Market Access for Orphan Drugs: assessing the global landscape

A FirstWord Overviews Report
Market Access for Orphan Drugs: assessing the global landscape

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### Access to medicines for rare diseases in the US

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Executive summary

By definition, a rare disease affects a small number of people. However, multiply this small number by around 7,000 rare diseases and the total number of patients with rare diseases becomes significant. In fact, rare diseases affect millions of people around the world.

The unmet medical need of patients with rare diseases and the desire to promote research into medicines to treat them has officially been on government agendas for more than 30 years, with the US being the first to approve legislation specifically for orphan drugs in 1983. Since then, the profile of orphan drugs has been raised, with various incentives available for drug development, including accelerated approval and market exclusivity. In 2011, the International Rare Diseases Research Consortium was launched, to foster international collaboration in rare diseases. Its aims are to be able to diagnose most rare diseases, and develop 200 new therapies for rare diseases by 2020.

Scientific advances and technological innovation are also contributing to a growing knowledge pool on rare diseases. The development of biomarkers and clinical diagnostics is making it increasingly possible for companies to develop targeted therapies that address the needs of specific disease sub-groups. These have become particularly significant in the development of therapies for rare forms of cancer, but are also being used for specific non-oncology indications.

The potential rewards for pharmaceutical companies are clearly considerable, with analysts predicting that orphan drugs could account for more than 15 per cent of the global pharmaceutical market by 2018. But, in the current economic climate, when healthcare budgets are stretched and payers need to balance the needs of the majority with the high cost of orphan drugs, what strategies are being employed to ensure patients with rare diseases have access to much-needed treatments?

This report examines the regulatory environment for orphan drug development, as well as some of the challenges companies will face on the route to market, and some of the schemes employed to enable patients to gain access to treatment.
How rare is an orphan disease?

Orphan diseases can be generally defined as rare conditions that affect small numbers of patients. There are regional variations in the precise definition of what constitutes an orphan disease, and when orphan drug designation is available.

- In the US, the Food and Drug Administration (FDA) defines a rare disease or disorder as one that affects fewer than 200,000 people within the US. Orphan drug status may also be available where the disease affects more than 200,000 people, but only when the costs of developing and marketing the drug are not expected to be recovered.¹

- In the EU, an orphan disease is defined as a life-threatening or chronically debilitating disease affecting not more than five people in every 10,000. Orphan drug designation is also possible if it is "unlikely that the marketing of the medicine would generate sufficient returns to justify the investment needed for its development."²

- In Japan, “rare and intractable diseases” have unknown aetiology, affect fewer than 50,000 people in total, have no effective treatment, and present a major financial and psychological burden.³

- In Australia, the prevalence of an orphan disease is considered to be 2,000 people or fewer in the Australian population.⁴ According to the Therapeutic Goods Regulations, an orphan drug must be intended to treat, prevent or diagnose a rare disease; or not commercially viable to supply to treat, prevent or diagnose another disease or condition.⁵

¹ FDA. Developing Products for Rare Diseases & Conditions. Retrieved from: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm
# Table 1: Orphan disease definitions around the world

<table>
<thead>
<tr>
<th>Country</th>
<th>Definition of a rare disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Affects fewer than 200,000 people within the US</td>
</tr>
<tr>
<td>EU</td>
<td>Affects fewer than 5 in 10,000 people</td>
</tr>
<tr>
<td>Japan</td>
<td>Affects fewer than 50,000 people and has no effective treatment</td>
</tr>
<tr>
<td>Australia</td>
<td>Affects no more than 2,000 people in Australia</td>
</tr>
<tr>
<td>Canada</td>
<td>Affects fewer than 5 in 10,000 people</td>
</tr>
<tr>
<td>China</td>
<td>Affects fewer than 1 in 500,000 people or has a neonatal morbidity of less than 1 in 10,000 (proposed classification)</td>
</tr>
<tr>
<td>South Korea</td>
<td>Affects fewer than 20,000 people or an appropriate treatment or medicine has yet to be developed</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Affects fewer than 1 in 10,000 people, has a genetic origin and is difficult to diagnose and treat</td>
</tr>
<tr>
<td>Brazil</td>
<td>Affects fewer than 1 in 10,000 people</td>
</tr>
<tr>
<td>Russia</td>
<td>Affects fewer than 1 in 10,000 people</td>
</tr>
<tr>
<td>India</td>
<td>Rare diseases affect a population of 72.6 million (from a total population of 1.2 billion)</td>
</tr>
</tbody>
</table>

*Source: FirstWord elaboration of data from Orphanet,*<sup>6</sup> *Interfarma,*<sup>7</sup> *and Song, P. et al 2012,*<sup>8</sup> *Rare Diseases India*<sup>9</sup>

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9 Rare Diseases India. Estimated rare diseases population in South Asian countries. Retrieved from: [http://www.rarediseasesindia.org](http://www.rarediseasesindia.org)
There are around six to eight thousand diseases classified as “rare”, according to one definition or other, and advances in genetic research contribute to a growing number of new diseases being identified. Orphanet, an EU-based database of information on rare diseases and orphan drugs, provides an inventory of more than 6,000 diseases.

While the number of patients affected by each rare disease may vary from just a handful to around 245,000, EURORDIS estimates that rare diseases may affect 30 million people in the EU. The prevalence of most rare diseases is extremely low, however. Orphanet provides regularly updated reports concerning the prevalence distribution of rare diseases. This type of data is not available for the US, although it is likely to be similar in the two regions.

The most common orphan diseases are genetic conditions, which are often chronic and life threatening. EURORDIS suggests 80 per cent of rare diseases are of genetic origin. Other rare diseases are the result of bacterial or viral infections, allergies or environmental causes. They may be diseases that are common in other regions but rare in others, or they may be small, targeted populations identified from within larger ones, such as genetically distinct populations in oncology.

Despite the large number of identifiable rare diseases, just 250 have a coding in the 10th version of the International Classification of Diseases (ICD) compiled by the World Health Organization (WHO). In June 2009, the Council of the European Union published a Recommendation on “an action in the field of rare diseases” (2009/C 151/02), which supports improved codification for rare diseases in the 11th version of the ICD. According to the WHO, ICD-11 will be presented to the World Health Assembly in 2015.
Orphan drug policy and regulation

The US was the first country to introduce specific legislation for orphan drugs, with the Orphan Drug Act in 1983. Since then, regulations have been introduced in several countries around the world, including the EU (2000), Japan (1993), Australia (1998) Taiwan (2000) and South Korea (2003). A number of other countries, including Canada, have orphan drug policies in development.

Table 2: Orphan drug policy and regulation around the world

<table>
<thead>
<tr>
<th>Country</th>
<th>Legal framework</th>
<th>Regulatory authority</th>
<th>Orphan drugs policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Orphan Drug Act (1983)</td>
<td>FDA, Office of Orphan Products and Development</td>
<td>Policy focused on encouraging R&amp;D. There is no specific policy for access to orphan drugs, although most are covered by health insurance and/or patient access schemes.</td>
</tr>
<tr>
<td>EU</td>
<td>Regulation (CE) 141/2000</td>
<td>European Medicines Agency (EMA), Committee of Orphan Drug Products</td>
<td>There is a unified policy of incentives for R&amp;D. Policies for access to orphan drugs are created at national level.</td>
</tr>
<tr>
<td>Australia</td>
<td>Orphan Drug Policy (1998)</td>
<td>Therapeutic Goods Administration</td>
<td>The focus is on access to orphan drugs; there are no incentives for R&amp;D.</td>
</tr>
<tr>
<td>Canada</td>
<td>Orphan drug framework in development</td>
<td>Health Canada</td>
<td>The focus is on access to drugs and there is a list of medications funded by the government. There are no incentives for R&amp;D.</td>
</tr>
<tr>
<td>China</td>
<td>Not yet established</td>
<td>China Food and Drug Administration (CFDA)</td>
<td>There are government incentives and a mechanism in place for quick approval of orphan drugs. There is also a bill in Congress that establishes mechanisms for reimbursement of orphan drugs.</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Rare Disease Control and Orphan Drug Act (2000)</td>
<td>Department of Health</td>
<td>Reimbursement is available for patients with rare diseases.</td>
</tr>
</tbody>
</table>
### Table 2: Orphan drug policy and regulation around the world continued

<table>
<thead>
<tr>
<th>Country</th>
<th>Legal framework</th>
<th>Regulatory authority</th>
<th>Orphan drugs policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Law No. 9.782/99 (not specific to orphan drugs)</td>
<td>ANVISA</td>
<td>Orphan drugs have priority analysis from market entry. Protocols exist for a number of rare diseases but no coherent national policy yet.</td>
</tr>
<tr>
<td>Mexico</td>
<td>244 BIS, Gen. Congress (2012)</td>
<td>Federal National Commission for Protection against Health Risks (COFEPRIS)</td>
<td>Laws are being established to make orphan drugs available and foster their development.</td>
</tr>
<tr>
<td>Chile</td>
<td>Bill drafted in September 2011 awaits approval in Congress.</td>
<td>National Medicines Agency (ANAMED – Agencia nacional de medicamentos)</td>
<td>There are principles that guarantee healthcare, but specific bills remain pending.</td>
</tr>
<tr>
<td>Colombia</td>
<td>Ley 1392, Congress of the Republic (2010)</td>
<td>National Institute of Food &amp; Drug Safety (INVIMA - Instituto Nacional de Vigilancia de Medicamentos y Alimentos)</td>
<td>Legislation provides full assistance to patients, but does not deal with access to orphan drugs in particular.</td>
</tr>
<tr>
<td>Russia</td>
<td>Fundamentals of Protection of Public Health (2011)</td>
<td>Federal Service on Surveillance in Healthcare &amp; Social Development (Roszdravnadzor)</td>
<td>Procedure for the drug supply and funding for treatment of orphan diseases defined in legislation. However, funding for orphan drugs relies on regional health authorities (not available from the federal budget). Very few medications are on the reimbursement list.</td>
</tr>
<tr>
<td>India</td>
<td>n/a</td>
<td>Drug Standard Control Administration</td>
<td>No policy for R&amp;D of orphan drugs; very little reimbursement and out-of-pocket costs means the use of expensive orphan drugs is not feasible. There are calls for an orphan drugs policy, similar to that in the US.</td>
</tr>
</tbody>
</table>

Source: FirstWord elaboration of data from Orphanet, Interfarma, Song, P. et al 2012, and various regulatory agencies

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Figure 1: Orphan drugs policy around the world

Source: Pharma Pricing & Market Access Outlook Europe 2013

Regulation in the US

The Orphan Drug Act (ODA) was introduced in January 1983 by Public Law 97-414, which amended the Federal Food, Drug, and Cosmetic Act. The ODA provided the first framework of regulations specifically to facilitate the development of drugs for rare diseases and conditions. The ODA outlined the provision of incentives for orphan drug development in the public interest.

