Orphan medicinal products

Putting a value on drugs for rare diseases

Rare diseases have been identified as a priority area for the European Union within the framework for action in the field of public health. On 16 December 1999, the EU adopted *Regulation (EC) 141/2000,* which outlines incentives for research and development in the area of rare diseases. This regulation has been an effective tool for stimulating market access of new medicines for rare and ultra rare diseases. However, getting these products onto the market where they can be administered to patients in need has been a surprisingly slow process.

In this article we argue that the process of delivering orphan medicines to patients needs to be improved, starting with how patients are recruited for clinical trials, through to the criteria that health technology assessment (HTA) bodies use to decide whether to reimburse these medicines or not.

Background

The term orphan medicinal product has a specific meaning in EU law. *Regulation (EC)141/2000* defines these products as medicines which are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EU. Or they may be medicines intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition. In either case, the medicine must address an unmet medical need.

The regulation outlines specific incentives for pharmaceutical companies in order to encourage them to develop orphan drugs which otherwise would not be developed because of the lack of a return on the sponsor's investment. These include reduction in the fees which the European Medicines Agency charges for assessing marketing authorisation applications. If an orphan medicinal product is approved, the developer is also entitled to 10 years of market exclusivity, protecting the product against competition from generics as well as from 'similar' products.

A special EMA committee, the Committee for Orphan Medicinal Products (COMP), assesses whether a product qualifies for an orphan designation. If assessed positively, the European Commission may grant an 'orphan designation' for the medicinal product.

Since the orphan regulation came into effect more than a decade ago, the COMP has issued 1,000 positive opinions on orphan designation. To put this into perspective: there are believed to be between 5,000 and 8,000 different rare diseases affecting an estimated 29 million people in the EU.[1]

Orphan designation is the first step. Like other medicines, however, orphan-designated medicines must also pass the EMA's criteria for quality, safety and efficacy and get a marketing authorisation before they can be put onto the market. For a variety of reasons, this means that the number of approved orphan medicines is much smaller than the number of designated products. To date, the EMA has approved 70 orphan drugs and granted a marketing authorisation. The approved drugs correspond with 62 documented rare diseases.

While the EU legislation has been successful in stimulating new orphan drug research, clinical development is still a difficult area for many companies. Summing up the situation, Françoise Grossetête, a member of the European Parliament, who was *rapporteur* for the orphan medicinal product regulation, noted that "many patients still face delays in access to treatment, and many of these diseases remain impossible to treat".[2]

Because orphan diseases are by definition rare, developers initiating clinical trials have to recruit patients over a wide geographical area. This is even more true for the so-called 'ultra-rare' diseases which affect even smaller populations than 'rare' diseases covered by EU legislation. 'Ultra rare' diseases are not defined by the EU legislation. But the UK's National Institute for Health and Clinical Excellence (NICE) does have an approach, which is to define 'ultra-rare diseases' as conditions with a prevalence of less than one in 50,000.

In theory, orphan medicines should be ideal candidates for centrally-administered multi-site clinical trials. Clinical trials should be performed where the patients are located and should be authorised quickly, incorporating both the scientific and ethical considerations. Timely and efficient decision-making would increase the attractiveness of Europe as a site for trials and facilitate academic work in the area of incremental research such as line extensions. However, under the current *Clinical Trials Directive*, this has been very difficult given the directive's requirement for country-by-country approvals for clinical trials.

But now the European Commission is proposing to revise this legislation to make trial approvals simpler and less costly (*COM 2012 369*), which should have an impact for the area of rare diseases.[3]

Achievements of the regulation

The achievements of the orphan regulation are clear to see. Among the 70 approved medicines are new treatments for paroxysmal nocturnal haemoglobinuria, a life-threatening condition characterised by a low red-blood count; Gaucher disease, an inherited enzyme disorder; mucopolysaccharidosis type 1, a severe progressive skeletal disease; and cystic fibrosis, a genetic disorder that can severely impair the lungs and digestive system.

The European Commission approved orphan-designated Kalydeco (ivacaftor), a new treatment for cystic fibrosis, on 23 July. This is the first approved cystic fibrosis medicine that treats an underlying cause of the disease (please see related article on page 11 of this issue).

Despite these clear successes, the uptake of orphan medicines at a national level has been slow. This is due to concerns by some payers about the cost of orphan medicines, at a per-patient level, and in aggregate.[4] There are not many studies documenting the impact of orphan medicine reimbursement on national health budgets. Among those

that have been published however is an article by Carina Schey and colleagues in the *Orphanet Journal of Rare Diseases* and entitled, 'Estimating the budget of orphan medicines in Europe: 2010-2020'. According to this article, the reimbursement of orphan medicines represented about 3.3% of national healthcare budgets in 2010. This is expected to rise to a maximum of 4.6% by 2016.

