factors such as insufficient efficacy or serious safety issues.

With regard to the United States, dividing the total number of designations by the total number of approved products indicates that ~15–20% of products that have been granted orphan drug designation are approved. Given the length of the research to market cycle is 10–12 years, compared with the average time from filing for marketing authorization to its approval, it is expected that the number of orphan drug designations will always greatly exceed the number of marketing authorizations for orphan drugs. EURORDIS, the European umbrella rare disease patients’ organization, provides a figure for the likelihood of obtaining marketing authorization following orphan drug designation in the United States and arrives at 17% of approved orphan drugs versus designations. Those designations that have not yet resulted in an approved product may have been abandoned, the company may have disappeared or the projects may be delayed but still in development. Little research has been carried out on this topic to date. Closer interaction with the regulators at the time of development of the drug and the experience of sponsors in designing and conducting clinical trials are crucial factors for obtaining regulatory approval. Orphan drug development incentives are insufficient for extremely rare diseases and new incentives and other initiatives will be required.

A suitable indicator of the success of orphan drug regulations is the number of orphan drug approvals before and following the enactment of the regulations. For example, as noted above, there were only 10 orphan drugs approved in the United States in the decade before the ODA, but more than 350 have been approved in the 26 years since it was passed. In the European Union, 8 orphan drugs were approved before orphan drug regulation was enacted in 2000 compared with more than 60 now.

**Orphan drug numbers and health-care budgets.** Some have suggested that the growth in interest in orphan drugs could lead to a surge in the number of approved products, which could be a threat to future health-care budgets given their high costs. This concern is often linked to the trend towards more personalized health-care for common diseases based on the identification of patient subpopulations whose size could be compatible with orphan drug status.

However, according to EURORDIS, the authorization in the European Union of the 100th orphan drug product may occur in 2012–2014 and of the 200th product in 2017. Data have been reported indicating that an average of approximately 10–12 new orphan drugs are approved annually in the European Union and approximately 15 new orphan drugs are approved annually in the United States. These data do not suggest that a surge in the number of orphan drug approvals is imminent. Also, although the price of some orphan drugs can be very high, these prices relate to the rarity of the disease. Consequently, the number of patients treated will be small and therefore the impact on the health-care budget will also be relatively small.

Furthermore, the evolution of the use of orphan drugs will depend on technology, on competition entering when a market exists, but also on society learning about the cost of disease versus the cost of treatment. Weeding out inefficiencies may also be more effective in controlling costs than denying orphan drug reimbursement as, at least in Europe, orphan drugs receive regulatory approval based on their uniqueness or their significant benefit for patients, and this is accepted for most (if not for all) products by the member-state authorities.

It is true that, based on new scientific findings, common diseases and syndromes are being divided into smaller patient subpopulations and that these subpopulations may be eligible for orphan status. However, size alone is not the key determinant; as discussed above, the regulators are the decision-makers on the acceptance or not of a certain therapeutic indication, filed for by the sponsor for orphan drug designation. Moreover, such evolution allows for more predictive and targeted treatments, with earlier intervention and improved patient outcomes. Whether this will ultimately be more costly for society will depend on how society chooses to adapt to this new paradigm and whether new pathways for drug development could actually reverse the current trend of spiralling drug development costs, as discussed further below.

**Drug pricing, access and reimbursement**

**Pricing and profit.** Orphan drug prices are often substantially higher than those of other drugs, and one common view is that this is so that developing companies can make high profits compared with those for other drugs. Indeed, some consider that orphan drugs should only be allowed on the market when they make no or marginal profits.

However, this view misses the key point that in the absence of profit potential, those orphan drugs would most probably not have been developed. A company exists through the support of its shareholders and investors, and profit drives both further research and further investor support, which is vital to creating new successes. Many companies involved in the field of orphan drugs therefore set up strategic programmes consisting of several orphan drug projects. The number of patients to be treated is not
known upfront and neither is whether or not reimbursement will be granted and where. As a consequence, profits cannot be reliably predicted per product and must instead be estimated for the entire programme. Moreover, products will be in different phases of development or marketing and will create different returns depending on their status in a given year.