The definition of an orphan drug that was introduced by the ODA in 1983 referred to a rare disease as “any disease or condition which occurs so infrequently in the US that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such a drug”.\(^1\) However, it became clear that application of this definition was too difficult and it has since been quantified, specifying that a rare condition affects fewer than 200,000 people in the US; or if it affects more than 200,000 people in the US, “there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug”.\(^2\)

Orphan drug designation may be granted for a product that aims to treat an “orphan subset” of a non-rare disease or condition. In its June 2013 Final Rule, the FDA clarified an “orphan subset” as meaning that “use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.”\(^3\)

\(^1\) Public Law 97-414 (1983, January 4). Orphan Drug Act, section 526(a)(1)
According to the amended regulations, an orphan drug designation may be requested for "a previously unapproved drug, or of a new use for an already marketed drug." In addition, it is possible for a sponsor of "a drug that is otherwise the same drug as an already approved drug [to] seek and obtain orphan drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug."

All foreign sponsors that seek orphan drug designation must name a permanent resident of the US as their agent, “upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the sponsor.” Name and address details of the agent must be supplied to the FDA's Office of Orphan Product Development (OOPD).

The FDA publishes a monthly-updated cumulative list of drugs that have been granted orphan drug designation. In its Final Rule, the FDA has amended section 316.28 to state that “this publicly available posting will include whether a drug no longer has designation and, if so, as of what date.” Previously, this information was only deducible from the quarterly produced hard copy of the list, where a drug that was no longer designated was excluded. From the effective date of this ruling, the FDA will indicate that a drug is no longer designated, but it will not specify a reason; this could be voluntary withdrawal or revocation by the Agency. The Agency’s reason for not publishing full information is that this “mitigates any competitive concerns”.

21 Op cit
Figure 2: FDA orphan drug designation procedure

Sponsor submits request for orphan drug designation to FDA, to include information that verifies orphan drug status.

If anything is inaccurate or incomplete, FDA sends deficiency letter.

Foreign sponsors must name a permanent resident of US to act as agent.

FDA grants orphan drug designation.

FDA refuses orphan drug designation.

Drug added to FDA’s monthly publication of cumulative list of designated orphan drugs.

Source: FDA
Regulation in the EU

In the EU, orphan designation is based on the criteria laid down in Regulation (EC) No 141/2000, which was published in the Official Journal of the EC on January 22, 2000. The legislation is based on the premise that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients, and provides incentives for the pharmaceutical industry to develop orphan medicinal products. To be eligible for incentives, products should be designated through the orphan designation procedure.

An orphan medicine is defined as one that is 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 community when the application is made. Orphan designation is also possible where a company can prove that without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment. Where alternative treatments for a particular condition exist, it must be established that the new product will offer significant additional benefit for patients.

The legislation set up the Committee for Orphan Medicinal Products (COMP), under the auspices of the European Medicines Agency (EMA). Through the COMP, the EMA is responsible for reviewing orphan designation applications from companies or other sponsors who intend to develop orphan drugs for rare diseases. The EMA provides free pre-submission meetings to help sponsors to prepare orphan designation applications, as well as protocol assistance on the development of orphan medicinal products.


Following orphan designation, the COMP works with the Committee for Medicinal Products for Human Use (CHMP) during the review and approval stages of the process. Additional legislation relevant to many orphan drugs is the regulation on advanced therapy medicines [(EC) 1394/2007], which came into force on December 30, 2008. This legislation introduced the Committee for Advanced Therapies (CAT), which is responsible for the evaluation of gene therapy, somatic cell therapy and tissue-engineered products.

Since the introduction of orphan medicinal products regulation, the EMA has undertaken continuous policy development around rare diseases. Rare diseases
were identified as a priority within the EU Health Program 2008-2013,\textsuperscript{24} leading to a Commission Communication on rare diseases,\textsuperscript{25} which proposed the adoption of Council Recommendations. The Council recommended strategies for Member States, which included:

- Putting in place national action plans for rare diseases;
- Establishing mechanisms for definition, codification and inventory of rare diseases and production of good practice guidelines;
- Encouraging research on rare diseases, including cross border cooperation; and
- Setting up national centres of expertise and European reference networks.

A [European Union] Committee of Experts on Rare Diseases (EUCERD) was established by Decision 2009/872/EC in November 2009 to bring together the specialised bodies in Member States. The committee comprises one representative per Member State from ministries or government agencies responsible for rare diseases, representatives of patients' organisations, the pharmaceutical industry and rare disease experts.\textsuperscript{26} The Committee provides input into EC actions in the field of rare diseases.

\textsuperscript{25} Communication from the Commission to the European parliament, the Council, the European Economic and Social Committee and the Committee of the Regions – On rare diseases: Europe’s challenges. Retrieved from: \url{http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf}
\textsuperscript{26} EC Public Health, Rare Diseases. Retrieved from: \url{http://ec.europa.eu/health/rare_diseases/experts_committee/detailed/index_en.htm}
International harmonisation

International collaboration between regulatory agencies, industry and patient advocacy groups has resulted in harmonisation of certain aspects of orphan drug regulation and policy, in particular with respect to orphan drug designation and assessment:

- The EMA\(^{27}\) and the FDA have an information-sharing scheme for orphan drugs under their confidentiality arrangement. This arrangement, which has been in operation since 2003, allows the confidential exchange of information between the US and EU as part of their regulatory and scientific processes.

- The EMA and FDA have developed common procedures for applying for orphan medicinal product designation, and a joint application form is available for submission to the EMA and the FDA's OOPD. In the interest of clarification, the regulators note that the term “medicinal product” is used on the application document in place of the word “drug”, which is used in the FDA Orphan Drug Regulations (21 CFR Part 316) without any intention to alter its regulatory meaning.\(^{28}\)

- The EMA and FDA have agreed to accept the submission of a single annual report from sponsors of orphan products (drugs and biologics) designated for both the US and the EU.

- The EMA encourages sponsors to consider coordinating the timing of protocol assistance from the Agency with a request for scientific advice from the FDA. Parallel scientific advice with the FDA is available for orphan drugs.\(^{29}\)

- The EMA also collaborates with Japan’s MHLW on issues related to orphan drugs.

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In addition, the EMA works with organisations representing patients with rare diseases through the European Organisation for Rare Diseases (EURORDIS).

However, a recent FirstWord Dossier report\(^{30}\) highlighted a pressing need to encourage harmonisation between the EU and US with respect to clinical trial design. During an interview for the report, Theresa Heggie, senior vice president of global commercial operations for Shire Human Genetic Therapies suggested, “If there was greater harmonisation it would speed up the availability of treatments of orphan diseases enormously,” because it would alleviate the need for separate trials.

EU national rare disease policies

France

*First national rare disease plan*

France was the first EU country to set up a comprehensive rare disease plan with allocated funding. The National Rare Disease Plan 2004-2008 formed part of the August 2004 law relating to public health policy. Through ten strategic priorities, the aim of the plan was to “ensure equity in the access to diagnosis, to treatment and to provision of care for people suffering from a rare disease”.\(^{31}\) The key priorities set out in the plan were to:

1. Increase knowledge of the epidemiology of rare diseases, partially enabled through the creation of a health surveillance institute, the Institut de veille sanitaire (InVS). The InVS has responsibility for coordinating the epidemiological surveillance of rare diseases in France.

2. Recognise the specificity of rare diseases, with the intention of assisting patients with rare conditions in gaining reimbursement for certain medicines and medical expenses. Under the plan, the Haute Autorité de santé was specifically asked to: “Deliberate with the aim of ensuring that rare diseases are reimbursed

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30 Effective sales and marketing strategies for orphan drugs (2012, June). More information on this report is available from the FirstWord website: [http://www.firstwordplus.com/effective_sales_and_marketing_strategies_for_orphan_drugs.do](http://www.firstwordplus.com/effective_sales_and_marketing_strategies_for_orphan_drugs.do)

within the framework of the procedure for long-term disorders, when these
diseases are serious, debilitating and costly.”

3. Develop information for patients, health professionals and the general public
concerning rare diseases, including making Orphanet the reference portal for
rare diseases, and improving the information on rare diseases available by
telephone through the Maladies Rares Info Service
and the Fédération des
maladies orphelines.

4. Train professionals to better identify them.

5. Organise screening and access to diagnostic tests.

6. Improve access to treatment and the quality of healthcare provision for patients.
Initiatives included the certification and funding of more than 100 national
centres of reference for rare diseases.

