

Orphans come in from the cold

Rare diseases are less rare than you might think, reports Bea Perks, and finding drugs for them can mean big business

In short

- There is no single, globally accepted definition of a rare disease, each affects between 1 in 1500 and 1 in 2500 of the population
- While patients are few, collectively they represent more than 60 million people in Europe and the US alone
- Findings on rare diseases open new avenues for research into common diseases
- The cost of developing drugs that would generate relatively small sales is offset by the Orphan Drug Act in the US, the Committee on Orphan Medicinal Products in the EU, and mirror organisations worldwide

Political incentives have made investigating rare diseases and the 'orphan' drugs to treat them more attractive to industry



Most of us have heard of Huntington's disease and Tourette's syndrome, but how many are familiar with Duncan's syndrome, Madelung's disease, or Ohtahara syndrome? Many of these so-called rare diseases may not be well known, but they are devastating and – between them – affect tens of millions of people worldwide. Ohtahara syndrome reached the headlines in the UK recently, though you might not have known it, when UK Prime Minister David Cameron's son Ivan died of the disorder in 2009.

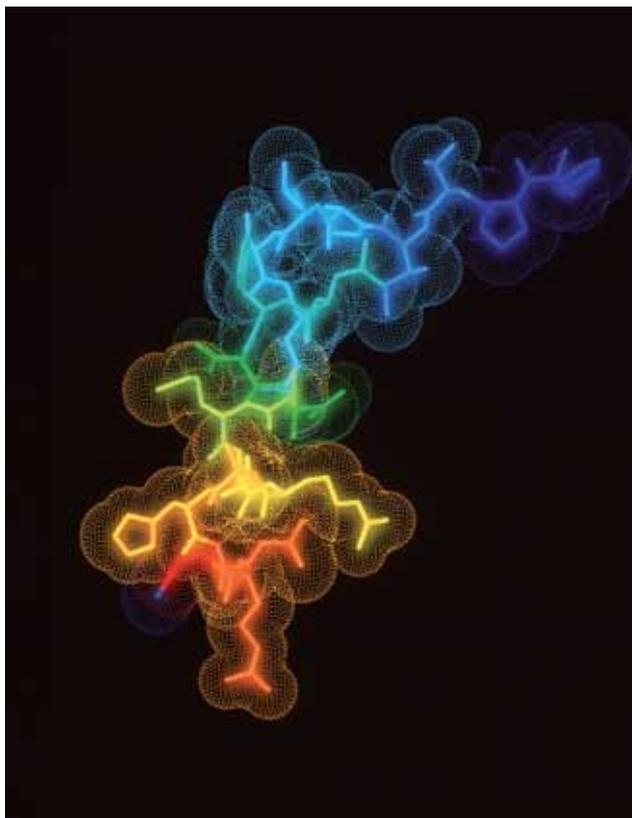
Years ago, it was clear that rare diseases did not affect enough people to attract the attention of the pharmaceutical industry. The cost of developing a drug that would generate relatively small sales made it a distinctly unattractive proposition. But that began to change in the 1980s, when the US Food and Drug Administration's (FDA's) Orphan Drug Act (ODA) and, subsequently, the EU's Committee on Orphan Medicinal Products and mirror organisations around the world, stepped in.

In 1983, lobbying by the National Organization for Rare Disorders (Nord) persuaded the US Congress to pass the ODA. The act serves to encourage pharmaceutical companies to develop drugs for diseases that individually affect less than 200 000 people in the US. Under the law, companies that develop these drugs may sell them without competition for seven years.

Orphan drugs generally follow the same regulatory development path as any other pharmaceutical product, but some statistical burdens are lessened in an effort to maintain development momentum. For example, orphan drug regulations generally acknowledge the fact that it may not be possible to test 1000 patients in a Phase III clinical trial, as there may not even be 1000 patients with a particular disease. Government intervention to create the market for so-called orphan drugs can include tax incentives, enhanced patent protection and financial subsidies for clinical research.

Carrot not stick

Before the ODA stepped in, only 38 drugs were approved in the US specifically to treat rare diseases. From the passage of the ODA in 1983 until May 2010, the FDA approved 353 orphan drugs and granted orphan designations to 2116 compounds. In contrast, in the 10



years running up to 1983, fewer than 10 such products came to market. As of 2010, 200 of the roughly 7000 officially designated orphan diseases have become treatable.

