Orphan medicinal products

Rare diseases become common for pharma

The pharmaceutical industry's interest in developing orphan drugs for rare diseases has been increasing rapidly over the past few years and looks set to continue into the foreseeable future. One only needs to look at the business models of large multinational companies, typically known for ploughing R&D investment into the next blockbuster, to see that having an orphan drug development programme is now becoming the rule rather than the exception.

A number of approaches have emerged. Some large companies, for example, are partnering with small and medium-sized enterprises (SMEs) that specialise in a specific therapeutic area; others are establishing a rare diseases business arm as a core part of their organisational structure. Many are doing both. As rare diseases become a growing public health priority, public-private partnerships are also sprouting up.

The term 'orphan drug' was coined because the pharmaceutical industry was not willing to develop products for rare diseases, which are life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union (or fewer than 200,000 people in the US). There was simply no way to recoup R&D costs until governments started putting incentives in place to encourage their development. The US was the first to do so in 1983, with the passage of the Orphan Drug Act.

In the EU, incentives are set out in *Regulation (EC) No 141/2000*, which offers orphan drug developers access to the European Medicines Agency's (EMA) centralised review process, free pre-submission meetings, reduced regulatory fees and 10 years of market exclusivity following authorisation. SMEs are eligible for additional benefits: they are exempt from fees for EMA regulatory services such as protocol assistance, inspections and initial applications for marketing authorisation.[1]

In part because of these incentives, SMEs have historically been more focused on orphan drug development than their larger counterparts: in 2012, SMEs accounted for 68% of all EU applications for orphan designation.[2] Often regarded as powerhouses of innovation, SMEs have used their limited resources to their advantage by developing expertise in niches which require relatively small clinical trials.

So why is orphan drug development suddenly so popular amongst the larger companies when economic incentives have been around for years? Clearly there must be a strong business case for going down the rare disease pathway.

Beyond the incentives

SMEs and large pharmaceutical companies have a different business perspective and as such, their approaches to orphan drug development will vary. However, a fundamental element in any company's decision making is its scientific prowess. In the case of orphan drugs this is particularly relevant, as 80% of the 6,000-8,000 rare diseases that exist have identifiable genetic origins.

Scientific advances such as gene sequencing have enabled companies to identify the underlying causes of diseases where this was not possible before. This not only means that it is less costly from a research perspective, but also that it is easier to identify mutations and possibly even qualify new biomarkers that could lead to the development of new therapies or extended indications for existing drugs.

Vertex Pharmaceuticals Inc, for example, is carrying out three Phase 3 label-expansion studies for its cystic fibrosis drug Kalydeco (ivacaftor). The drug is approved in the US and the EU – at a cost of €234,000 per patient annually – for children aged six years and older who have a G551D mutation in the *CFTR* gene (cystic fibrosis transmembrane conductance regulator).[3] The studies for new indications involve children with other *CFTR* gene mutations.[4] Also in Phase 3 is VX-809, a *CFTR* corrector being studied in combination with ivacaftor for CF patients with the F508del mutation.

Despite the scientific advances that have taken place since governments first stepped in with programmes to encourage orphan drug development, there is still a huge unmet medical need "that we can't lose sight of," says Wills Hughes-Wilson, vice president external affairs, chief patient access officer at Swedish Orphan Biovitrum (Sobi). Indeed, there are over 1,000 orphan designations in the EU, but only 78 orphan drugs have been authorised.[5] In the US there is also a significant disparity between the number of orphan designations (over 2,500) and the number of orphan drugs approved (432 indications).[6,7]

As chair of the European Biopharmaceutical Enterprises/EuropaBio Joint Rare Diseases and Orphan Medicinal Products Task Force and a member of the European Commission's Committee of Experts on Rare Diseases (EUCERD), Ms Hughes-Wilson is well placed to provide insight into this evolving sector. In her view, two main drivers of change are the growing international collaboration amongst stakeholders and awareness-raising by patient groups, whose involvement is vital at every stage of the development process.

A look at the statistics may lead to the conclusion that gaining authorisation for orphan drugs is much more difficult than for non-orphan drugs. But Ms Hughes-Wilson, who spoke to *MedNous* in a telephone interview, commented that she does not believe this is necessarily a valid conclusion. "The system encourages companies to apply for orphan designation as early as possible, so many fail. But are the failure rates any larger than with non-orphan drug development? I would say 'no' overall. I wouldn't read anything into that other than it's the nature of drug development," she said.

Comments from the EMA are along the same lines. Not all designated products will reach the market because the designation is given in the early stages of development, an agency spokesperson explained to *MedNous*. "Orphan designation is an enabler procedure with a high success rate (70%), whereas marketing authorisation is more stringent,"

she pointed out.

Orphan designation is just the first regulatory step in the process and to be authorised the drugs are subject to the same standards of quality, safety and efficacy as other drugs. Furthermore, the EMA said: "Due to market exclusivity and significant benefit, marketing authorisations of orphan drugs progressively increase the requirements for subsequent applications, so some sort of plateau for each condition is expected." Companies also face greater challenges with regard to clinical trial recruitment as populations are small and geographically dispersed.