7. Continue efforts in favour of orphan drugs, including the continued exemption
for the promoters of orphan drugs, with respect to taxes and other payments
due by the pharmaceutical industry and destined for the national health
insurance and the AFSSAPS; the inclusion of orphan drugs on a list of
innovative and expensive health products in the context of the reform of the
“activity rate”, an initiative intended to allow the distribution of orphan drugs as
soon as they have their marketing authorisation; and the continuation of the
“autorisation temporaire d’utilisation” (ATU) scheme, which allows drugs that
do not have marketing authorisation, but which are presumed to be efficient
and of an acceptable level of safety, to be made available to patients with
rare diseases.

8. Respond to the specific needs of accompaniment of people suffering from rare
diseases and develop support for patients’ associations.

9. Promote research and innovation on rare diseases, notably for treatments.

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32 Op cit, 11.

33 More information is available on this service from the organisation’s website, in French: [http://www.maladiesraresinfo.org](http://www.maladiesraresinfo.org)

10. Develop national and European partnerships in the domain of rare diseases, such as the Plateforme Maladies Rares (rare diseases platform), which brings together a number of French and European organisations, including:

10.1. Alliance Maladies Rares, a French collective of 135 patients associations;
10.2. EURORDIS;
10.3. Maladies Rares Info Service;
10.4. Orphanet; and
10.5. GIS - Institut des Maladies Rares, which coordinates and promotes research into rare diseases.

Second national plan for rare diseases
The second French national plan for rare diseases, Plan national maladies rares 2011-2014, was elaborated by the Ministry of Health during 2009-2010 from the results of the evaluation of the first plan and from the conclusions of seven working groups. The plan was launched on Rare Disease Day in February 2011, with a budget of €180 million. The second plan has three main objectives:

1. Improve access to diagnostics and quality of care for patients with rare diseases. Initiatives include:
   
   1.1. Haut Conseil de la Santé Publique (High Council of Public Health) recommendations based on the regrouping of the existing structure of 131 national centres of reference and 501 regional competence centres to foster collaborative initiatives through a federation of centres of reference for rare diseases (fédération des centres de reference maladies rares).
   
   1.2. Ensure quality of care for every patient with a rare disease, including access to specific medications and experimental drugs.
   
   1.3. Continue to develop Orphanet as a tool for information and research.

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2. Develop research on rare diseases. Initiatives include:

   2.1. Promotion of tools to increase knowledge of rare diseases.
   2.2. Optimisation of data collection and storage of biological samples based on existing collections.
   2.3. Promotion of the development of therapeutic research (preclinical and Phases I and II) in collaboration with the pharmaceutical industry.

3. Boost European and international co-operation in the field of rare diseases. Initiatives include:

   3.1. Promoting the sharing of expertise internationally through the European reference networks.
   3.2. To improve capacity to conduct multinational clinical trials, share and standardise diagnostic tests at a European level, and improve quality control testing.

According to EUCERD, specific measures included in the plan include the creation of a national rare disease database (Banque Nationale de Données Maladies Rares – BNDMR) to facilitate mapping of patients' needs and healthcare delivered, as well as recruitment for clinical trials; and organisation of access to next-generation sequencing (NGS) technology for genetic diagnosis. The EUCERD report indicates that the majority of French academic laboratories should be equipped with NGS facilities to optimise molecular diagnosis for a large set of rare diseases by the end of the second year of the plan. During the plan, various levels of NGS will be developed to maximise diagnosis coverage.

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Cancer plan 2009-2013

The national cancer plan 2009-2013 was launched in November 2009, following on from the previous cancer plan of 2003-2007. The plan includes measures for the development of specific care management for patients with rare forms of cancer, as well as the dissemination of information for healthcare professional and patients with rare forms or cancer via Orphanet and the national cancer institute (Institut national du cancer – INCa). In accordance with the rare diseases plan, a number of national rare cancer reference centres have been certified. Other specific measures include systematising the double reading of lymphomas and all rare malignant tumours, which the plan states is essential for diagnostic confirmation.

Orphanet

Orphanet, created in 1997, is a multilingual online server, providing information on rare diseases and orphan drugs. Planned developments for Orphanet included the extension of its medical encyclopaedia with detailed information for rare diseases, and making Orphanet better known to health professionals and patients.

Orphanet has grown internationally over the last few years and currently operates through a consortium of around 40 countries, which is coordinated by the French national institute of health and medical research (Institut national de la santé et de la recherche médicinale – Inserm). The French coordinating team has responsibility for “the infrastructure of Orphanet, management tools, quality control, rare disease inventory, classifications and production of the encyclopaedia,” which is produced in English and French. Inserm and the EC jointly fund the infrastructure and coordination activities of Orphanet.

Germany

In August 2013, the Federal Ministry of Health and the German Alliance of Chronic Rare Diseases (ACHSE) announced the national action plan for people with rare diseases (Der Nationale Aktionsplan für Menschen mit Seltenen Erkrankungen). The plan contains 52 distinct proposals for action, aimed at addressing the most pressing problems of patients with rare diseases and their relatives. The aim of the plan is to better inform doctors and patients in order to more quickly reach a more reliable diagnosis. According to the National Action League for People with Rare Diseases (Nationalen Aktionsbündnis für Menschen mit Seltenen Erkrankungen, or NAMSE) there are around four million people in Germany who are living with rare diseases.\(^{41}\)

The NAMSE aims to bring better care to people with rare diseases through coordination and communication. The organisation was founded in March 2010 by the Federal Ministry of Health, the Federal Ministry of Education and Research, and the ACHSE with the explicit aim of developing a national rare disease plan.

Announcing the adoption of the plan in October 2013, EURORDIS explains that the German plan is based on nationally recognised centres of excellence for diseases, or groups of diseases, that collaborate nationally and internationally in order to provide patients with the best, targeted care available. Other features of the plan include the provision of current, validated information for professionals and patients, improving diagnostics, and supporting research.\(^{42}\)

Under the plan, funds are provided for research into rare diseases in order to provide better diagnosis and treatment.\(^{43}\)

Previously, in 2009, the Federal Ministry of Health had published an in-depth evaluation of the rare diseases situation for patients in Germany. The study was entitled *Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen in Deutschland* (Measures to improve the health situation of people with rare diseases in Germany).\(^{44}\)


\(^{44}\) The report is available for download from: [http://ec.europa.eu/health/rare_diseases/national_plans/detailed/index_en.htm](http://ec.europa.eu/health/rare_diseases/national_plans/detailed/index_en.htm) (in German)
Italy

Italy published its draft national plan for rare diseases (Piano nazionale per le malattie rare, or PNMR) in October 2012. The plan focuses on the monitoring system, comprising national and regional registers, and the problems related to the encoding of rare diseases, as well as the route to diagnosis and care, the tools for therapeutic innovation (including orphan drugs) and the role of various associations in the field of rare diseases.

The plan aims to address the need for early diagnosis so that people with rare diseases can receive appropriate treatment at an early stage when it is most likely to make a significant improvement to their lives. The draft national plan was subject to public consultation, which was concluded on February 8, 2013.

The development of policies on assistance for rare diseases, strategies, objectives and actions outlined by the Italian national plan are largely the subject of previous regulatory interventions, which had identified rare diseases as a public health priority area. The plan proposed the creation of a framework, through which to provide guidance to address the problem of rare diseases across different institutional levels and levels of care, including primary care, palliative care, rehabilitation and home care.

Assistance to patients with rare diseases is funded by resources allocated to the national health system (SSN) and distributed annually among the regions. While it is recognised that expenditure on rare diseases is likely to vary between regions, the plan stresses that care for people with rare diseases is included under the essential levels of care (Livelli Essenziali di Assistenza, or LEA) provided to all citizens through regional systems under the SSN. The LEA was established by Ministerial Decree 279 in May 2001, which identified a list of 284 individual rare diseases and 47 disease groups. Patients suspected to have one of these diseases is entitled to diagnosis and treatment, free of charge, under the SSN.

45 The national plan for rare diseases is available for download from AIFA's website (in Italian): http://www.salute.gov.it/malattieRare/paginainternaMalattieRare.jsp?id=3296&menu=piano&lingua=italiano
The Decree also established a national network for rare diseases, enabling interventions related to prevention, surveillance, improving diagnosis and treatment, and the promotion of information and training. The network includes accredited centres, specifically identified by the regions and authorised to provide benefits for the diagnosis and treatment of rare diseases, according to agreed clinical protocols and in collaboration with family physicians and community services.

Monitoring was centralised through the establishment of the national registry of rare diseases at the National Institute of Health, in order to obtain an overall picture at the national level of the spread of rare diseases and their distribution in the area and improve the knowledge about the causes and risk factors associated with them.

Patients with rare diseases in Italy can access medicines through a number of different legislative measures. The centralised authorisation procedure represents the main route of access. Where drugs that are indicated for an orphan disease are not authorised for marketing under the centralised procedure, Law 648 of 1996 allows for national use. In addition, Law 326 of 2003, article 48, allows for compassionate use of a drug, while Law 94 of 1998 provides for prescription of a pharmaceutical for a single, named patient.

The Italian pharmaceutical agency (Agenzia Italiana del Farmaco, or AIFA) is the main body responsible for the introduction of orphan drugs onto the Italian market. AIFA established the National Registry for Orphan Drugs, which is managed in collaboration with the national centre for rare diseases (NCRD) and includes data on diagnosis and follow-up of patients treated with orphan medicinal products. According to a EUCERD report, the goal of the registry is “to have a nationwide coverage, to address all Italian centres qualified to distribute and prescribe orphan medicinal products”. 46

Spain
The rare diseases strategy of the Spanish national health system (NHS) was approved by the Interterritorial Council of the Spanish NHS in June 2009. The strategy is set within the framework of the Quality Plan of the Spanish NHS. The strategy sets out seven lines of action:

(i) Information on rare diseases and available resources;
(ii) Prevention and early detection;
(iii) Healthcare;
(iv) Therapies;
(v) Integrated health and social care;
(vi) Research; and
(vii) Training.  

