

Executive Summary

Global opportunity

In January 1983 the Orphan Drug Act was signed in the US, amending the Federal Food, Drug, and Cosmetic Act. The Act guaranteed the developer of an orphan product (serving a rare disease affecting fewer than 200,000 individuals in the US) 7 years of market exclusivity following the approval of the product by the Food and Drug Administration (FDA) and tax credits for clinical research undertaken by a sponsor to generate the required data for marketing approval.

Japan and Australia follow US and introduce orphan policies

In October 1993 the Organization for Pharmaceutical Safety and Research (OPSR) started a programme to promote research and development of orphan products in Japan. An orphan product was defined as targeting rare and serious diseases which affect fewer than 50,000 patients in Japan.

Australia's orphan drugs policy was established in November 1997. The orphan drugs programme aims to ensure the availability of a greater range of treatments for rare diseases and allows the Australian Therapeutic Goods Administration (TGA) to use information from the US FDA's orphan drugs programme as part of the Australian evaluation process.

Since the introduction of orphan drug legislation in the US, a total of 1,129 different orphan drug designations have been granted by the Office of Orphan Products Development (by June 2004). Over the 20-year period of orphan drug designations the annual number of designations has risen steadily. Between 1984 and 1993 the average annual number of orphan drug designations in the US was around 43. In the period 1994–2003 the average annual number of orphan drug designations in the US increased by more than 50% to around 66. In 2003 a total of 95 orphan drug designations were awarded.

Almost 250 orphan drugs have received marketing approval in the US

A total of 249 different orphan drugs have received marketing approval in the US (by June 2004). Over the 20-year period of orphan drug designations the annual number of orphan drugs receiving marketing approval in the US has risen and fallen following a peak of 24 in 1996. In 2003 a total of 11 orphan drugs received US marketing approval.

In 2003 the leading orphan drug by worldwide sales revenue was Amgen's Epogen, with sales of \$2.4bn. In 2003, a total of nine orphan drugs generated blockbuster sales revenues in excess of \$1bn. Amgen marketed three different blockbuster orphan drugs in 2003, while Johnson & Johnson marketed two blockbuster orphan drugs through its subsidiaries Ortho-McNeil and Centocor.

European regulations

European regulations are 4 years old

Regulation (EC) No. 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products (COMP) came into force on 27 April 2000 and sets out the key regulatory framework relating to orphan

drug provisions in the EU. The legislation provides Community-level incentives to stimulate the development of medications for diseases where the market provides insufficient incentives.

An orphan drug is defined as intended for the diagnosis, prevention or treatment of a serious disease affecting not more than 5 in 10,000 individuals, or a disease where marketing of a drug would be likely to generate insufficient returns to justify investment. No satisfactory drug must currently be available for the disease, or the orphan drug must be of significant benefit to those receiving currently available treatment.

The designation process for orphan medicines is determined by the COMP and takes a maximum 90 days from application submission to opinion. The Commission Decision follows in a maximum of 30 days.

There are many incentives to encourage the sector

Key incentives available for the development and approval of orphan medicines include free protocol assistance, access to the centralised Community procedure for marketing authorisation with 50% fee reduction, and 10 years of post-approval market exclusivity. Other Community-wide incentives are available by way of research funding and grants, and possible tax incentives at the individual Member State level.

Key protagonists in European orphan drug designation are primarily the COMP, which forms designation opinions and provides protocol assistance, and the European Medicines Evaluation Agency (EMA) and the Commission, which manage the receipt of orphan drug applications and give final designation Decisions, respectively. Other key protagonists include patients groups, industry representatives and learned societies.

European orphan drug legislation includes a number of ambiguities in relation to the definitions of 'significant benefit', 'similar product', 'medical plausibility', 'prevalence' and the use a single or multiple trade names. The interpretation of these regulatory provisions will be further clarified by application over the coming years.

Future funding for orphan medicines in the EU is likely to match current levels with protocol assistance fees waived 100%, and 50% of all other regulatory fees waived. Greater continuity between the US, Japanese and European orphan drug programmes is expected in the future, but any reciprocal agreements for designation are unlikely.

History

Over 200 orphan drugs are recognised

By June 2004 the European Commission had granted 204 orphan drug designations, generating more than double its forecast of 67 designations over the first 3 years following the COMP's inaugural meeting in April 2000. After a surge of activity in 2001, designation rates appear to have flattened out at around 50 new orphan drugs per year.

Out of a total of 365 orphan drug applications submitted, the COMP gave 220 positive opinions and five negative opinions, while a further 102 applications were subsequently withdrawn. There are no appeals against negative opinions currently ongoing.

Of the total of 204 orphan drug designations, 33 different indications have received more than one designation, with the most frequently cited indications being the treatment of cystic fibrosis, glioma and

multiple myeloma. A total of 133 different orphan indications are shared amongst 179 different compounds, with 15 different compounds designated for more than one orphan indication.