Notwithstanding these and other hurdles, there is still plenty of opportunity to profit from orphan drug development. Trials for orphan drugs require fewer participants and are generally shorter than those for non-orphan drugs. Companies can benefit from testing and marketing a drug on a small scale before rolling it out to a larger population. By starting with narrow indications for a high unmet medical need with little or no competition, they can also secure substantially higher prices.

In search of a healthy pipeline

Exploring niche markets may be especially attractive for large companies under pressure to bolster their pipelines as their blockbusters come off patent. Establishing business units dedicated to rare disease R&D is one way to do this, as is partnering with or acquiring SMEs that are already established in this sector.

GlaxoSmithKline (GSK) is a case in point, with a rare disease division that reported a Q1 2013 sales increase of 12% to £113 million, as well as partnerships with two companies specialising in drugs to treat rare diseases.[8] One partner, the Dutch company Prosensa, has teamed up with GSK to develop its lead compound drisapersen for Duchenne muscular dystrophy. On 6 May 2013, GSK investigator John Kraus told a webinar hosted by the US non-profit organisation Cure Duchenne that the company was encouraged by the results to date from an exploratory Phase 2 study of the drug. Another and more important pivotal study is still ongoing, but it is expected to conclude by the end of this year.

Sanofi is another example of a company that has strategically bought into the rare disease business. In acquiring Genzyme two years ago, it gained a portfolio of orphan drugs, many of which fetch premium prices. In Q1 2013, Genzyme's sales were up by 25.5% to €493 million, in contrast with the performance of the parent company which recorded a decline in group sales for the quarter due to generic competition after Plavix (clopidogrel), Avapro (irbesartan) and Eloxatin (oxaliplatin) came off patent.[9]

Shire has also evolved in the direction of orphan drugs over time through a number of collaborations and acquisitions. It recently announced acquisition of Lotus Tissue Repair, a biotechnology company whose proprietary recombinant form of human collagen Type VII for the treatment of dystrophic epidermolysis bullosa could potentially be a first-in-class systemic therapy for the rare skin disease. According to Shire, the product complements one of its regenerative medicine products – a dermal substitute therapy for the treatment of wounds in patients with epidermolysis bullosa.

On 2 May 2013, the company's new chief executive, Flemming Ornskov, announced a reorganisation that introduces a new rare disease unit as one of the company's five new business areas intended to drive the company's future growth and innovation.[10]

Ms Hughes-Wilson pointed out that the concept of public-private partnerships is an even more recent trend in the orphan drug space. For example, Sobi is involved in findAKUre, an EU-funded project under the Seventh Framework Programme for Research (FP7) that is running clinical studies on the company's nitisinone for the treatment of Alkaptonuria (AKU), a debilitating genetic disease commonly known as 'black bone disease'. Nitisinone is currently marketed in the EU as Ordafin for the treatment of tyrosinaemia type 1. What is noteworthy about findAKUre and other FP7 projects is that the funding now covers clinical development, whereas in the past only pre-clinical programmes could benefit from such opportunities.

The reimbursement hurdle

Pricing and reimbursement decisions fall to the individual EU member states and this has posed some challenges for orphan drugs, whose high prices are unlikely to meet the traditional cost-effectiveness thresholds applied by health technology assessment (HTA) bodies. Ms Hughes-Wilson said: "The small number of patients means you have a small dataset. 'Adaptive' clinical trial designs used to address this may well be valid from a regulatory perspective, but they may not be robust enough for pricing and reimbursement authorities. To avoid hurdles, it's important to bring everyone (including payers) together from the beginning so there are no surprises." She noted that collaborative work in this regard is under way via the European Commission-led Platform on Access to Medicines in Europe.[11]

References

1. EMA, 'Fee reductions for designated orphan medicinal products', 6 December 2012, www.ema.europa.eu.
2. EMA, '2012 Annual Report', April 2013, www.ema.europa.eu.
3. Irish Department of Health, 1 February 2013, www.dohc.ie.
4. Vertex Pharmaceuticals, Q1 2013 results, 30 April 2013, http://investors.vrtx.com.
5. EMA, Fostering Orphan Medicines Development, International Rare Diseases Research Consortium (IRDiRC) conference, Dublin, Ireland, 16-17 April 2013, www.irdirc.org.
6. US FDA, Search Orphan Drug Designations and Approvals, accessed on 5 May 2013, www.accessdata.fda.gov.
7. EvaluatePharma, Orphan Drug Report 2013, April 2013, www.evaluategroup.com.
8. GSK, Q1 2013 results, 24 April 2013, www.gsk.com.
9. Sanofi, Q1 2013 results, 2 May 2013, http://en.sanofi.com.
10. Shire, Q1 2013 results, 2 May 2013, www.shire.com.
11. European Commission, Platform on Access to Medicines in Europe, http://ec.europa.eu.

This article was written by Karen Finn, contributing editor to *MedNous*.