These seven strategy lines were established with the support of a Technical Office located in the Centre for Biomedical Network Research on Rare Diseases (CIBERER). The CIBERER is the reference centre in Spain for investigating rare diseases and is one of nine public consortiums set up under the Carlos III institute of health (Instituto de Salud Carlos III). It was set up in 2006 to coordinate and foster biomedical, clinical and epidemiological research into rare diseases.

In Spain, Law 29/2006, on Guarantees and the Rational Use of Medicinal and Health Products, refers to orphan medicinal products in Article 2, Supply and Dispensing Guarantees: “In order to guarantee the supply of medicines, the Government may adopt special measures regarding their manufacture, importation, distribution and dispensing. In the cases of ‘orphan medicinal products’, in keeping with the provisions of Regulation (EC) No. 141/2000, and of drugs “of no commercial interest”, the Government may adopt, besides the aforementioned measures, additional measures relating to the economic and fiscal regime of those drugs.”

48 More information is available on the CIBERER website at: http://www.ciberer.es
In a 2012 report, the EUCERD points out that the decentralised nature of healthcare provision in Spain means that the strategy essentially provides a framework and a set of recommendations for the autonomous communities, which are responsible for implementation. In order to facilitate implementation, funds from the national health budget are allocated through a call for proposals to the autonomous communities.

Prior to the launch of the national rare diseases strategy, some regional initiatives were already in place. For example, the regional government of Andalucía had created a genetics plan, the Plan de Genética de Andalucía 2006-2010, which was followed by specific plan concerning care for people with rare diseases, the Plan de atención a personas afectadas por enfermedades raras 2008-2012. Other regional policies identified in the EUCERD report include the Plan integral de enfermedades raras 2010-2014, which was approved by the Extremadura Autonomous Community in December 2010, based on general recommendations from Europe and the Spanish National Strategy; and the creation of an advisory commission on rare diseases by the Health Department of the Autonomous Government of Catalonia.

50 Aymé, S. and Rodwell, C. eds. (2012, July) 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases, 156-158.
UK
The UK plan on rare diseases was published for consultation by the Department of Health in February 2012. The plan was developed jointly by the four nations of the UK (England, Wales, Scotland, Northern Ireland). Specific areas addressed by the plan include speedy diagnosis and early intervention, coding and classification, research, centres of expertise and networks, patient information and support, and sustainability. As part of the consultation, an additional document was published specifically on equality analysis of the UK plan for rare diseases.

The rare diseases consultation recommends the use of specialist centres for diagnosis to ensure early treatment, which the Department of Health believes could, in some cases, save lives. It is acknowledged that, “all doctors should have the right training to be aware of the possibility of a rare disease”. In addition, “care of patients with rare diseases should be better co-ordinated”.

Among the priorities identified in the plan is “to give NHS patients better access to effective and innovative medicines”, which it suggests is a reason for the new system of pricing for branded medicines in the UK. From January 2014, the value-based pricing scheme will apply to all new branded medicines, including those for rare diseases. More information on value-based pricing is provided in the pricing and reimbursement chapter of this report.

The consultation document also suggests that “equal consideration should be given to patient safety through active surveillance of adverse drug reactions for orphan medicines performed at selected sentinel sites, through drug event monitoring, the use of registries and by comparative observation studies”. It is envisaged that these activities with respect to orphan medicines would be aligned to the remit of the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC).

With regard to the use of unlicensed or off-label medicines for patients with rare
diseases, in circumstances where there are no clinically licensed alternatives,
the Department of Health has appointed the National Institute for Health and
Care Excellence (NICE) to provide information on “the best available evidence
for selected unlicensed and off-label medicines where a demand for information
has been identified in the NHS in England”.

Responses to a number of specified consultation questions were invited from
participants before May 25, 2012. The final plan is due to be produced by the
end of 2013.
Orphan drug policy and regulation in selected countries around the world

Japan

The Japanese government introduced special provisions relative to orphan drug research and development through a revision to the pharmaceutical law in October 1993.

According to these provisions, orphan drug status can be granted to a drug, provided it fulfills the following criteria:

- The disease for which use of the drug is claimed must be incurable. There must be no possible alternative treatment; or the efficacy and expected safety of the drug must be excellent in comparison with other available drugs.

- The number of patients affected by this disease in Japan must be fewer than 50,000, which corresponds to a maximum incidence of four per ten thousand.\(^{52}\)

Orphan drug status is granted by the Ministry of Health, Labour and Welfare (MHLW). In order to receive orphan designation, sponsors must submit data to the authorities that shows the estimated size of the patient population, non-clinical and early-phase clinical study and development protocol.

According to Orphanet, orphan drugs benefit from a fast-track Marketing Authorisation procedure. In particular, the law requires priority of evaluation of applications made for indications concerning rare diseases. In addition to this measure, the Organisation for Pharmaceutical Safety and Research provides pharmaceutical companies launching orphan drugs with a consultation on development protocols and some advice concerning the preparation of approval applications.\(^{53}\)

The registration validity period is extended to ten years for orphan products, compared with four to six years for traditional drugs.

\(^{52}\) Orphanet. Orphan Drugs in Japan. Retrieved from: [http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_JAP](http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_JAP)

\(^{53}\) Orphanet. Op cit.
Orphanet elaborates that funding is available for scientific activities and the Japanese authorities reimburse up to 50 per cent of development costs for orphan drugs. In addition, a tax reduction of six per cent is granted for research and development costs, other than those related to funding grants and within the limit of ten per cent company tax. However, companies that make profits on sales of orphan drugs must return a proportion of the subsidy granted as a contribution to these funds.

**Australia**

Orphan drugs are regulated in Australia under the Therapeutic Goods Regulations, 1990. An orphan drug is defined as a medicine, vaccine or *in vivo* diagnostic agent that is:

- Intended to treat, prevent or diagnose a rare disease; or
- Not commercially viable to supply to treat, prevent or diagnose another disease or condition.

Medicines must be designated as orphan drugs by the Therapeutic Goods Administration (TGA) prior to an application being submitted to register an orphan drug on the Australian Register of Therapeutic Goods (ARTG).

According to the TGA, to be eligible for designation as an orphan drug, a product must not have been rejected on safety grounds by the TGA, the FDA, the EMA, the UK MHRA, the Therapeutic Products Directorate of Canada, the Medical Products Agency of Sweden, or the Medicines Evaluation Board of the Netherlands for use for the disease in question. The product must also have not been registered for use for the disease or condition before January 1, 1998.  

Australia’s Orphan Drug Program was set up in 1997 and aims to bring orphan drugs to the market by reducing development costs. This is achieved primarily through waiving of the various fees associated with registration. In addition, orphan drugs can be considered for priority evaluation.

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54  TGA (2004, June) Australian Regulatory Guidelines for Prescription Medicines. Retrieved from:  
According to Orphanet,\(^{55}\) the main characteristic of the programme is based on a close collaboration of the TGA with the FDA and takes into account the FDA’s orphan drugs evaluations. For identifying and evaluating drugs in Australia that have not been evaluated in the US, or do not meet US criteria, additional criteria are established.

There is no specific regulation concerning intellectual property rights for orphan drugs; they simply have the same legal status as any other drugs registered for supply in Australia.

**Taiwan**

Taiwan was the fifth country to introduce legislation for orphan drugs, with the Rare Disease Control and Orphan Drug Act, which was implemented in 2000. The legislation aims to encourage research into rare disease, provide support and assistance to patients with rare diseases, and raise public awareness. The regulatory authority is the Department of Health. Taiwan provides ten years market exclusivity for orphan drugs.

According to the Taiwan Foundation for Rare Disorders (TFRD), by 2011, the government had categorised 184 rare diseases, and 74 orphan drugs and 40 special nutrients had been approved. The TFRD represents patients with around 211 rare diseases, which affect more than 6,000 people.\(^{56}\)

The legislation allows patients with rare diseases to apply for reimbursement for their medical expenses, including diagnosis, treatment, drugs, and special nutritional supplements. There is a reimbursement cap of 70 per cent, but families that qualify for low-income status can receive reimbursement of up to 100 per cent for drugs and nutritional supplements for the patient.


\(^{56}\) TFRD. Rare diseases in Taiwan. Retrieved from: http://www.tfrd.org.tw/english/rare/cont.php?kind_id=16&top1=About%20rare%20diseases&top2=Rare%20Diseases%20in%20Taiwan
Canada

Canada is unusual among developed countries in having no specific regulatory policy for orphan drugs. According to the Canadian Organisation for Rare Diseases (CORD), rare conditions affect one in 12 Canadians. Despite the adoption of specific orphan drug regulations in the US, Japan, Australia and the EU, Health Canada concluded in 1996 that such a regulation was not needed in Canada. In practice, however, even when approved by Health Canada, reimbursement for orphan drugs - which currently have no legal definition in Canada - can be difficult to obtain at provincial level.

In addition, Canadian patent law does not provide any guaranteed data exclusivity for orphan drugs, over and above that to which a new product would normally be entitled.

Special Access Programme

Health Canada maintains a Special Access Programme, which allows a manufacturer to sell a product that has no marketing authorisation in Canada, to a seriously-ill patient whose physician can demonstrate that existing therapies have failed or are unsuitable. The physician must make a patient-specific request, and if granted, the amount of drug authorised is limited to six months’ supply; a further request may be made to prolong the availability.

