Challenges and opportunities in the treatment of rare diseases

There are approximately 7,000 rare diseases, which from a regulatory perspective are defined as those diseases where there are less than 200,000 patients in the US or that affect no more than five in 10,000 of the general population in the EU.

By Dr Philip J. Vickers

Such diseases usually have a genetic basis, often affecting patients early in childhood, and are frequently progressive, disabling and life threatening in nature. These characteristics can have a devastating psychological impact on families of children suffering from these diseases. Better known examples of rare disease include Duchenne Muscular Dystrophy, Cystic Fibrosis, the Mucopolysaccharidoses (MPS) and rare cancers. While each rare disease alone affects a small number of patients, it has been estimated that the combined number of people suffering from a rare disease in the US and EU exceeds 55 million[1], highlighting the huge societal impact of these diseases.

A number of unique clinical, regulatory and commercial challenges are associated with the development of therapies for the treatment of rare diseases. In recognition of these challenges, there has been legislation in the US, EU and elsewhere in the world which provides regulatory and financial incentives aimed at stimulating investment in 'orphan drugs' to treat rare diseases (**Table 1**). In addition, the FDA has created the Office of Orphan Products Development to focus on the challenges of developing therapeutics for the treatment of rare disease and to help companies navigate the regulatory review process. In addition, in 2010 the FDA created the Rare Disease Program within the Office of New Drugs with the specific focus of developing the policies and procedures for the review of new drug applications for orphan drug products and to ensure the appropriate training for FDA reviewers. In both the US and the EU, orphan drug designation can be applied for at any stage of the development process.

Orphan drug legislation has generally been considered to be extremely successful. Prior to these legislative acts there were essentially no drugs specifically developed to treat rare diseases, whereas since passage of the Orphan Drug Act in the US in 1983, 2,755 agents have received an orphan drug designation in the US, with 424 orphan drug approvals. An analysis of compounds progressing from clinical development to approval in the US between 2006 and 2010 shows that 28% of all new drug applications were for rare diseases, and that approval rates for rare and common disease applications have been similar[2].

Recent success in the development of orphan drugs coupled with productivity challenges in the classic pharma R&D model for indications with a higher prevalence, has resulted in a number of major pharmaceutical companies recently establishing business units focused on rare diseases. In turn, this has resulted in increased investment of venture capital companies and early stage biotechs in rare disease programmes. In part the increased

Table 1: Incentives for orphan drug development

COUNTRY	United States	European Union	Japan
Prevalence Criteria for Orphan Designation	200,000 people	5/10,000 people	50,000 people
Market Exclusivity	7 years	10 years	10 years
Tax Credits for Clinical Research	Yes (50% of clinical costs)	Not at EU level	Yes (6% of clinical and non-clinical costs)
Application Process for Waivers	Yes	Reduced fees	No

interest in rare diseases may also be attributed to advances in the knowledge of disease biology and genomics which has made it clear that a number of more prevalent diseases may be categorised into several distinct subsets of disease with unique characteristics. We are indeed edging closer to the era of 'personalised medicine' and what is learned from drug development for rare diseases may well prove to be applicable to treatments for these subsets of patients. This is already starting to be the case for other diseases, such as subsets of different types of cancer.

While there have been significant advances in the field of rare diseases, effective therapies are still not available to more than 95% of the patients suffering from these diseases. In addition, while orphan drug designations have increased, there continues to be only a consistently small number of annual approvals for orphan drugs[3-5]. So while there have been successes in the development of treatments for diseases such as Fabry Disease, Hunter Syndrome, Gaucher Disease and Pompe Disease, much remains to be achieved to the benefit of patients suffering from rare diseases. Learning from drug development programmes for rare diseases has made it clear that the R&D paradigm in this field has very different challenges from that associated with more prevalent diseases. If the development of orphan drugs is to build on the early success associated with rare disease legislation, key stakeholders need to further align on ways to address these challenges.

The major challenges for R&D in the rare disease field stem from the impact of the unique characteristics of rare disease patient populations on the clinical development process in rare diseases (**Figure 1**), and the interface between clinical development and the regulatory process. Legislation demands that potential therapies demonstrate safety and efficacy in the clinic in order to be approved by regulatory authorities. Generally the final step in this process is two adequately powered Phase III, double-blind, placebo-controlled trials (or a single study with confirmatory evidence), with statistically-significant benefit being demonstrated by an investigative agent compared to placebo in order to be considered appropriate for approval. Increasingly, clinical benefit is also compared to that achieved by a comparator agent representing the current standard of care for a disease. A direct measure of clinical benefit specifically related to disease is generally considered appropriate for approval, such as benefit to the functioning of an organ. For ethical reasons, it is also generally considered appropriate for therapies to be tested in adults before being assessed in the pediatric population. While these expectations are appropriate and realistic for the majority of common diseases, for drugs under investigation for the treatment of rare diseases these requirements are either very challenging or implausible for technical, practical or ethical reasons.

