

biotechnology-based ORPHAN DRUGS achievements and challenges

For many patients suffering from rare diseases there are simply no medicines available to treat their condition. With an estimated 20-30 million such patients in Europe alone, rare diseases collectively represent a significant unmet medical need. Individual disease groups, however, may have few sufferers worldwide. Historically, pharmaceutical companies had no incentive to develop drugs for such rare conditions because the chances of recovering the necessary investments from such small patient populations were very slim, especially for biotechnology-based medicines, which require specialised development and up scaling, as well as a large investment in manufacturing processes and a dedicated plant.

Public concern about the lack of drugs to treat rare diseases in the US led patient groups such as NORD (the National Organisation for Rare Disorders) to lobby US Congress. As a result, the US became the first country to propose a step forward through the FDA's Orphan Drug Act of 1983. This introduced a series of incentives designed to actively encourage healthcare companies to develop products for rare diseases. Following the US lead, Singapore, Japan, Australia and, in 2000, the European Union have also introduced their own form of orphan medicine legislation although they differ greatly in their scope (see Table 1). In the article, we examine the impact that orphan drug legislation has had on orphan drug development. Has it succeeded in encouraging companies to develop medicines for rare disease groups? What impact has legislation had on companies and patients? And what issues remain to be resolved?

Defining an orphan drug

An orphan drug is for the diagnosis, prevention or treatment of a disease so rare that the costs of

developing it would not be recovered without additional incentives, ie under normal market conditions. Around 6,000 rare diseases have been identified. Many of these diseases are genetic in origin, chronic, progressive, serious, disabling and in many cases life-threatening. They include diseases such as cystic fibrosis, Pompe disease, acromegaly, Gaucher's disease, hyperammonaemia and many forms of cancer. Without appropriate treatment, these conditions can result in a lifetime of suffering for the affected patients and a long-term dependence on healthcare systems and institutional care.

The legal definition of 'rare' in the context of orphan drug legislation varies. In the US a rare disorder must affect less than 0.075% of the population; in Europe less than 0.05%; Japan less than 0.04% and in Australia less than 0.01%. The consequence of such different definitions is that one disease may be designated orphan in one country and not in another. Multiple Sclerosis (MS), for example, is not an orphan condition in Europe, but it is just falling within the prevalence limits in the US. For example, three drugs have been approved

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Table I

	USA	SINGAPORE
Date	1983 (modification of US Federal Food, Drug and Cosmetic Act)	1991 Orphan Drugs Exemption (defines legal imports into Singapore)
Definition (orphan designation is non-exclusive)	For rare disease therapies designation based on no expectation that the cost of development and provision of the drug in the US will be recovered in US sales	A life-threatening and severely debilitating illness An appropriate or essential remedy with no effective substitute Should be approved in country of origin or any other country where it has been used
Rarity	Less than 200,000	Unknown
Prevalence	0.075%	
Market Exclusivity in respect of similar products plus clinical superior products can break exclusivity	7 years	None
Other benefits	<ol style="list-style-type: none"> 1. Tax credits for up to 50% of clinical trials costs 2. Protocol assistance 3. Discretionary research grants for clinical studies 4. Fee waivers for product license marketing application 5. Transfer, with FDA consent of designation as IP (??) 6. Abbreviated environmental assessments 	
Administration	OOPD of FDA	

to treat MS in the US: first Betaseron® from Schering-Plough, subsequently through proving clinical superiority over Betaseron, Avonex® from Biogen, and last year, again through proving clinical superiority over Avonex, Rebif® from Serono. These products are orphan drugs in the US, but not in Europe, where they are approved as medicines without orphan designation.

The incidence of many rare diseases, however, falls well below these limits and there are no additional incentives for developing what have become

known as very rare diseases or ‘ultra-orphan’ – diseases with prevalence of less than 10,000 in the population of the US or the EU (the prevalence numbers quoted above mean that the cut-off prevalence for a rare disease is 200,000 affected patients in the US and about 175,000 in the EU). The so-called lysosomal storage disorders belong to these very rare diseases. Examples of lysosomal storage disorders are Gaucher’s disease, Fabry disease, Hunter disease, mucopolysaccharidoses, Pompe disease and Niemann-Pick disease. There are