The Special Access Programme does not pay for drugs it authorises; where the manufacturer does not provide the drug free of charge, the cost must be borne in the usual way, by public/private reimbursement or paid for out-of-pocket.

57 http://raredisorders.ca/documents/CanadaOrphanDPFinal.pdf, page 2
Reforms announced, 2012

In October 2012, the Federal government announced two measures to improve access to orphan drugs in Canada.

The first is a new regulatory framework. Details have yet to be released, but according to Health Canada:

*A key focus of this new approach will be on international information-sharing and collaboration for the development and regulation of orphan drugs. Enabling Canadian scientists and regulators to participate with trusted global counterparts will make better use of scarce resources and benefit Canadian patients.*

*The new framework will maintain evidence requirements based on clinical trials and will be supported by greater information sharing amongst international partners who are committed to pooling scarce resources for maximum benefit. Once authorized, drugs will continue to be closely monitored for effectiveness and safety while in use.*

The second is the Canadian involvement in Orphanet, through the Canadian Institutes of Health Research.

Both moves were strongly welcomed by BIOTECanada, which noted that they would put Canadian patients on the same footing as in other developed countries, and that it looked forward to working with Health Canada to develop the regulations.

The reform announcement was also welcomed by CORD, which voiced its hope that the measures would spur provincial governments to offer a more comprehensive and equitable approach to the funding of rare disease treatments.

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61 Orphanet website: [http://www.orpha.net](http://www.orpha.net)


Brazil

In April 2013, Interfarma, the pharmaceutical research industry association in Brazil, published its contributions for a national policy on rare diseases. The report was the result of two years’ work in defence of a national policy for rare diseases in Brazil.

Brazil lacks specific policies, but the subject of rare diseases is not a new one for the health authorities. According to Interfarma, it has been the subject of discussions since the early 2000s, although it has been limited to genetic diseases. As such the Ministry of Health set up a working group in 2004 that developed a proposal for a national policy for clinical genetics in the national health system (SUS), but this did not move forward. Some five years later, the National Policy for Complete Attention for Clinical Genetics was instituted, the results of which are considered by industry experts to be insufficient.

Interfarma suggests that Brazil lags behind other countries, both in the lack of an official policy for rare diseases and the lack of an official concept to define them. In an effort to move forward, the association refers to bills related to rare diseases that are under consideration in Congress, both to establish guidelines for a national programme for the treatment of rare diseases under the SUS and to define the prevalence of a rare disease using the same parameters as the EU.

According to the Ministry of Health, there are 26 clinical protocols related to rare diseases within the SUS. Among these, 18 were developed under the aegis of the new National Policy for Complete Attention for Clinical Genetics. These protocols represent the official entryway to care for rare diseases in the public system. However, Interfarma states that 17 of the protocols do not use orphan drugs that alter the progression of the disease, but treat only the symptoms. Only one, the protocol for the treatment of Gaucher disease, incorporates orphan drugs. The association also points out that, although cited by the Health Ministry, some diseases such as Pompe, Homocystinuria, Fabry and all forms of mucopolisaccharidosis have not been included in any clinical protocol since the policy was established.

Currently, almost all rare diseases registered with ANVISA that use orphan drugs remain outside protocols, thereby representing a significant barrier for accessing these drugs under the SUS. According to the Interfarma study, 14 diseases rely on drugs that are approved by ANVISA and marketed in Brazil, but excluded from the government’s agenda.

In conclusion, Interfarma recommends that, “given the countless challenges to be considered, it is important that the implementation of a national policy for rare diseases occurs in a progressive manner.”

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Please click here to send your ideas to the FirstWord Dossier Research Team. We look forward to hearing from you.
## Incentives for orphan drug development

**Table 3: Orphan drug incentives around the world**

<table>
<thead>
<tr>
<th>Market exclusivity (years)</th>
<th>Research grants</th>
<th>Tax credits</th>
<th>Fast track approval</th>
<th>Protocol assistance</th>
<th>Regulatory fee waivers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td>7</td>
<td>Government grants for clinical research</td>
<td>Up to 50% for clinical expenses</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>EU</strong></td>
<td>10</td>
<td>Framework programmes plus national measures</td>
<td>Managed by member states</td>
<td>Yes (centralised approval)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>10</td>
<td>Government grants for clinical and non-clinical research</td>
<td>15% tax credits, up to 14% corporate tax reduction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td>5 (as for other drugs)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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<td><strong>China</strong></td>
<td>n/a</td>
<td>NSFC research grants*</td>
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</tr>
<tr>
<td><strong>South Korea</strong></td>
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<td><strong>Taiwan</strong></td>
<td>10</td>
<td>Government grants and awards from central competent authority</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Source: FirstWord elaboration of data from Orphanet, and Song, P. et al 2012*

*NSFC: National Natural Science Foundation of China*

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Incentives in the US

**Market exclusivity**

In the US, seven years’ market exclusivity applies from the date of marketing approval of a drug with an orphan designation. The FDA provided clarification of orphan drug exclusive approval in its final regulations, amending the 1992 Orphan Drug Regulations issued to implement the Orphan Drug Act, which became effective on August 12, 2013. According to the amended regulations, orphan drug exclusive approval means that, with effect from “the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug for the same use or indication for seven years, except as otherwise provided by law or in this part. A designated drug will receive orphan drug exclusive approval only if the same drug has not already been approved for the same use or indication.”

Market exclusivity is available to all orphan drugs, whether or not they are patented. This means that, when a non-patented drug has been granted market exclusivity, the Agency may not approve another application under section 505(b) or issue another licence under section 351 of the Public Health Service Act for a similar drug for the same disease or condition until the seven years’ market exclusivity has expired.

However, orphan drug market exclusivity protects only the approved indication or use of a designated orphan drug. According to the regulations, “FDA may later approve the drug for additional indication(s) or use(s) within the rare disease or condition not protected by the exclusive approval.”

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Grants for orphan drug development

The FDA’s Office of Orphan Products Development (OOPD) administers the Orphan Grants Program, which supports the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the proposed product will be superior to the existing therapy. The FDA provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products.

Applicants must include in the application’s Background and Significance section documentation to support the estimated prevalence of the orphan disease or condition (or in the case of a vaccine or diagnostic, information to support the estimates of how many people will be administered the diagnostic or vaccine annually) and an explanation of how the proposed study will either help gain product approval or provide essential data needed for product development.

Around $14.1 million is available for funding per fiscal year. Of this, around $10 million will fund non-competing continuation awards, and $4.1 million will fund 5-10 new awards, subject to availability of funds. Phase I studies are eligible for up to $200,000 per year for up to three years. Phase II and III studies are eligible for up to $400,000 per year for up to four years.70

Tax credits and fee exemption

Tax credits of up to 50 per cent of the cost of conducting clinical research for designated orphan drugs. These tax credits were made permanent by Congress in 1997 and have a 20-year carry forward and a one-year fall back provision.

The Orphan Drug Act also provides a waiver of Prescription Drug User Fee Act (PDUFA) filing fees for orphan drugs.


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Accelerated approval processes
The FDA has developed four schemes through which the review and approval of new drugs to treat serious or life-threatening conditions can be accelerated: Priority Review, Accelerated Approval, Fast Track and Breakthrough Therapy.

Fast Track
According to the FDA, the Fast Track process is designed to “facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need”. 71 Many orphan drugs will fall into this category, since, by definition, they are designed to treat or prevent serious conditions where there is no current therapy, or where the available therapy is inadequate and a new drug can offer a significant improvement.

Following Fast Track designation, early and frequent communication between the FDA and the drug company is actively encouraged throughout the drug development programme and review process. Drugs with Fast Track designation may also be eligible for Accelerated Approval and Priority Review.

Accelerated Approval
In 2012, Congress passed the FDA Safety Innovations Act (FDASIA). Section 901 of FDASIA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to enable the FDA to base the accelerated approval of drugs for serious conditions that fill an unmet medical need on whether or not the drug has an effect on a surrogate or an intermediate clinical endpoint.

The FDA defines a surrogate endpoint for accelerated approval as a “marker”, or a “laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit”. Similarly, an intermediate clinical endpoint is defined as “a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM)”. 72

72 Op cit.
According to the FDA, valuable time can be saved in the drug approval process by using surrogate or intermediate clinical endpoints.

**Priority Review**

The FDA operates a two-tier system of review times under the Prescription Drug User Act (PDUFA). A *Priority Review* designation reduces the time taken by the FDA to review an application within six months, compared to ten months under a standard review.

**Breakthrough Therapy**

In order to expedite the development and review of drugs to treat serious conditions, the FDA is able to grant *Breakthrough Therapy* designation where “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint”. A drug that is designated as a *Breakthrough Therapy* is entitled to all of the benefits of *Fast Track* status.

**Incentives in the EU**

**Market exclusivity**

Following the granting of marketing authorisation, orphan medicinal products benefit from market exclusivity in the EU for ten years. Two years’ extension is also available for medicines that comply with an agreed paediatric investigation plan.

Market exclusivity is awarded by the EC and is specifically linked to a specific orphan designation for which a marketing authorisation has been granted. However, medicines can have more than one orphan designation, so it is possible to have separate market exclusivities for each designated orphan indication.