Ultimately, the price of a drug and the corresponding cost per patient is determined by the size of the patient population requiring therapy and by the risk taken to develop the product, which is reflected in the profit potential. Generally, higher-risk projects need higher profit potential to find enough investor support. In a study carried out for the European Commission in 2004, the independent consulting firm Alcimed confirmed that the price of an orphan drug is a function of the rarity of the treated disease. In the event that the market size increases, competition will enter, introducing both pricing pressure and potentially better therapies. If the market remains small, then little or no competition will enter because the clinical problem has been addressed or the market is simply not large enough to attract other companies. In both cases, the overall cost to society remains small.

In summary, it is because of the lack of return on investment without incentives in the field of rare diseases that governments introduced orphan drug regulations in the first place. The success of a development programme cannot be guaranteed, but for each successful orphan drug, our view is that a market should be guaranteed through reimbursement, to provide incentives and the money that companies need to invest in further product developments and to attract further companies to develop products. Ultimately, this should also decrease prices owing to competition — in part because the second company developing an orphan product analogous to the pioneer product is facing substantially less risk and uncertainty, as illustrated for second-generation enzyme replacement therapies — but this will require time and patience (BOX 1).

Access to orphan drugs. It is often said that the reason that patients do not get access to approved orphan drugs is because companies are not registering for reimbursement or because they are simply not active in a country. In this section, we explain briefly a few of the factors affecting the activities of a company with an approved orphan drug in attempting to provide patients with access to such a product. Before marketing authorization, the development cost for an orphan drug is totally borne by the sponsoring company and the risk associated with it can only be rewarded when the product is approved. At that stage, reimbursement is a prerequisite for companies to achieve a return on their investment in its development, as orphan drugs are in most cases not affordable for individual patients. Reimbursement is not guaranteed upfront and so the risk taken by the company continues after regulatory approval until reimbursement has been granted. In Europe, some member states provide reimbursement on approval, whereas others may wait up to 4 years, while requiring the company to provide the product for compassionate use in the meantime, because rare diseases are often serious diseases. Such compassionate-use materials could be a substantial proportion of company resources, especially for smaller companies. Furthermore, in some countries or even parts of Europe, reimbursement may not be granted at all or reimbursement may only be granted for a smaller subpopulation than the authorized indication.

Because it is needed to receive return on investment, companies would like to apply for reimbursement of an approved product speedily and globally, but launching products requires substantial personnel resources, finance, knowledge and skills, and is complicated by the wide range of reimbursement systems across the globe. For example, in Europe alone, there are 33 different national reimbursement systems, not to mention the many regions that have autonomy to approve — or refuse — reimbursement (BOX 2).

Cost-effectiveness and reimbursement. Some consider that because many orphan drugs have not been shown to be cost-effective, they should not be reimbursed. However, at present, the cost-effectiveness of orphan drugs, especially those for very rare diseases, cannot be established with the standard methods used by health technology assessment bodies to inform reimbursement authorities. As an example, the standard cost limit for reimbursement recommended by the UK’s National Institute for Health and Clinical Excellence (NICE) is generally £30,000 per quality adjusted life year gained. Most reimbursement authorities currently accept that it does not make sense to use such standard methods for orphan drugs, at least not those for very rare diseases, based on the rarity of the underlying disease, the unknown costs of not treating these patients and the fact that they are affected by a life-threatening or chronic and serious disease.

At the same time, more research into the impact of rare diseases on society, both from an epidemiological and from a financial perspective, should be supported and the social, ethical and legal aspects of treating rare diseases examined. For example, the fact that most patients with a rare disease require much support from their families, and that most rare diseases are genetic and therefore may affect other members of the family, should be factored into the financial equation. In addition, a dialogue is starting on the input of payer considerations into clinical trial design, and some regulators believe that this will have an effect on the evaluation of orphan drugs.

A second concern expressed by some related to the reimbursement of orphan drugs, in particular in view of their high costs per patient, is that it occurs at the expense of therapies for patients with more common diseases and that it risks bankrupting health-care systems in the future as more orphan drugs are approved, as noted above. In this respect, the European Commission published in 2006 that orphan drugs represented less than 1% of the national health-care spending in the European Union and are a low percentage of the cost of medicines in general. Because of the growing number of approved products, the impact of orphan drugs on health-care budgets will increase. At the same time, the goal of the orphan drug regulations was to make more treatments for rare diseases available so they can contribute to cost savings and provide social returns. Unfortunately, these returns have not yet been calculated. Crude predictions have been made about the number of patients with rare diseases who require treatment, such as in the EPOSOr report of 2007. This states that: “Overall, one estimate is that if there were treatments for all orphan diseases in the categories of rare diseases where there are already orphan medicinal product designations, about 1.6% of the population could be defined as treatable patients. Knowing that only 1 in 10 medicinal products in development successfully reach the market, the figure becomes 0.16% of the population. But given that medicines will not exist for most theoretically treatable orphan diseases for a long time and that many treatable patients are not diagnosed, the number of treated patients will be even smaller.”