Some critics have questioned whether orphan drug legislation was the real cause of this increase (claiming that many of the new drugs were for disorders that were already being researched anyway, and would have had drugs developed regardless of the legislation), and whether the ODA has really stimulated production of truly non-profitable drugs; the act also received some criticism for allowing some pharmaceutical companies to make a large profit from drugs that have a small market but still sell for a high price.

Although the European Medicines Agency grants market access to its 27 member states, in practice, medicines only reach the market when each member state decides that its national health system will reimburse for the drug. For example, 35 orphan drugs reached the market in Belgium, 44 in the Netherlands, and 28 in Sweden in 2008.

Under the ODA and EU legislation, orphan drugs have been developed to treat conditions including glioma, multiple myeloma, cystic fibrosis, phenylketonuria, snake

Human growth hormone is one of the drugs approved under the US Orphan Drugs Act

'Worldwide sharing of information to boost research is currently hampered by the absence of an exhaustive rare disease classification'

venom poisoning and idiopathic thrombocytopenic purpura.

How rare is rare?

There is no single, globally accepted definition of a rare disease. In the US, the Rare Disease Act of 2002 defines a rare disease as any disease or condition that affects fewer than 200 000 people in the US; about 1 in 1500 of the population. Meanwhile, according to the EU's Orphan Drug Regulation 141/2000, a disease or disorder is defined as rare when it affects fewer than 1 in 2000 European citizens. In Japan, a disease is considered rare when it affects fewer than 50 000 people in Japan; about 1 in 2500. And the list goes on. To add to the confusion, a disease that is rare in one country might be more common in another – particularly if it is genetic, which most rare diseases are.

The European Commission on Public Health defines rare diseases as 'life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them'. The term low prevalence is later defined as generally meaning fewer than 1 in 2000 people. Diseases that are statistically rare, but not also life-threatening, chronically debilitating, or inadequately treated, are excluded from the European definition.

Diagnosis remains a challenge for most patients affected by rare diseases, and most rare diseases still lack dedicated therapies. Recent progress in human genomics and associated research has increased the prospect of developing effective therapies, but there are calls for this to be backed up by effective collaboration of researchers worldwide.

An issue of logistics

The unifying characteristic of rare diseases – their rarity – means that further progress will require increased coordination and renewed efforts among multiple stakeholders worldwide. To this end, research funders, patient advocacy groups, researchers, regulatory agencies and industrial organisations from Europe and the US met in Bethesda, US, in April this year to define a framework of cooperation to work out the causes of most of the 7000 known rare disorders.

According to an early summary report in the run up to the meeting: 'Worldwide sharing of information, data and samples to boost research is



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currently hampered by the absence of an exhaustive rare disease classification [and] standard terms of reference.'

The International Rare Disease Research Consortium (IRDiRC) was launched at the meeting, concluding with the endorsement of objectives to deliver diagnostic tests for all rare diseases by 2020 along with 200 new therapies for patients affected by some of those diseases.

To achieve this, issues like promoting access to existing chemical libraries is under discussion. It will be necessary to draw up legal agreements for testing or repurposing chemical and biological agents; to promote access to screening facilities; and to share the data from molecular screening.

Standing together

This ambitious vision can only be realised through unprecedented cooperation at the international level. 'The members of the consortium are not yet finalised, but will certainly include the EU, US National Institutes of Health, Genome Canada and several national funders,' says Sharon Terry, president and chief executive of Genetic Alliance,

a US-based nonprofit health advocacy organisation. Terry was at the meeting where IRDiRC was launched, and led breakout sessions on data, information and intellectual property sharing. The consortium will next develop the scientific and policy framework to guide research activities. It aims to foster collaboration among stakeholders to systematically explore avenues

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to accelerate the development of diagnostics and therapies for rare diseases. The next meeting of IRDiRC is set for Montreal, Canada, in October 2011. Continued efforts until the next meeting will include strengthening cooperation among consortium members and reaching out to new partners.

Although rare diseases affect only a small proportion of the population, that's still a lot of people. According to a report published last October in the Organisation for Economic Cooperation and Development's newsletter *OECD Observer*: 'While patients are few, collectively they represent more than 60 million people in Europe and the US alone.'