**Protocol assistance**

Scientific advice is available from the EMA to optimise development, as well as guidance on preparing a dossier that will meet European regulatory requirements. According to the Agency, this assistance is designed to help applicants to maximise their chances of the marketing authorisation application being successful.
Protocol assistance is available at a reduced charge for designated orphan medicines, linked to a fee-reduction scale that depends on the status of the sponsor. Sponsors are encouraged to consider coordinating the timing of protocol assistance from the Agency with request for scientific advice from the FDA. The EMA and FDA offer a programme of parallel scientific advice, which aims to provide a mechanism for both agencies and sponsors to exchange views on scientific issues during the development phase of new medicinal products. More information on the general principles of this parallel guidance is available from the EMA website.74

In Germany, according to the EUCERD, orphan medicinal products are exempted from the mandatory rebate to the statutory and private health insurance funds on sales of products outside the German maximum reimbursement prices (Festbeträge) system, though evidence for the need of this exemption must be provided by the company.75

**Fee reductions**

The EMA has a special fund from the EC, agreed annually by the European Parliament, in order to grant regulatory fee reductions. According to the Agency, reduction of fees is considered for various centralised activities, including applications for marketing authorisation, inspections and protocol assistance. Additional fee reductions apply for small and medium-sized enterprises (SMEs).

Fee reductions are revised annually according to the available budget. Companies may be eligible for full or partial fee reductions. In 2013, SMEs are eligible for 100 per cent fee reductions for protocol assistance, pre-authorisation inspection, initial marketing authorisation application and post-authorisation applications and annual fee during the first year following granting of a marketing authorisation.

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The fee reduction for protocol assistance varies for non-SME sponsors, depending on whether or not the assistance is related to a paediatric patient population. For paediatric-related protocol assistance, regarding the development of an orphan medicinal product for the paediatric population, where the advice requested does not include the adult population, the sponsor is eligible for 100 per cent fee reduction. For non-paediatric-related protocol assistance, non-SME sponsors are entitled to a fee reduction of 40 per cent.  

**Tax incentives**

In France, sponsors of orphan medicinal products are exempted from certain taxes usually paid by enterprises promoting pharmaceutical specialities under health and social legislation. These are identified in a EUCERD report as:

- The tax on pharmaceutical promotion, based on the promotion costs of laboratories;
- The tax paid by the laboratories for the ANMS;
- The safeguard clause for medicinal products;
- The tax on direct sales;
- The tax on the distribution of medicines.

In Spain, under Royal Decree 8/2010, manufacturers of orphan medicinal products have had a reduced rebate of four per cent (as opposed to five per cent, or 7.5 per cent in the case of products directly distributed to hospitals) on the VAT-exclusive public price of medicines financed by the NHS if they are not included in the reference price system since June 2010.

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**EU-funded research**

Grants may be available to sponsors developing orphan medicinal products from EU and Member State programmes and initiatives supporting research and development, including the EC’s Seventh Framework Programme (FP7).  

**France**

In France, research support is available through the foundation for rare diseases (Fondation maladies rares). A co-operative framework that was co-founded by the French national institute of health and medical research (Inserm), the French muscular dystrophy association (AFM-Téléthon) and the national federation of patients organisations for rare diseases (Alliance Maladies Rares), as well as major hospitals and universities, the foundation acts as a strategic hub to coordinate, federate and fund rare diseases research. The foundation provides financial support to innovative projects and stimulates cross-sector co-operation to accelerate scientific, medical and social innovations for benefit of patients.

**Spain**

In Spain, there has been an annual call since 2007 for public financing of clinical trials of medicines with no commercial interest. Medicines for rare diseases are among the priorities of this call, whether or not these have been designated as orphan medicines. An EUCERD report suggests that, “in the scope of this call, proposals for studies concerning medicines for the treatment of rare diseases have an outstanding rate of success in obtaining full public financing”.

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79 For more information on FP7, see the CORDIS website: [http://cordis.europa.eu/fp7/home_en.html](http://cordis.europa.eu/fp7/home_en.html)


Finding the right patients for clinical trials

Identifying potential candidates for inclusion in clinical trials can be problematic for researchers, due to the relatively small number of people who have been diagnosed with a particular rare disease. Patient organisations and registries can be a valuable resource for both researchers and patients alike, since they can provide a knowledge base about the characteristics of a rare disease and, in some instances, can help with research and funding for the development of an innovative therapy.

Patient organisations

The European Organisation for Rare Diseases (EURORDIS) is a non-governmental, patient-driven alliance of patient organisations, representing more than 500 rare disease patient organisations and over 4,000 rare diseases in more than 50 countries. As an umbrella organisation, EURORDIS provides “support for research and medicines development, facilitating networking amongst patient groups.” EURORDIS represents European national rare disease alliances and rare disease federations.

Rare disease federations provide a network of national patient organisations for specific rare diseases, which can facilitate contact between people from different countries who suffer from the same disease. They can also collect and publish information about rare diseases at an international level.

One example of a successful collaboration between industry and patient organisations involved the approval of an orphan drug for a sub-group of cystic fibrosis patients. In January 2012, the FDA approved Kalydeco (ivacaftor) for use in patients who have a rare form of cystic fibrosis (CF) with a G551D mutation in the CFTR gene. In July 2012, Kalydeco was approved in the EU for the same indication.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test must be used to detect the presence of the G551D mutation, which only occurs in around four per cent of CF patients. In a January 2012 blog article, Janet Woodcock, director of the FDA’s CDER explained, “What makes the availability of Kalydeco even more unique is that the drug’s developer, Vertex Pharmaceuticals, teamed up with the Cystic Fibrosis Foundation to develop and study the drug.”

Woodcock suggests the CF Foundation “pioneered… a new form of patient power”, explaining that the Foundation provided assistance with “a portion of the drug’s development costs, provided researchers with useful insights about the CF patient population and helped in the recruitment of study participants”. These contributions, she says, were “critical to quickly bringing the innovative new therapy to patients”.

National rare disease alliances bring together numerous rare disease organisations into a larger group, in order to better represent the needs of patients with rare diseases when liaising with government bodies, scientific and medical organisations.

The umbrella organisation in the US is the National Organization for Rare Disorders (NORD), a federation of voluntary health organisations dedicated to assisting individuals with orphan diseases and the organisations that serve them. NORD supports innovative research and access to “medically necessary treatments”, as well as “fair and consistent government policies”.

84  About NORD. Retrieved from: http://www.rarediseases.org/about
Table 4: National rare disease alliances

<table>
<thead>
<tr>
<th>Country</th>
<th>Alliance</th>
<th>Website</th>
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<tbody>
<tr>
<td>France</td>
<td>Alliance Maladies Rares</td>
<td><a href="http://www.alliance-maladies-rares.org">www.alliance-maladies-rares.org</a></td>
</tr>
<tr>
<td>Germany</td>
<td>Allianz Chronischer Seltener Erkrankungen (ACHSE)</td>
<td><a href="http://www.achse-online.de">www.achse-online.de</a></td>
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<tr>
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<td>Federazione Italiana Malattie Rare (UNIAMO)</td>
<td><a href="http://www.uniamo.org">www.uniamo.org</a></td>
</tr>
<tr>
<td>Spain</td>
<td>Federación Española de Enfermedades Raras (FEDER)</td>
<td><a href="http://www.enfermedades-raras.org">www.enfermedades-raras.org</a></td>
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<tr>
<td>UK</td>
<td>Genetic Alliance UK</td>
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<td>Rare Diseases UK</td>
<td><a href="http://www.raredisease.org.uk">www.raredisease.org.uk</a></td>
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<tr>
<td>USA</td>
<td>National Organization for Rare Disorders (NORD)</td>
<td><a href="http://www.rarediseases.org">www.rarediseases.org</a></td>
</tr>
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Source: FirstWord

Patient registries

In an article published in Applied Clinical Trials Online, Gliklich and Leavy suggest that, when designing a rare disease trial, it may be impossible “to find fundamental information on the disease on which to base the study protocol”. The authors point out that further complications may arise if there are multiple, simultaneous studies of a rare disease, since enrolment in one trial may exclude the patient from another. Patient registries are playing an increasingly important role in medical research, as they can provide a central resource of real-world data on patient outcomes. For drug developers, patient registries can provide valuable information on the disease and its effect on a patient’s quality of life, which may contribute to the design and operation of successful clinical trials.

In the US, the Office of Rare Diseases Research (ORDR) under the National Institutes of Health (NIH) has launched a pilot project to establish a Global Rare Diseases Patient Registry and Data Repository (GRDR). The goal of this project is to establish a data repository of anonymous patient data, aggregated in a standardised manner, using Common Data Elements (CDEs) and standardised terminology. These data “will be available to all investigators to enable analyses across many

rare diseases and to facilitate various biomedical studies, including clinical trials, in pursuit of developing drugs and therapeutics to improve the healthcare and the quality of life for the many millions of people who are diagnosed with rare diseases.”

Following a February 2012 request for information from patient groups, the ORDR selected 30 patient organisations to take part in the two-year GRDR pilot scheme. Among these groups, 15 have an established patient registry and 15 do not. The groups without a registry were selected to assist in testing the implementation of ORDR common data elements in the newly developed registry infrastructure. During the pilot programme, the GRDR will fund the development and hosting of the new registries. Participating registries must have a means of exporting “de-identified” registry data that will facilitate its loading into the GRDR repository on a regular basis. The GRDR will also develop the capability to link data and medical information to donated bio-specimens by using a voluntary global unique patient identifier (GUID).

Figure 4: Global Rare Disease Registry and Data Repository overview

Source: NIH Office of Rare Diseases Research

Biomarkers and companion diagnostics

In recent years, a number of drugs have been approved alongside companion diagnostics, which are used to identify specific groups of patients for whom a particular targeted therapy is more likely to have a positive effect. This is particularly relevant to sub-groups of cancer patients, but may also be useful for non-oncology rare diseases, particularly those that are caused by a gene mutation.