A fundamental challenge in drug development for the majority of rare diseases is that there is relatively little known about the pathophysiology or the natural history of disease; there are usually only a small number of experienced clinical investigators worldwide, and in contrast to higher prevalence diseases there is usually very little scientific literature published. For example, a PubMed search demonstrates that while there were close to 6,000 publications in the scientific literature related to arthritis in 2012, there were only 25 related to MPS-II, or Hunter Syndrome – despite the fact that there is an approved therapy for MPS-II. The consequence of this is that there is frequently uncertainty about disease mechanisms in rare diseases, a lack of adequate preclinical models of disease and incomplete knowledge of

potential biomarkers of disease. In addition to these challenges, for the many rare diseases where there are no available therapies, the clinical development path has not yet been defined and hence there is increased risk and uncertainty as to the clinical endpoints which would be considered appropriate for regulatory approval. R&D organisations therefore need to make a significant commitment to effectively engage the relatively few physicians and opinion leaders who work on any rare disease, in addition to engaging with patient associations and families dealing with the consequences of these disorders to gain a greater understanding of the natural history of disease, and those therapeutic effects that would have a meaningful impact on the lives of patients. Umbrella patient organisations such as NORD in the US and EURORDIS in the EU, as well as patient organisations representing individual diseases, have important and complementary roles to play in supporting the development of therapeutics for rare diseases. Project leaders and key decision-makers in rare disease companies clearly need to be 'patient-centric' in their thinking. In addition, payors also need to be engaged early in a programme to define what will be considered appropriate measures for reimbursement, with information on these measures being built into a clinical development plan.

As there is little or no precedent from earlier clinical development programmes for the majority of rare diseases, companies frequently need to commit to natural history studies, which are managed in a similar way to clinical trials, prior to initiating any clinical programmes. These studies aim to provide important insights to suggest potential clinical endpoints for inclusion into the clinical development programme and discussion with regulatory authorities, may identify biomarkers that correlate with clinical endpoints, can assess the trajectory of disease progression and may define the variability in clinical progression between subsets of patients. For example, a study of nearly 2,000 individuals from families affected by Huntington Disease who had different demographic, clinical and genetic features at baseline[6] revealed differences that emerged before clinical diagnosis, and will inform the design and conduct of future clinical trials. In addition, a natural history study of patients with infantile-onset Pompe Disease[7] carefully described the rapid progression and fatal course of this devastating disease, and confirmed that early symptom onset was correlated with an increased risk of early death. It is important that data from studies such as these are readily available in the public domain as they will underpin future drug discovery and development programmes. The cost and time associated with natural history studies can be an impediment to the initiation of clinical programmes, and moving forward such studies, that provide insights into the basic biology of disease, may be an appropriate area for increased future partnership between industry and research funding agencies. In addition, patients with rare diseases are particularly active in online patient communities, some of which collect patient-reported outcomes. In effect, they are conducting natural history studies through social networking. While data integrity needs to be ensured, it will be important to consider how such information may provide helpful insights to shape clinical programmes and provide support for regulatory submissions.

The most obvious challenge in conducting clinical trials in rare diseases is the small numbers of patients available for clinical studies. Enrolment of patients into clinical studies in sufficient numbers to generate meaningful comparative data is therefore a major challenge, usually requiring the participation of many sites across multiple geographies, frequently with very few patients enrolled at each site. This may cause delays in the recruitment process which can add cost and uncertainty to the programme. Higher per patient clinical costs are also driven by the fact that the fixed costs for setting up each clinical site are spread over a smaller number of patients. In addition, the manufacturing process to support biological products in rare diseases can have some specific challenges. For example, changes or improvements in the manufacturing process for complex glycoproteins frequently results in some changes in the characteristics of the protein products. Generally, comparability studies between the two different products in man are required to support approval for substitution. However, in rare diseases such comparability studies are particularly challenging as there are few patients available for