Over 140 companies are involved in orphan drugs Of the total of 204 orphan drug designations, 42 different sponsor companies have received more than one drug designation, with the most frequently cited companies being Genzyme, Orphan Europe and Novartis. A total of 141 different sponsor companies are shared amongst 179 different compounds, with six different compounds designated for the same indication by more than one sponsor.

The average time from designation to market authorisation is 20 months As of June 2004, 15 orphan drug designations had been followed by a successful market authorisation in the EU, including two orphan drug indications for Novartis's Glivec. Of the 14 different orphan drugs approved for marketing, 10 received approval in 'exceptional circumstances' and are required to submit post-marketing trial data. The average timeline between designation and market authorisation is 20.8 months, ranging from just 6.1 months to 30.8 months.

Of the 204 orphan drug designations to date, 38 designations involving 30 different compounds were given for extended indications and/or formulations for compounds currently or previously approved for non-orphan indications. Special licences for use and reimbursement prior to market authorisation were given to nine orphan drug designations involving seven different compounds. The prevalence rates for orphan drug designations ranged from as low as 190 (equivalent to less than 0.01 per 10,000) to as high as 185,000 (equivalent to 4.9 per 10,000).

Leading orphan drugs

Glivec is the star performer Fabrazyme is one of a number of orphan drugs making up Genzyme's portfolio of marketed and pipeline drugs. It currently generates sales in excess of \$100m and competes effectively against TKT's Replagal, following orphan drug exclusivity in the US.

Trisenox holds the potential to generate sales for Cell Therapeutics in both orphan and non-orphan markets. However, without a significant clinical benefit in wider oncology indications, it is unlikely that Trisenox will grow to generate annual sales far in excess of \$100m.

Zavesca fills Actelion's marketed orphan drug portfolio as a result of a long-term licensing agreement originally signed with Oxford GlycoSciences. However, the drug is unlikely to generate sales in excess of \$100m in the future.

Carbaglu is marketed to one of the smallest patient populations of all orphan drugs by Orphan Europe, forming part of a specialised orphan drug business model.

Busilvex is a new orphan drug made available as part of Pierre Fabre's specialist product portfolio.

Genzyme's strong portfolio in orphans Aldurazyme is one of a number of orphan drugs making up Genzyme's portfolio of marketed and pipeline drugs. It has the potential to generate future annual sales in the region of \$100m.

Novartis's Glivec is the star performing orphan drug, generating annual global sales in excess of \$1bn. The drug also has huge potential in a number of non-orphan disease indications.

Pfizer's Somavert is approved for a limited genetic orphan disease patient population. The drug is unlikely to generate annual revenues in excess of \$100m in the future.

Tracleer is Actelion's key product and has the potential to be successfully launched to treat both orphan and non-orphan diseases. The drug already generates annual sales in excess of \$100m and is likely to grow in the future.

Patient trial sizes are very small The approval of Fabrazyme, Replagal, Trisenox and Zavesca involved pivotal trials consisting of fewer than 100 patients. Only Glivec presented significant trial data comprised of more than 1,000 clinical patients. The majority of orphan drug approvals were in 'exceptional circumstances', where long-term efficacy and safety will need to be confirmed following wider use. Novartis, TKT, Actelion, Cell Therapeutics and OGS are involved in significant trial activity for the development of their orphan drugs in various sub-populations and indications.

There has been considerable variation in the length of time elapsed between a company's initial application and the European Commission's final approval for orphan drugs. The average timeline has been around 21 months, ranging from Glivec's 8 months for its first indication in adult Philadelphia-chromosome-positive chronic myeloid leukaemia (Ph+ CML), excluding newly diagnosed patients, to Ventavis's 33 months. This range is due to factors such as the quality and range of data provided to the CPMP by the companies, issues with the quality of the product being manufactured or with the site inspection of the manufacturing plant.

Marketing approval times vary greatly Glivec's initial approval followed an expedited review characterised by a high-quality application and an in-person response to any outstanding issues. Widening of the initial indication for Glivec occurred 6 months and 10 months, respectively, after initial approval. A high price point has allowed Glivec to benefit greatly from the increases in patient numbers derived through its initial and subsequent indication approvals.

Pharmacia/Pfizer's Somavert was delayed in its application for marketing, with pivotal trial data published only 6 months after commencing the application procedure. Further delays followed, with three separate requests for clarification over a number of outstanding issues and delays in receiving the company's responses. Eventually, safety concerns and trial limitations meant that the drug was indicated in a smaller patient population, with a caveat added to the summary of product characteristics (SPC) to monitor pituitary tumour growth.

The main business strategies can be grouped by key groupings, including company, designation, indication and development strategies. When ranked by historical uptake, global and multiple orphan drug strategies are most prevalent, followed by high-indication-prevalence and early-stage-designation strategies.