In February 2013, KineMed, Isis Pharmaceuticals, and CHDI Foundation announced a collaboration to utilise KineMed’s translational biomarker platform with Isis’s antisense therapeutic programme for Huntington’s disease (HD). This collaboration, which builds on an earlier alliance between CHDI and KineMed to develop companion biomarkers of therapeutic response in HD, will provide Isis with access to novel biomarkers for use in the development of an antisense drug to treat HD.

Commenting on the agreement, Director of Molecular Pharmacology for CHDI Foundation, Jonathan Bard suggested, “There is a critical need to identify appropriate biomarkers to determine target engagement and predict early clinical efficacy for future Huntington’s disease clinical trials.” The combination of “Isis’s knowledge of antisense therapies [and] KineMed’s expertise in developing unique pharmacodynamic biomarkers creates a collaboration with great potential for discovering such tools for HD,” he added.87

Novartis Institutes for BioMedical Research (NIBR) is investigating potential treatments for around 40 orphan diseases. Among these is Fragile X syndrome, the most common cause of inherited mental impairment. A potential biomarker was discovered during proof-of-concept study for an investigational drug. This biomarker identified a subset of Fragile X patients who responded positively to the investigational therapy. Consequently, a companion diagnostic is being used in clinical trials.88

88 Novartis Institutes for BioMedical Research. Rare Disease Research and NIBR. Retrieved from: http://www.nibr.com/newsroom/stories/2013Feb22_RareDiseases.shtml
Pricing and reimbursement

Pricing and reimbursement in the EU

While EU initiatives seek to foster co-operation between national authorities, member countries remain free to set their own reimbursement policies. Consequently, access to orphan drugs varies between countries.

At EU level, member states are working towards greater co-operation on health technology assessment (HTA) in order to avoid duplication of efforts and resources within industry and by HTA bodies and national decision-makers.

In 2004, the EC and Council of Ministers targeted HTA as “a political priority”, recognising “(...) an urgent need for establishing a sustainable European network on HTA”. Subsequently, the EUnetHTA was established to create an effective and sustainable network for HTA across Europe. The organisation works to develop “reliable, timely, transparent and transferable information to contribute to HTAs in European countries.”

France

Drug pricing

Following marketing authorisation in France, drugs are assessed by the Haute Autorité de santé (HAS). The HAS is an independent public body with financial autonomy, set up by the French government in 2004 with a remit to improve the quality of patient care and guarantee equity within the healthcare system. The HAS provides health authorities with opinions on the actual or expected clinical benefit of drugs, as well as medical devices, diagnostics and therapeutic procedures that are reimbursed by national health insurance. HAS opinions are based on an assessment of the benefit for both patients and public health.

90 EUnetHTA. Retrieved from: [http://www.eunethta.eu/about-us](http://www.eunethta.eu/about-us)
91 HAS website: [http://www.has-sante.fr/portail/jcms/fr_1455134/fr/about-has](http://www.has-sante.fr/portail/jcms/fr_1455134/fr/about-has)
Prices for reimbursable pharmaceuticals are set by the Economic Committee for Healthcare Products (CEPS, or Comité économique des produits de santé). The CEPS also sets reference prices (TFR, or tarif forfaitaire de responsabilité) and a price list of hospital products outside the fee-for-service payment scheme.

Prices for reimbursable products are assessed according to the level of clinical benefit provided by the product (ASMR, or Amélioration du service médical rendu) in comparison with other products in the same therapeutic area.

The ASMR is assessed by the Transparency Commission (CT, or Commission de la transparence) under the HAS and is rated on a scale of levels I to V:

- ASMR I: major improvement such as a new therapeutic area or a reduction in mortality;
- ASMR II: important improvement in efficacy and/or reduction of side effects;
- ASMR III: moderate improvement in efficacy and/or reduction of side effects;
- ASMR IV: minor improvement; and
- ASMR V: no improvement.

Under the current system, the proposed price of innovative pharmaceuticals with ASMR levels I to III must be consistent with the prices of similar pharmaceuticals in other European countries (Germany, Italy, Spain, UK).

From October 2013, new pricing regulations will come into force, under which formal medico-economic assessment will be applied to drugs whose manufacturers request an ASMR rating of I to III, and/or drugs that are expected to have a significant impact on public insurance expenditure.93

The commission for the economic evaluation of public health (CEESP, or Commission d’évaluation économique et de santé publique) has had its role redefined and will be in charge of producing medico-economic assessment. The requirement for medico-economic assessment and the conditions under which

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it will be performed are defined under the October 2012 decree no. 2012-1116. CEESP assessments will rely on economic data submitted by the manufacturers of the products undergoing review. For products falling under the new reform, CEPS will make pricing decisions based on advice from both the CEESP’s medico-economic assessment and the CT’s clinical evaluation.

**Orphan drug reimbursement**

In France, pharmaceutical reimbursement is determined by the Ministry of Social Affairs and Health (Ministère des Affaires sociales et de la Santé) after receiving technical advice from the Transparency Commission and the price decision from the CEPS.

Reimbursement rates are set by the National Union of Health Insurance Funds (UNCAM, or Union nationale des caisses d’assurance maladie). The rate is based on the level of actual clinical benefit (SMR, or Service médical rendu) assessed by the Transparency Commission. SMR categories are major/important and moderate/weak. The general rate for reimbursement is 35 per cent. However, the majority of orphan drugs will be for serious diseases, so reimbursement is likely to fall under the major/important category, the rate for which is set at 65 per cent.

Health insurance funds pay 100 per cent of the expenses for a list of 30 chronic and costly diseases. Certain other diseases may also be free of charge if they constitute a progressive or disabling disorder, if they are costly or if there are multiple diseases present for more than six months. Exemption from co-payment is only valid for long-term illnesses (ALD - Affection de longue durée), whereas for other diseases normal reimbursement applies.

According to an EUCERD report, of 62 orphan drugs that were granted marketing authorisation in the EU, “all but one have been granted a positive advice for reimbursement in France.” 94

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Germany

Drug pricing

The act on the reform of the market for medicinal products, Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) became effective for the mandatory pricing assessment for newly introduced drugs in the German healthcare system in January 2011. Under AMNOG, the price of medicines is determined by the added benefit they bring to patients in comparison to existing products, ending the previous free pricing regime. The German Ministry of Health expected AMNOG to contribute to savings in the statutory health insurance system amounting to €2.2 billion per year.95

When a product with new active ingredients has been approved for the German market, manufacturers are required to provide evidence of the added benefit for patients. Companies must submit a dossier to the Gemeinsame Bundesausschuss (G-BA, or Federal Joint Committee) based on the authorisation documents and clinical studies. The dossier must prove that the new drug has an additional benefit over the appropriate comparator therapy, which is specified by the G-BA. The G-BA may delegate the benefit assessment of the drug to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG, or Institute for Quality and Efficiency in Healthcare) or third parties.

The IQWiG is an independent scientific institute, established with the healthcare reform of 2004 and financed by contributions from members of the Gesetzliche Krankenversicherung (GKV). The IQWiG is responsible for producing independent, evidence-based reports on the quality and efficiency of drugs and other health interventions, based on international standards.

In January 2011, the IQWiG received its first commission from the G-BA with regard to the early benefit assessment of new drugs under AMNOG. The IQWiG has also started undertaking cost-benefit assessments.

Following the expiry of the transitional regulation of the AMG on December 31, 2012, manufacturers are now able to apply to the IQWiG for “a new benefit assessment if the added benefit is not regarded as proven due to incomplete submission of the necessary evidence”.  

If the G-BA agrees that a prescription medicinal product has an added benefit and that it qualifies for reimbursement by the statutory health insurance funds, the reimbursement price is negotiated based on the evaluation of this benefit. The level of benefit is assessed on a scoring system ranging from one to six, where the first four levels concern drugs that are perceived to have added benefits over the comparator product and levels five and six represent either no added benefit or a product that is considered inferior to the comparator. If a product falls within levels one to four, it qualifies for price negotiations between the central federal association of health insurance funds (GKV) and the pharmaceutical company. The negotiated price takes the form of a rebate on the retail price originally set by the company. If no agreement is reached, an arbitration board determines the reimbursement price using European pricing levels as its standard.

**Orphan drug reimbursement**

Prior to the introduction of the act on the reform of the market for medicinal products, Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) from January 2011, all orphan drugs with marketing authorisation at European level were fully reimbursed by the statutory health insurance (Gesetzliche Krankenversicherung, or GKV). Since January 2011, all new drugs are subject to cost/benefit analysis. However, according to a EUCERD report, orphan drugs authorised by the EMA under EU regulation 141/2000 with an annual turnover below €50 million are exempted from the benefit assessment, because the benefit is taken for granted.

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Italy

Drug pricing

The prices of all drugs reimbursed by the SSN are established through negotiation between AIFA and pharmaceutical companies in accordance with Law no. 326 of November 2003 and the February 1, 2001 resolution of the Comitato Interministeriale per la Programmazione Economica (CIPE, or Inter-ministerial Economic Planning Committee). Specifically, prices are negotiated by the Pricing & Reimbursement Commission (CPR, or Commissione Prezzi e Rimborso), which represents AIFA, CIPE, the regions and the Ministry of Industry. Pricing decisions take into account the following criteria:

- A positive cost/efficacy ratio, where the product is considered useful for the treatment of diseases for which there is no effective therapy, or provides a more appropriate response than drugs already available for the same therapeutic indications;

- A favourable risk/benefit ratio compared with drugs already available for the same indications;

- An evaluation of the economic impact on the SSN;

- The daily cost of the therapy compared with similar products;

- An estimate of the market shares to be acquired; and

- A comparison with prices and consumption levels in other European countries.  