JAPAN	AUSTRALIA	EUROPE
1993 (based on US law)	1994 (addition to Regulations to Therapeutic Goods Act)	2000
For rare and serious disease No alternative available – or new product expected to have greater efficacy or safety High probability of successful development	Not commercially viable to treat or prevent a rare disease or condition	For (<i>in vivo</i>) diagnosis, prevention or treatment of life-threatening or chronically debilitating condition. Designation based on prevalence defining rare disease OR non-profitability criteria No existing approved alternative in a EU member state, except if clinical benefit
Less than 50,000	Less than 2,000 (about 11 per 100,000)	Less than 5 per 10,000
0.04%	0.01%	0.05%
Extended re-examination period of 10 years in lieu of exclusivity (see below)	None: TGA brochure mentions 5 year exclusivity for a superior drug – but there is no legislative backing for this	10 years (revision possible after 6 years if criteria for designation are no longer met)
1. The registration validity period (4-6 years for standard drugs) is extended to 10 years for orphan drugs 2. Tax credits – applies to non clinical as well as clinical studies: 6% of authorised expenses and up to 10% of corporate or income tax 3. Protocol assistance 4. Discretionary grants for both clinical and non-clinical studies 5. Only available to pharma companies and sponsors may have to pay back a % of sales generated to pay admin costs 6. Shorter approval times	1. Fee waiver for application and evaluation fees for registration 2. Priority evaluation (no tax credits or grants)	1. Protocol assistance 2. Fee waivers (partial or full) for marketing authorisation procedure 3. Exclusivity does not prejudice IP rights 4. Eligibility for EU research funds 5. Additional, cumulative member state incentives possible
Ministry of Health and Welfare	TGA	COMP for designation CPMP for marketing approval EMEA EU Commission Member states

approximately 40 different diseases known to belong to this group, but only for a few are medicines already available.

One of the tragedies of rare disease is that it can take many, many years before the correct diagnosis is made. With Fabry disease, for example, the average age for the onset of symptoms is 10 years, but the average age at diagnosis is 29 years. As a consequence, there is a great need to share knowledge on rare conditions and to create better systems for early diagnosis and for screening. It can be seen that

the development of a treatment can in itself create greater incentives to find the patients in need of that therapy, and this has an impact on the diagnosis of the disease – patients are referred, by other patients and by physicians, due to successful cases and treatments. An example is Gaucher disease. In the 1980s, when Genzyme first began developing Ceredase® as a treatment for Gaucher disease, the number of patients in need of treatment worldwide was estimated to be in the region of 1,500. Ceredase, a natural enzyme extracted from human

tissue, has been replaced by Cerezyme®, the recombinant form of the enzyme, which is now used to treat around 3,500 Gaucher patients worldwide.

Incentives and local variations

The importance of the orphan drug legislations is that it has made developing drugs for rare diseases, except for the extremely rare ones with a very low prevalence, economically viable. The costs of developing any drug are hugely expensive and financial incentives, such as tax benefits and market exclusivity, are required to help companies recoup the costs of development. Fast-track approvals may also be a great inducement and help to accelerate time to market, although this is less true in Europe because of the different roles of the bodies leading to regulatory approval on the EU level and those responsible for price setting and reimbursement in the member states, which sometimes leads to long delays in access, even for approved products to treat serious diseases. A recent survey published by EURORDIS, the umbrella patient group for rare disease patients in Europe, has underlined this phenomenon.

Market exclusivity applies to the first company obtaining marketing approval for a drug which has previously received orphan drug designation, and may confer a valuable period in which income can be generated without the pressure of competition. As proven by the survey above, this may prove to be partially theoretical as the 10-year exclusivity is eroded by the delay in access in some of the European member states. In addition, the pressure from competition is not often there, since very few companies embark on the development of orphan drugs. However, when there is competition, as in the case of the interferon-based treatments for multiple sclerosis in the US, and in the case of treatments for Fabry disease in the US and in Europe illustrate, the market exclusivity can be an important factor, and in such case, there are winners and losers in the race. The concept of exclusivity only applies to the US and Europe, while it is not a part of the orphan medicine legislation in the other countries mentioned above. Europe gains 10 years market exclusivity, while the US has seven years. The difference is partly explained by the fact that Europe, unlike the US, does not confer tax benefits, as tax legislation comes under the remit of individual member states.