The report's authors, Yann Le Cam and Paloma Tejada of the European Organisation for Rare Diseases (Eurordis), continue: 'policymakers looking to contain long-run healthcare costs are doing themselves a great disservice by ignoring this category of diseases, which affects some 30 million people in the EU-25 alone, a figure equivalent to the combined populations of Belgium, Luxembourg and the Netherlands.' (The EU-25 was the EU before the inclusion of Romania and Bulgaria



Snake venom poisoning is one condition that has benefited under orphan drug regulations

in 2007; the EU currently has 27 member states).

‘Investing in rare diseases makes sense,’ write Le Cam and Tejada, ‘Findings on rare diseases open new avenues for research into common diseases and lead to the development of new therapies and drugs.’

Similarly, a summary report from the IRDiRC notes that rare diseases can serve as models for the development of personalised medicine, requiring personalised and timely diagnosis and treatment for the individual patient. The small number of patients for each rare disease poses significant challenges for collecting data and biological samples and for performing conclusive clinical trials, hence the need for greater international cooperation to optimise scarce resources and accelerate the development of new diagnostic and therapeutic options.

Attracting industry

Big pharma joined the quest to develop drugs to treat rare diseases with the recent arrival of two new research units. February 2010 saw GlaxoSmithKline (GSK) launch a standalone unit specialising in the development and commercialisation of medicines for rare diseases. Five months later, Pfizer announced the launch of its own Rare Disease Research Unit.

Pfizer says it is building on its

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Pfizer’s Rare Disease Research Unit has programmes covering a range of conditions, including pancreatic cancer

existing experience in rare diseases, such as haemophilia (there’s a rare disease we’ve probably all heard of). ‘Pfizer has a long history in discovering, developing and commercialising medicines that treat rare diseases,’ says Jose Carlos Gutiérrez-Ramos, senior vice president of Pfizer’s biotherapeutics research and development. ‘We are hopeful that this research unit will lead to additional new medicines for patients suffering from devastating illnesses for which there is no cure.’

Pfizer has a long-standing presence in rare diseases and has created a Rare Disease commercial group in its Specialty Care business unit, as well as an Orphan and Genetic Disease unit within its research organisation. While work on rare diseases will continue across various parts of the company, these groups will collaborate to serve as a point of contact for potential external partners wishing to explore research collaborations, commercial links or policy initiatives in the field.

The company’s current portfolio of licensed therapies includes treatments for a range of conditions including growth hormone deficiency in children and Turner syndrome (where girls are born without their second X chromosome); pulmonary arterial hypertension; gastrointestinal stromal tumour and pancreatic neuroendocrine tumour; renal

cell carcinoma and mantle cell lymphoma; and haemophilia A and B.

Pfizer’s rare disease pipeline includes late stage programmes in Gaucher’s disease, transthyretin amyloid polyneuropathy, chronic myeloid leukaemia and Ewing’s sarcoma, together with earlier projects in a range of rare diseases including muscular dystrophies, cystic fibrosis and a number of rare cancers.

‘Pfizer welcomes opportunities to collaborate with researchers in leading universities, research centres and other companies to advance projects in rare diseases and share complementary skills and expertise,’ says a company spokesperson. ‘Such collaborations reflect a wider trend to conduct more of our research through external alliances. The company is keen to pursue a strategy of licensing-in technologies or potential medicines from other organisations where we feel our expertise and scale can add value. Previous deals with Protalix [a biopharmaceutical company] and FoldRX [now a Pfizer subsidiary focused on rare diseases] are examples of how we’ve advanced our presence in the rare disease area.’

So is this all about bringing an end to suffering no matter what cost, or might treating rare diseases have some commercial benefit?

GSK makes no bones of the fact that its entry into this therapeutic area forms part of a strategy to deliver more products of value and improve returns in R&D through a focus on areas with a higher probability of success. ‘The risk associated with product discovery and development in rare diseases is generally lower than for other disease areas as disease definitions are very clear and clinical trials tend to be smaller with robust endpoints,’ says Patrick Vallance, GSK’s senior vice president of drug discovery. ‘In most cases the molecular target is known, making it easier for specialised physicians to diagnose patients.’

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Further reading

European Organisation for Rare Diseases (EURORDIS)
www.eurordis.org
National Organization for Rare Disorders (NORD)
www.rarediseases.org
Orphanet database of information on rare diseases and orphan drugs
www.orpha.net
Rare diseases: a hidden priority
<http://bit.ly/raredisease-hiddenpriority>