Orphan drugs, because of their generally high cost per patient, which increases with increasing rarity, also face higher scrutiny in ensuring that the right patient is getting the right treatment. For many orphan products, additional post-marketing requirements are
imposed by the regulators, such as further studies and the setting up of patient registries. Before reimbursement is granted and patient access is allowed, a confirmed diagnosis is required. It is also recommended in most cases that treatment be supervised by a specialized physician, to ensure — especially for injectable drugs and because of the serious nature of the disease — higher adherence. As few patients with rare diseases are being treated per country, follow-up information is gathered in longitudinal disease registries and clinical data is collected on an international basis so that treatment guidelines can be adapted. Another result of the high price per patient is that national orphan drug budgets are being predetermined and strictly followed.

If the trend points to the introduction of more orphan drugs in the future, it is because there are many unmet medical needs in the field of rare diseases, which can now be addressed through advances in biomedical research. The further trend towards personalized medicine shows the need for treatment with better patient outcomes, fewer side effects, higher adherence and greater effectiveness in general. This may be what orphan drugs offer as a model for the future: better control, less waste and more predictable health-care budgets, in spite of higher prices. However, whereas rare diseases and orphan drugs share some features with personalized medicine, they are also different in other aspects. Rare diseases may still not be economically interesting, are characterized by low awareness and expertise, and are highly heterogeneous. By contrast, personalized medicines are aimed at subgroups of mostly well-known large patient populations often already addressed by the health-care systems and with well-established infrastructures.

When generic versions of many of the most widely used drugs for common diseases become available, this may also provide more financial room and scope for innovation in the treatment of rarer diseases. Also, even before patent expiry, products that have shown commercial success in broad populations could be applied in rare diseases. One example is provided by sildenafil, which has achieved blockbuster sales in erectile dysfunction. It has subsequently received orphan drug approval for pulmonary arterial hypertension. With the aim of catalysing the repurposing of drugs for rare diseases, the FDA has recently launched a database of products that have received orphan designation and are already approved for the treatment of some other disease.

Ideally, a sustainable health-care system should be capable of caring for all patients, including those with rare diseases. The components of the system would include educational programmes to ensure a high level of awareness among patients and health-care providers, expert centres where patients can be evaluated by knowledgeable care-givers with access to appropriate testing and, ultimately, with access to the best therapies. Most companies developing orphan drugs are willing to work in partnership with the health-care authorities, making life-saving drugs available to patients in advance of reimbursement and supporting the development of a system that can deliver expert care to rare disease patients. Ultimately, however, a sponsor and its shareholders who have supported the development of an orphan drug will need to have a return on their investment, with higher potential returns for higher-risk projects.

**Outlook**

In the past 25 years, orphan drug regulations, started in the United States and boosted by a host of coordinated health policy actions in the European Union, have increased interest in rare diseases as a health priority and have catalysed a sharp increase in orphan drug development. Nevertheless, it is estimated that only ~10% of rare diseases have an available treatment (also including food supplements, devices and nutraceuticals in addition to drugs), and such treatments can often still be improved.
So, the medical need in the field of rare diseases remains high. Commonalities between rare and common diseases are being researched, and in the future, rare diseases may be increasingly investigated as models for treatment of more common diseases. This is not only the case in the field of oncology, but also in other disease areas, such as neurology and respiratory diseases, and generates increasing interest from large pharmaceutical companies in the field of rare diseases.

Looking at the current orphan drug legislation, it is noteworthy that so far it has dealt with the regulatory aspects of the development and the approval of orphan drugs, and the economic incentives for such development. The prioritization of research, or issues related to diagnosis and access, are not covered by such regulations. With an increasing number of orphan drugs available, these aspects are gaining in importance. It would be worthwhile to also develop incentives for the repurposing of medicines that are already approved for a more common disease into a new rare disease indication (as discussed above). In this respect, the first aspect that needs attention is the documentation of off-label use of both orphan drugs and drugs approved for common diseases for a rare disease indication. Based on such documentation, it will become clearer which drugs will be worth developing for such new indications and what incentives are needed.