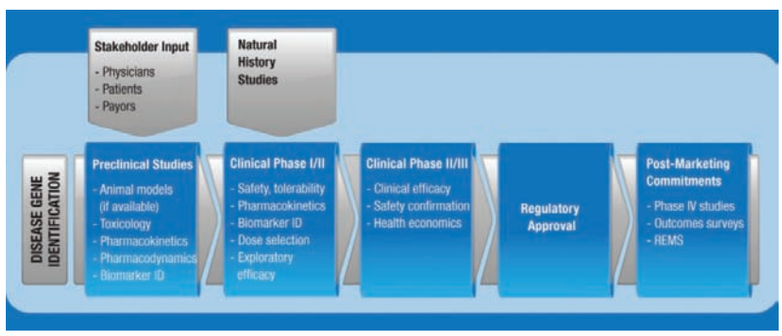

Figure 1
The R&D paradigm in rare diseases

Table 2: The treatment of MPS diseases. See drugs@FDA.com and www.ema.europa.eu/ema/

MPS TYPE (EPONYM)	Biological Markers Used in Clinical Practice	Drug Brand (Generic) Name	Primary Endpoint	Major Post-Marketing Clinical Commitments (US & EU)
MPS I (Hurler)	Urinary Glycosaminoglycans: Heparan Sulfate Dermatan Sulfate	Aldurazyme® (Laronidase) (BioMarin/ Genzyme LLC)	Improved Walking Capacity and Pulmonary Function	Further develop IgE and neutralizing antibody assays Study effect of different doses and schedules on clinical response Evaluate long-term safety, efficacy, and biomarker analysis Assess correlation between endogenous enzyme activity and patient antibody responses and infusion reactions Treatment of patients younger than age 6 years
MPS II (Hunter)	Urinary Glycosaminoglycans: Heparan Sulfate Dermatan Sulfate	Elaprase® (Idursulfase) (Shire Human Genetic Therapies, Inc.)	Improved Walking Capacity and Pulmonary Function	Long-term safety and efficacy Pharmacokinetics, pharmacodynamics, and safety in pediatric population Assessment of binding and neutralizing antibodies
MPS VI (Maroteaux-Lamy)	Urinary Glycosaminoglycans: Dermatan Sulfate Chondroitin-4-Sulfate	Naglazyme® (Galsulfase) (BioMarin)	Improved Walking and Stair-Climbing Capacity	Screening assay to detect antibodies Validate an assay for detecting IgE antibodies Long-term safety and efficacy Evaluate the effect of Galsulfase on pregnancy and lactation Efficacy and safety in children age 5 years or younger Effect of Galsulfase on skeletal dysplasia in patients less than age 1 year

such studies, and only a small proportion of these patients may be treatment-naïve. In these cases, comparison of physicochemical characteristics and data in preclinical models may be appropriate, followed by careful monitoring in the clinical setting to ensure safety and efficacy.

The challenge of finding patients may continue in the post-approval setting, where identifying patients is usually critical for commercial success of rare disease therapies. The requirement to find patients highlights the need for rare disease companies to establish effective educational programmes and develop and validate diagnostic tools. Diagnostics can also play an important role in identifying patients as early as possible in the course of their disease as history studies and clinical experience have established that for a number of rare diseases the earlier that diagnosis can occur and therapy initiated, the greater the clinical benefit that may be achieved for patients. Indeed, it has been projected that for the top 350 rare diseases, approximately 27% of patients will not reach their first birthday. Furthermore, it is clear that expansion of newborn screening, possibly in parallel with a potential treatment for a rare disease, has the potential to provide tremendous benefit to patients suffering from such a disease, which may be severe and progress rapidly in the pediatric population. For example, assessment of a variety of clinical endpoints and functional tasks in patients of different ages with Pompe disease[8] provides a strong argument for the value of neonatal screening for this rapidly progressing disease. In the US there is currently a panel of 29 diseases that are routinely screened for at birth[9], with certain States having expanded newborn screening beyond this panel. With the expansion of knowledge related to the genetic basis for disease and improvements in technologies to measure specific biomarkers[10,11], there will be an increasing opportunity to expand newborn screening such that clinical outcomes may be predicted earlier for individual patients, with therapeutic intervention improving outcomes for these patients.