While five-year market exclusivity was under discussion in Australia for several years, no legislation was ever enacted. Any references to proposed market exclusivity were withdrawn in late 2001. In Australia, orphan drug legislation now basically saves initial registration fees and allows for priority and 'fast-track' registration, although this has to

be sought separately and is not an automatic right. Japan, in lieu of exclusivity, has an extended re-examination period. Normally post marketing evaluation of a new chemical entity is required for six years for any new drug, and for four years for a new indication. This period has been extended to 10 years for orphan drugs. During this period, any company wishing to apply for approval for the same drug is required to submit a completely new application, and this virtually assures market exclusivity during the entire period.

Getting results for patients and companies

The effects of the different orphan drug legislations are relatively easy to measure. It is clear, simply from the large increase in the numbers of new orphan drugs on the market, or the large numbers of orphan drug designation applications that this legislation is having a significant impact. The potential for profitability is making a big difference by creating interest from companies, but also to patients who are reaping the benefits of new treatments.

Comparative studies of legislation in the US, Japan, Singapore and Australia demonstrate that policies based on market exclusivity and R&D incentives have had a very positive effect¹ on the number of orphan drugs. Before the Orphan Drug Act was enacted in the US there were only about 10 orphan-like products on the market, now there are in excess of 230 such products. Similarly, before orphan drug legislation in Japan, there were only 42 drugs that would have met orphan drug designation. To date, 175 products have received orphan drug designation and 91 have been approved, although 21 products have also been revoked between 1993 and 2003². While European law is still very much in its infancy, figures in July 2003 show that 292 applications for orphan drug legislation have been made and 11 have already gained market approval. If approximately one in four applications succeed to market, as is the case in the US, then we may expect to see about 75 new drugs emerge from these 292 applications in the next few years – a dramatic change for Europe. Before 2000, only six medicines got fee waivers from the EMEA as 'orphan drugs avant la lettre'.

Orphan drug legislation has also helped to create new enterprises. In the US, the Orphan Drug Act has led to a considerable number of biotech companies founded in the 1980s. Companies such as Orphan Medical were conceived solely to produce drugs for rare diseases. Genzyme, too, has grown because of its interest in the development of orphan drugs. In the EU, many applications for orphan medicines come

from young or start-up companies, sometimes created to develop an orphan drug as their first product, as a direct result of the EU regulation. Most orphan drug developers are small to medium-sized companies and many are biotech companies. Biotechnology is playing an ever-increasing role in drug discovery as it offers novel approaches for the development of drugs and in particular for genetic disease. With the help of orphan drug legislation these approaches are delivering new drugs for patients; approximately 50% of US orphan drugs are biotech-based. In Europe, since the development time for new biotech-based drugs is longer than for reformulation of existing classical drugs for orphan indications, this percentage is about 35-40% but increasing.

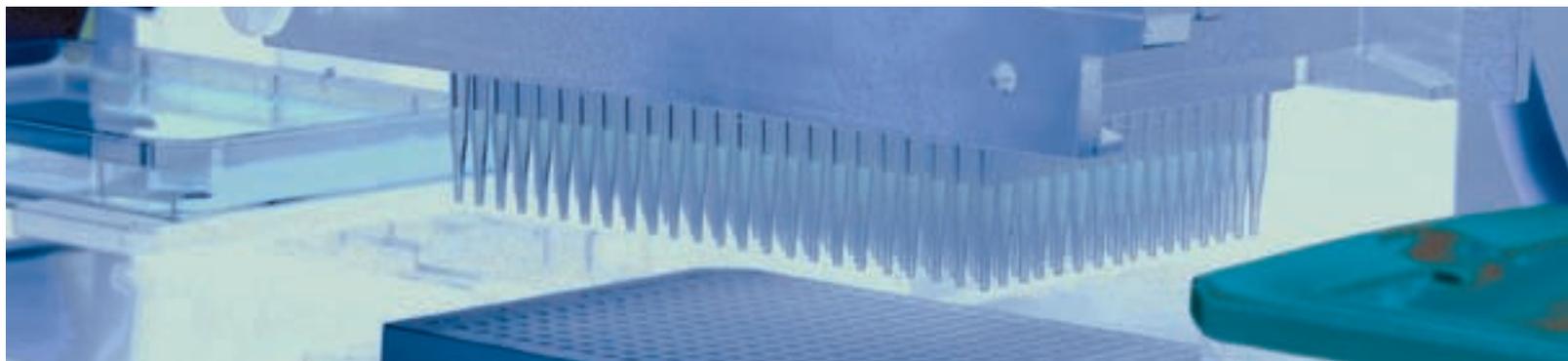
On-going challenges for orphan medicines, worldwide and particularly in the EU