The European Organisation for Rare Diseases, Eurordis, has come to the same conclusion, noting that the "economic criticism formulated against orphan drugs lacks any real basis and the costs involved are not going to blow out of proportion".

In this context it should also be noted that the reason the orphan regulation was introduced was the fact that companies couldn't justify investing in medicines for small patient populations because of the small expected return on their investment. If therefore a way has been found to stimulate investment in these medicines, it should follow that they should be reaching patients.

Health technology assessment

Health technology assessment is an evolving phenomenon used by payers. At the moment it appears that the criteria which HTA bodies use to assess orphan medicines for reimbursement has not been tailored to the specific characteristics of rare diseases. In many cases, newly approved orphan medicines are filling a medical need where there is no other approved medicine. If this is the case, then how do the HTA bodies measure the comparative effectiveness of the new drug?

One recent case from Germany illustrates this problem. On 15 December 2011, the German Institute for Quality and Efficiency in Health Care (IQWiG) ruled that the orphan medicine Esbriet (pirfenidone) had no proven added benefit for patients compared with best supportive care. Esbriet was approved for marketing on 28 February 2011 for the long-term treatment of patients with idiopathic pulmonary fibrosis, a disease that causes scarring of the lungs. The regulator approved the drug because it addressed an unmet medical need. However in its assessment, the IQWiG said the benefit could not be confirmed.

The IQWiG opinion was later overruled by Germany's G-BA (*Gemeinsamer Bundesausschuss* or Federal Joint Committee), which is the decision-making body in the new German HTA procedure. The G-BA said Esbriet offered patients 'unquantifiable' added therapeutic benefit.[5] The G-BA further stated that this therapeutic benefit did not have to be proven, in the case of an orphan medicine, if the yearly turnover of the product did not exceed €50 million in Germany, which is completely in line with the German law.

While this decision does not address the specific characteristics of orphan medicinal products, it does at least give developers an exemption from the usual document requirements connected with a health technology assessment in Germany. Such an approach isn't yet taken in other EU countries, even in the UK where health technology assessment is relatively developed for some parts of rare diseases.

At European level, there are at least three initiatives underway to harmonise health technology assessment decision-making. The first initiative aims to encourage the member states to exchange information, including data about how a drug performs on the market. This is taking place within the Working Party for European Collaboration Towards a Common Scientific Assessment of the Clinical Added Value for Orphan Drugs.

The second initiative, which has been launched by the European Commission and relevant stakeholders, aims to define the concept of 'coordinated real-life access' for use in pricing and reimbursement. This approach is being called the Mechanism of Coordinated Access to Orphan Drugs.

The third initiative, EUnetHTA, is a network of government-appointed organisations and others that work in the area of health technology assessment. The aim is to exchange information on best practice. This network could have relevance for assessing orphan medicinal products as well.

Conclusion

While European legislation has proven to be an effective tool for fostering research and development into new therapies to treat rare diseases, major challenges exist at the member state level. One of the biggest obstacles is health technology assessment bodies, which aren't taking sufficient account of the specific characteristics of orphan medicines when making decisions on reimbursement. Health technology assessment methodology and practice also differs across the member states and companies are confronted with various different dossiers to be submitted for HTA bodies. To ensure patient access, different methods and approaches to defining value of orphan and ultra-orphan therapies must be considered. For example, could the German exemption from certain health technology assessment requirements for products with revenues below a specific threshold be applied elsewhere?

In addition, the European Commission's proposal on a revision of the *Transparency Directive 89/105/EEC* of 1 March 2012 is another opportunity to help orphan medicinal products reach patients. The proposal says that Member States shall not re-assess information on which a marketing authorisation has been based, including the product's quality, safety, efficacy or bioequivalence. It is essential that the orphan designation is included in this clause so that national health technology assessment bodies cannot re-assess decisions already taken by the European Commission.

References:

1. 'Estimating the budget of orphan medicines in Europe: 2010-2020', Schey C., Milanova T. and Hutchings A., *Orphanet Journal of Rare Diseases,* p.2, 6:62, 2011. www.ojrd.com.

2. Ms Grossetête was speaking at the EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicines on 4 June 2010.

3. Commission Proposal (*COM(2012) 369*), is available at http://ec.europa.eu/health/files/clinicaltrials/2012.

4. Ibid, 'Estimating the budget of orphan medicines in Europe: 2010-2020', Schey C. et al.

5. *Scrip Intelligence*, "Intermune's orphan Esbriet escapes reference pricing in Germany," 16 March 2012.

This article was written by Dr Alexander Natz, Director General, European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) in Brussels, and Marie-Geneviève Campion, economic adviser, EUCOPE.