In addition to the logistical challenges associated with running clinical studies with very few patients, small patient numbers result in challenges to generate the type of data achievable with diseases of higher prevalence. Specifically, it can be unrealistic to expect to be able to power studies to achieve the degree of statistical significance with certain clinical endpoints as can be achieved in more common indications, to explore multiple doses in the clinic, or to assess appropriate dose intervals. In studies where less than 20 patients may be enrolled, every patient makes an important contribution and trade-offs need to be made with regard to what may be explored in the clinic; for example, enrolling patients in placebo arms can compromise valuable data on drug effects if there are high quality alternate sources of historical control data. Moreover, in life-threatening pediatric diseases where there is no available therapy, if efficacy can be demonstrated in Phase II clinical studies it can provide an ethical dilemma to include a no treatment arm in subsequent pivotal studies, particularly in rapidly progressing diseases. This highlights the importance of industry and regulators carefully considering appropriately controlled natural history studies as no-treatment comparators for pivotal studies in certain rare diseases.

Even for the rare diseases which have been more widely studied such as MPS diseases, it is clear that there are frequently complex clinical phenotypes, with clear differences between patients and effects on multiple organ systems[12]. For MPS diseases where there is an approved therapy, **Table 2** shows the primary endpoints which were used as the basis for regulatory approval, and the major post-marketing commitments which were requirements in the US and/or EU. It is noteworthy that for these diseases there are biological markers which are

routinely used in clinical practice, but none of these biomarkers are considered validated from a regulatory perspective. There can also be significant variability in the rates of disease progression and differences in clinical outcome between patients with the same disease. For example, Gaucher Disease is an inherited lysosomal storage disorder caused by a deficiency in the enzyme glucocerebrosidase. However, there are three different forms of Gaucher Disease and within these forms clinical effects can be manifested in different ways and at different rates[13]. Such complexities can lead to significant challenges in defining the appropriate criteria for patient enrolment into clinical studies for rare diseases.

Even when rare diseases are linked to mutations in a single gene, there may be hundreds of mutations in these genes, and the link between genotype and clinical phenotype is complex and only partially understood. In Metachromatic Leukodystrophy (MLD) there is an infantile form of disease caused by mutations resulting in the lack of expression of the enzyme arylsulfatase A with this form of the disease being severe and rapidly progressing. In other MLD patients, there may be different mutations which result in reduced levels of expression of the enzyme or lower enzymatic activity; this can even manifest as adult forms of the disease which are less severe, more slowly progressing, and which can present with very different (eg psychiatric) phenotypes[14]. These findings also highlight a challenge of pediatric studies in rare diseases; the highest medical need for MLD patients is associated with the infantile form of the disease, and it would be very difficult to conduct clinical studies in a small population of adult MLD patients where the disease is slowly progressing and clinical endpoints may not be relevant to the infantile population.

In addition to complexity associated with different mutations in disease genes, it is likely that additional genetic variation in secondary genes associated with disease pathways will also modify clinical phenotypes. For example, there are founder effects with monogenic diseases, but even in isolated communities with the same genotype

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there may be differences in clinical phenotype which may be due to secondary genetic variation or environmental factors. As technological advances will result in individualised genome sequencing and predictive computational modelling of disease pathways being more commonplace in the future, there is the potential for an exciting era of powerful insights into the pathophysiology of rare diseases.

Largely in response to the need for the rapid development of therapies for the treatment of AIDS, in 1992 the Accelerated Approval Rule authorised the FDA to expedite marketing approval for certain new drugs intended to treat serious or life-threatening illnesses upon determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is 'reasonably likely to predict clinical benefit'. Recognising the difficulty and ethical issues associated with previously defined clinical endpoints in the context of rare diseases, new landmark legislation was signed into law on July 9, 2012 which has the opportunity to significantly benefit rare disease patients. The Food and Drug Administration Safety and Innovation Act (FDASIA) expanded the list of potential scientific data which could be used as surrogate endpoints. This included, for example, epidemiological, pathophysiological and pharmacological endpoints, as well as biomarkers. In fact, surrogate biomarkers have been used for a number of common indications in the past, including serum cholesterol and LDL for cardiovascular drugs, and CD4+ levels for antiretrovirals. When approval is granted under accelerated review there is a requirement that there be post-marketing studies conducted to verify the relation of the surrogate endpoint to clinical benefit. In the EU a similar approval pathway known as Conditional Marketing Authorisation exists. While the challenges associated with drug development in rare diseases suggests that these programmes may be appropriate for accelerated approval status, very few examples exist where an orphan drug product has achieved accelerated approval on the basis of a biomarker. Examples include Fabrazyme®, approved in 2003 for the treatment of Fabry Disease, and sapropterin (Kuvan®) approved in 2007 for the treatment of Phenylketonuria. It is likely that increased utilisation of accelerated approval for rare disease therapies, in conjunction with appropriate post-marketing commitments, would have the same positive impact as that realised in oncology and HIV therapy[15]. Indeed, in situations where there is clinical variation such as that observed in rare disease, biomarkers related to the measurement of the primary defect associated with disease (eg correction of enzyme activity in enzyme-deficient patients) may be considered 'reasonably likely to predict clinical benefit' and more generally relevant than the correction of clinical endpoints which may only be relevant to a subset of patients. While it may be considered that making an approval decision based on biomarkers in the absence of clinical outcomes adds risk, it is noteworthy that no drug with an orphan designation has been withdrawn for reason of safety or lack of efficacy.