While orphan drug legislation has undoubtedly fuelled interest in the development of orphan

drugs, there are still major challenges to overcome. Key areas are diagnosis of rare diseases, the conduct of clinical trials, patient access to new products, and awareness of both the difficulties related to rare diseases for patients and the difficulty for industry to get a fair return on investment in developing therapies for them.

As illustrated above, diagnosis of patients can take up to 20 years because of the heterogeneity of the clinical symptoms, the rarity of the disease or the inexperience of the clinicians in recognising the many different rare diseases that exist. Screening programmes may ultimately become part of the solution for this, but reliable diagnostic methods should be available. Screening programmes are set out to identify the risk of disease or its complications in those individuals who are apparently in good health and have the potential to save lives and improve the quality of life through early diagnosis of diseases. If no treatment exists, extreme care has to be given to provide this type of testing only to those patients that

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really consent to it and want to know the test result. Screening carries specific risks, as false positive or negative results may have a serious impact on the patient and the health decisions he or she takes. The best approach (eg working with schools, general practitioners, existing screening centres, etc) must be defined in order to obtain optimal efficiency and the implementation of timely follow-up strategies. As tests become more reliable and informative, various forms of active screening for chances of risk of serious diseases with options for treatment and/or prevention will be promoted. Screening programmes should be fully validated and regularly evaluated, and can only be set up providing strict conditions of quality have been met. Screening programmes could provide a currently lacking, but essential, surveillance system for the health of the populations.

Developing a medicine in general is extremely expensive, whether it is used by millions of people, or by a few hundred people. As a pioneer in this area, Genzyme's experience with investments to develop and manufacture new treatments which are spread over an extremely small patient population, are providing a learning experience for other companies entering this field.

It has successfully used the hamster cell system to produce its recombinant proteins for developing enzyme replacement therapies for Gaucher and Fabry disease and, with its partner BioMarin, for MPS-I. Many other biotech medicines have been produced and marketed in the European Union and the United States, based on this manufacturing method, including products which have been approved for chronic use over long periods of time (eg rh Factor IX, rh EPO, and rh IFN- β 1a). The manufacturing method has proven to produce biologically active ingredients, which are acceptable for regulatory approval, but they are expensive to produce. It is clear that the manufacturing of minute quantities of product for therapies to treat rare diseases using expensive manufacturing processes result in high costs.

It is also noteworthy that nine of the 11 already approved orphan medicines in the EU have been approved 'under exceptional circumstances'. This means that the authorities have put a number of post-marketing obligations on the sponsoring companies, which are reviewed each year, in order to further follow-up on safety and clinical effectiveness, and, while they constitute a necessary follow-up, these obligations also carry a high cost, and it may be important to review how this cost can be decreased without decreasing the intended result.

The recently published report by the Committee for Orphan Medicinal Products of EMEA (the European Medicines Evaluation Agency) for the period 4/2000

till 4/2003 emphasises that for rare diseases, by definition, the number of patients available for clinical trials is limited, and that clinical trials may require different methodological approaches, still complying with scientific standards and legal requirements, to ensure the development of a safe and effective product. Indeed, clinical trials are an area of concern since the clinical trial regulations designed for standard drugs cannot be easily met in rare diseases because of the shortage of trial participants. Trials may therefore take much longer, and regulators may find it difficult to understand why it is not possible to present data from more than a small number of trial participants. Clinical trials must be able to accommodate studies for rare diseases and new parameters, such as surrogate clinical endpoints, need to be established in deciding what constitutes clinical trial 'success'; how much evidence of safety and efficacy is required before a drug can be approved?

For rare diseases it is not possible to compare outcomes with another treatment because often there is no other treatment available, and even animal models may not exist. The evidence base is sometimes very poor, and needs to grow while already helping patients in need. There is a great need for centres to collect patient data for research, documenting the incidence of disease and responses to treatment. Such centres would provide opportunities for clinical development and research, including patient registries and databases, and ways of collecting data in the post-approval setting.