Two contradictory perspectives are currently expressed on orphan drug regulations. The first is that orphan drug regulations have not (yet) lived up to their promise; there is much more to do and time is of the essence, so regulations should be revised to provide more and improved incentives for industry, possibly combined with a stricter regulatory regimen and better priority-setting for development. The second is that orphan drug regulations have provided too many economic incentives for industry and should be revised, so that companies would not be able to create a lucrative monopoly by combining market exclusivity (sometimes for multiple indications per orphan drug) with high pricing. Both of these perspectives include some of the misconceptions and questions discussed in this article. However, as industry is nearly the only provider of orphan drugs, important questions about the role of industry in pricing, access and in setting development priorities are unavoidable. In order to proceed from here, several misconceptions will need to be addressed and industry will have to play a major part in this process. It is also clear that all stakeholders will need to increase their efforts to better implement the spirit of the regulation, to collect more data and to look positively at the achieved results.

Stakeholders, including industry, will need to communicate more clearly on several topics. For example, the challenge of developing a given treatment should be better explained, including clarification on the role of industry, and on some of the risks and pitfalls of the orphan drug regulations. This will help to build social consensus on the topic. It will also help to set proper expectations for patients about access to an orphan drug and for sponsors about return on their investments when reimbursement is denied.

In our view, the first and most important aim to achieve is a shorter time to diagnosis of rare diseases. This can only be done by creating diagnostic and treating centre networks and by educating physicians, in addition to the appropriate screening for rare diseases, primarily in children. Without timely diagnosis, no care plan or treatment can be effectively put in place. Then, price transparency in practice should be defined, to provide greater clarity on the returns for economic incentives. Such a clear consensus definition would then allow different stakeholders to work out what level of transparency is required and what will be possible in practice. However, because industry will have many other investment options, this is a difficult equation.

From a regulatory perspective, a clearer definition or interpretation of the definition for an orphan drug would help avoid possible misunderstandings, especially for products approved in Europe using ‘significant benefit to patients’ as one of the approval criteria. Indeed, if the definition of an orphan drug could be universally accepted to mean a product to treat a life-threatening or serious and chronic rare disease that meets a high medical need and has no suitable alternative, discussions with payment authorities and the reimbursement of orphan drugs would already be made easier and the value of orphan drug designation strengthened. In order to achieve such strengthened value, the differences between the interpretation of and the use in practice of the definition of what an orphan drug is at the European level, and its interpretation at the member state level in terms of uniqueness, significant benefit and/or level of innovation for each approved orphan drug, should be scrutinized and where possible, reduced or eliminated (see above). In addition, at present, the significant benefit of some orphan drugs is questioned in some member states in the European Union and reimbursement for the orphan drug in question denied, and this issue should be investigated. Then, if such a clear definition is accompanied by a system of conditional reimbursement, it would allow orphan drug access for patients while additional data on clinical added value are collected, which would go a long way to addressing patients’ needs.

At the global level, increased international regulatory and health policy collaborations and exchange of information would avoid duplicate work and ensure the best use of rare disease expertise. This would also allow cost savings for sponsors and authorities, and provide earlier access to patients. The European Union and the United States should take the lead in sharing their experience and expertise further than they are today.

The field of rare diseases is a ‘societal laboratory’ that is predicting future trends in patient-centred human health care, and as such it is a model for personalized medicine for some aspects. Therefore, it is important that societal consensus is maintained for solutions in this area, and multi-stakeholder platforms, including policy makers, regulators, patient groups, treating physicians, researchers, industry and payers, should work on improving communication and awareness of rare diseases by collaboration and by sharing expertise. The platform model (examples of which exist in the Netherlands and in Belgium) would be an excellent setting in which to discuss lowering costs, defining issues such as price transparency and applying best practices using all available expertise, and such models should be cherished and nurtured.

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doi:10.1038/nrd3275

Published online 9 November 2010


Acknowledgements

The author would like to thank M. Dooms, Pharmacist, University Hospital of Leuven, Belgium, for helpful suggestions and C. De Bie of Genzyme Corporate Communications for editing the text.

Competing interests statement

The author declares competing financial interests; see web version for details.

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