Irrespective of the potential utility of surrogate biomarkers for approval, companies developing rare disease therapies frequently need to commit to multi-year post-marketing commitments. Such commitments can include the need for clinical studies for assessing long-term safety, defining efficacy with regard to clinical endpoints that can only be assessed following long-term treatment, or measuring clinical effects on subsets of patients that were not sufficiently represented in clinical studies. Patient registries also provide the opportunity to assess therapeutic effect in the 'real world' outside of the clinical trial setting. In addition to addressing specific questions arising from the regulatory process, long term post approval studies can provide important insights into the pathophysiology of disease. For example, as some rare diseases are X-linked recessive genetic diseases, dogma has been that the diseases are limited to males. Fabry disease is an X-linked disease cause by deficiency of the enzyme alpha-galactosidase A. However, careful analysis of a Fabry Outcome Survey associated with an enzyme replacement therapy[16] has characterised the clinical manifestation of the disease in females and the benefit of enzyme replacement therapy in these patients has been observed. In rare diseases where there are multiple therapies with patient registries, there would be value in considering opportunities for cross-industry partnerships to combine data which may provide a deeper understanding of disease progression.

The numerous factors which add complexity to defining appropriate clinical endpoints in rare disease highlight the need for early engagement and a high degree of transparency between industry and regulatory authorities to define an appropriate regulatory path. While rigorous regulatory standards must be applied irrespective of the size of a patient population, there needs to be recognition that in clinical studies of rare disease the same evidentiary hurdles cannot be reasonably met as compared with those in more prevalent disease, and there must be flexibility and scientific judgment applied to each drug application. An analysis of approved

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orphan drugs in the US has shown that the FDA has applied regulatory flexibility during the approval process in a number of cases[17] – although it is unclear how many products were discontinued in earlier phases due to the challenges of drug development in rare diseases. A continued strengthening of the FDA Rare Disease Program could also facilitate progress by further educating and informing individual review divisions who may more frequently deal with higher prevalence diseases, and by this office being more directly involved in the development and review of orphan drug applications.

Bearing in mind the limited opportunity to run large or multiple clinical studies for rare diseases, it is encouraging that 62% of orphan drug applications were submitted in parallel in the US and EU, and that regulatory authorities in different regions are starting to look for opportunities to co-ordinate activities and align thinking on these applications. It would have a major impact on the ability of sponsors to rapidly bring forward therapies for patients suffering from rare diseases if there could be one consistent global assessment of an appropriate regulatory path. Likewise, it is a positive step that initiatives such as the International Rare Disease Research Consortium (IRDiRC), which has representation from research funding bodies around the world, is co-ordinating investments aimed at supporting the approval of novel orphan drugs and diagnostics for rare diseases.

There has been much success since the first orphan drug legislation 30 years ago, and the future is bright for the development of drugs to treat rare diseases. The field of genomics continues to rapidly advance, and in the near future this can be expected to provide further insights into the nature of rare genetic diseases and increased understanding of the link between genotype and specific clinical phenotypes. We are also seeing advances in the development of new therapeutic modalities (eg gene therapy, antisense therapeutics, tissue-engineered products, cell therapies) which have particular utility for the treatment of rare genetic diseases. However, the past 30 years have also provided important learnings about the unique challenges in clinical development for rare diseases, and how these impact on the regulatory process. These should result in further consideration of the application of natural history studies, newborn screening and early diagnosis, surrogate markers of disease, as well as novel clinical trial designs. Most importantly, a key to the future in realising the hopes of patients who suffer from rare diseases and their families is active engagement and alignment on these important issues between key stakeholders in the development of rare disease therapeutics, including industry, regulatory authorities, research funding bodies and patient associations. DDW

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