In Europe, there is an additional problem that trials may need to be conducted across several member states in order to achieve adequate patient numbers. This can create difficulties in complying with local clinical trial regulations – a situation that creates delays and increases costs as patients may need to travel great distances on a regular basis, or even relocate for a year or more, in order to participate in an ongoing trial for a rare disease. Also, the newly adopted Clinical Trial Directive in the EU is currently in implementation in the member states legislation, and it is hoped that special provisions will be made for clinical trials involving rare disease, although at this time it is also possible that this would not be the case and that clinical trials for rare diseases could get even more complicated.

An important issue in Europe is that orphan drug legislation has been enacted at the EU level, but many of the laws and regulations associated with clinical trials, taxation, pricing and reimbursement are determined at member state level – and this can cause problems in interpretation or practical consequences of the orphan medicines regulation. Marketing authorisation by the EMEA, for example, while it brings a

product to market does not guarantee that it will be paid for: each member state has to make its own reimbursement decisions. This may be almost immediate in some states, but decisions can take two years or more in others. Protracted decision-making, however, can have a negative impact on companies contemplating the development of orphan drugs. There may also be conflicts between existing legislation and what is practically possible for orphan drugs, such as in the case of the rules for comparative advertising, as many members of government administration may not be yet used to the intent and practicalities of such innovative legislation as the one discussed here.

Differences in US and EU approaches are illustrated in a very unusual case where Genzyme and TransKaryotic Therapies (TKT) filed applications for drugs treating Fabry disease at the same time. Genzyme's application for Fabrazyme®, and TKT's application for Replagal™ were submitted within the same month for FDA approval and within the same week for EMEA approval. The two authorities handled the situation in entirely different ways. EMEA, on the basis of clinical trial data from the two submissions, decided to approve both products on the same day resulting in co-exclusivity marketing authorisations for both products. In the US, the FDA scrutinised the trial data for a further two years and, after a hearing with an expert's panel, decided in favour of Fabrazyme. While the process of granting marketing authorisation took two years longer in the US than in Europe, once marketing authorisation was approved, Fabrazyme immediately became available to patients. In Europe, however, while Fabrazyme gained marketing approval two years earlier, in some EU countries patients may still be denied access, due to prolonged reimbursement discussions.

A survey carried out by Cordis (Community Research and Development Information Service) showed that of the first five orphan drug products granted marketing approval, only one EU country provided access to all five. Patients need a transparent system for reimbursement qualification. Compassionate use is also an issue. Some member states have compassionate use policies, while others do not. France, for example has a temporary use policy called ATU (Autorisations Temporaire d'Utilisation) and other countries such as Italy have similar initiatives, but some other European countries do not have such systems in place.

There is still a great need to promote an understanding of rare diseases and to stimulate interaction between physicians, regulators, industry, payers and patient groups. A sense of urgency needs to be built into the process – the availability of drugs for rare diseases can be a matter of life or death.

Patient organisations such as NORD in the US, and EURORDIS in Europe, as well as the European Platform for Patients' Organisations Science and Industry (EPPOSI) have a large role to play in communicating the problems that patients face – and they have been successful in doing this. Care needs to be taken not to raise false hopes for patients. Developing drugs for rare diseases, despite the help provided through orphan drug legislation, still remains risky. Few products ultimately reach the market, and it takes a very long time to get there.

Occasionally, a company produces a product that makes a profit and generates good returns and these successful products provide a very strong incentive and example for other companies to decide to enter the market. In some cases, however, profitability can lead some regulators to question the validity of high prices. What is often overlooked in such discussion is that in fact most orphan drug products do not generate large returns. Examples of successful drugs are absolutely necessary to sustain unprofitable drugs and to continue research and development for new medicines. While the price of biotech-based orphan drugs may be high, they can save healthcare systems the costs of a lifetime of chronic disease, or a patient's life.

Acknowledgements

With thanks to David C Lewis; Mary McGrane, Senior Vice-President Government Relations, Genzyme; Alison Lawton, Senior Vice-President, Regulatory Affairs and Corporate Quality Systems, Genzyme; and Paul Yamada. **DDW**

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