The Technical & Scientific Commission (CTS) and AIFA’s Administration Council further evaluate the results to establish the drug reimbursement classification and price. Innovative drugs are rated in three categories, according to the severity of the condition they address and the efficacy of existing treatments:

i) Treatments for serious and/or life-threatening diseases e.g. cancer, AIDS Parkinson’s disease;

ii) Treatments that reduce or eliminate the risk of serious disease (e.g. hypertension, obesity, osteoporosis); and

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98 Criteria retrieved from AIFA website in Italian and translated by the author: http://www.agenziafarmaco.gov.it/it/content/negoziazione-e-rimborsabilita

www.fwreports.com
iii) Treatments for non-serious diseases.\textsuperscript{99}

Where effective treatments already exist, new drugs are assessed to see whether they provide additional benefits, such as enhanced safety or a new method of action. Products are then rated according to whether they offer a major, moderate or minor therapeutic innovation.

\textbf{Orphan drug reimbursement}

In Italy, drugs are classified according to their reimbursement status. Class A medicines are reimbursed (regime di rimborsabilita), while Class C medicines are not reimbursed. Class A medicines are subdivided into Class A and Class A-H. Class A comprises essential drugs and drugs for chronic diseases, which are 100 per cent reimbursed by the national health service (SSN). These drugs are distributed in pharmacies. Some drugs can form part of the Territorial Hospital Formulary (PHT, or Prontuario Ospedale-Territorio) so they can be distributed via public establishments or normal pharmacies.

Class A-H comprises drugs exclusively used in hospitals; these are also 100 per cent reimbursed. These drugs are known as OSP drugs, due to their ‘hospital nature’. Some drugs under Class A-H can be classified as OSP 1 or OSP 2. OSP 1 drugs are prescription drugs used exclusively in hospitals or during day-hospital visits. OSP 2 drugs are prescription drugs used in hospitals, during day-hospital visits or outside of hospitals, depending on regional or provincial regulations.

According to an Office for Health Economics briefing,\textsuperscript{100} there are three channels through which orphan drugs have been made available in the SSN:

(i) The standard P&R process;
(ii) The Law 648/96; and
(iii) The five per cent AIFA special fund established in 2005 (Fondo AIFA).

\textsuperscript{99} International Society for Pharmacoeconomics and Outcomes Research website: \url{http://www.ispor.org/htaroadmaps/italy.asp#2}

Under the 'standard' process, medicines authorised either by the EMA centralised procedure or the national procedure have to go through the standard assessment of clinical value performed by AIFA. The reimbursement status is defined by AIFA based on the following criteria:

- Whether the new product is indicated for a disease with no alternative or adequate therapy;
- Whether the new product provides a better benefit-risk ratio than existing therapies;
- Whether the new product generates socio-economic benefits, which mainly refers to a lower price relative to the comparator(s).

AIFA operates a system of monitoring registers and conditional reimbursement for some drugs (mainly for oncology indications), which can provide patients with faster access to medicines. In a presentation for the Organisation for Professionals in Regulatory Affairs (TOPRA) Annual Symposium in 2011, Professor Guido Rasi identified three different ways to share responsibility and risk between pharmaceutical companies and the SSN:

- Cost sharing, which involves a discount on the price of initial therapy cycle(s) for all eligible patients;
- Risk sharing, which involves a discount on the price of initial therapy cycle(s) for non-responder patients; and
- Payment by results, whereby the initial cycle(s) is fully reimbursed by the marketing authorisation holder for non-responder patients and reimbursed by the SSN for responders.

Some orphan drugs are dispensed subject to details of the patient being entered into the National Registry of Orphan Drugs, which contains information on diagnosis, treatment response and clinical outcomes.

More information on Fondo AIFA and Law 648/96 is provided in the *Initiatives to improve access to orphan drugs in the EU* section of this report.


Spain

**Drug pricing**

Prices for prescription-only medicines are determined by the Comisión Interministerial de Precios de los Medicamentos (CIPM, or Inter-Ministerial Pricing Commission), which has representatives from the ministries of health, finance and industry. The CIPM will consider evaluation reports drawn up by the Agencia Española de Medicamentos y Productos Sanitarios (the Spanish Agency for Medicines and Medical Devices, or AEMPS), as well as reports produced by the Comité de Coste-Efectividad de los Medicamentos y Productos Sanitarios (Committee for Cost-Effectiveness of Medicines and Health Products). The committee comprises experts appointed by the Consejo Interterritorial del Sistema Nacional de Salud (Inter-territorial Health Council) at the proposal of the autonomous communities and the Ministerio de Sanidad, Servicios Sociales e Igualdad (the Ministry of Health, Social Services and Equality, or MSSSI, and formerly known as the Ministry of Health and Social Policy).

The MSSSI has the final decision making power and may establish a time period for which a reimbursement price is valid. Prices may be revised for technical, budgetary or health-related issues, although there are no formal post-launch price reviews.

Manufacturers receive a preliminary decision regarding the CIPM’s proposed price. If they disagree, manufacturers can appeal before a final decision is released. If the drug is not going to be reimbursed, the manufacturer is able to set a price and launch it as a non-reimbursed product.

**Orphan drug reimbursement**

Following marketing authorisation by the EMA or AEMPS, the MSSSI initiates a procedure to decide on reimbursement of this new product on the national reimbursement list. In its 2009 report on the rare diseases strategy, the MSSSI indicated that its efforts with regard to orphan drugs had significantly reduced the time taken to complete these procedures with regard to orphan medicinal products in Spain.103

At the time of writing its 2012 report on rare disease activities in Europe, EUCERD surmised that all orphan drugs approved by the EMA were reimbursed in Spain in one of two categories:

1) For use only in hospitals (hospital use: H) or;

2) In a non-hospital environment, but prescribed only by a specialist doctor (hospital diagnostic: DH).  

The EUCERD report indicated that 57 orphan medicinal products were fully reimbursed by the national health system and, in 2011, six new orphan drugs were included in the national reimbursement list: Vpriv (velaglucerase), Siklos (hydroxycarbamide), Cayston (aztreonam), Peyona (caffeine citrate) and Revatio (sildenafil).

However, while pricing and reimbursement issues are decided nationally in Spain, regional governments can add their own restrictions or cost-containment measures. These include issuing prescription guidance, setting a shadow reimbursement price, giving financial incentives to doctors and using health inspectors. In the case of orphan drugs, there may be protocols and systems to follow for patients to gain access to treatment under the national health system.

The regions are also able to set up managed entry agreements (MEAs), which usually involve price-volume agreements (PVAs) for new products, where the negotiated price is “conditioned by the expected number of units sold”. However, the final decision on how to manage the drugs budget of an individual hospital rests with the pharmacist.


UK

Drug pricing

Pharmaceutical pricing in the UK is set to change in 2014. The prices of all branded pharmaceuticals have been indirectly controlled by the Department of Health (DoH), under the Pharmaceutical Price Regulation Scheme (PPRS), which has been in place since 1957. The PPRS, which has undergone a number of major changes over the years, is the result of an agreement between government and the pharmaceutical industry, and provides a framework for negotiation.

The PPRS does not regulate prices directly, but limits the profits individual companies can make on their sales to the National Health Service (NHS). Manufacturers are free to set specific drug prices where they wish, but must not breach their overall profit limit. If they do, the excess must be paid to the government. The PPRS has been subject to renewal every five years, with the current scheme set to expire at the end of 2013.

In July 2010, the government published a White Paper, entitled Equity and Excellence: Liberating the NHS, in which it announced plans to introduce a value-based pricing (VBP) system in place of the PPRS. According to the White Paper, VBP would ensure that patients “get access to the medicines they need by linking the prices the NHS pays drug providers to the value of the treatment.” This point is reiterated in the consultation document on the UK plan for rare diseases, which states that “the price of a drug will be linked to its assessed value”.

The government plans to introduce VBP for new active substances placed on the market from January 1, 2014, equivalent to around 20 to 30 per year. Some existing medicines could be included within the system, but generics are not expected to be included. It is more likely that existing medicines will be included in a revised version of the PPRS.


The NICE has been given a new remit as part of the new scheme and will be responsible for assessing new drugs under VBP. According to a DoH press release, NICE will work with patient groups, the NHS and the pharmaceutical industry to decide how to value new drugs, based on the “best available evidence”.

Since inception, NICE has undertaken technology appraisals on the use of new and existing medicines and treatments within the NHS. NICE compares different treatments using a system that ascertains quality-adjusted life years (QALY). Having established the QALY for a drug, cost-effectiveness is measured in terms of how much the treatment costs per QALY. The appraisals programme is designed to ensure that people have equal access to new and existing medicines that are deemed to be both clinically- and cost-effective. Under VBP, NICE will be more involved in pricing decisions.

The influence of NICE technology appraisals has recently been further clarified, removing ambiguity at a local level. Previously, the wording of guidance for developing and updating local formularies included the phrase “if clinically appropriate.” In August 2013, this wording was removed and the recommendation now states: “Include medicines with a positive NICE technology appraisal into the local formulary automatically, if relevant to the services provided by the organisation. This process should take place within three months (see section 1.6). Include the medicine within the relevant care pathway(s), in line with NICE recommendations.”

The DoH also launched a consultation to strengthen the statutory pharmaceutical pricing scheme, which covers the prices the NHS pays for branded drugs not covered by the PPRS. According to the Association of the British Pharmaceutical Industry (ABPI), the statutory scheme applies to 10 per cent of the branded medicines used in the UK. The consultation, which ran from June 20 to July 31, 2013, sought views on a price cut on drug prices of between ten per cent and 20 per cent to ensure the NHS is getting good value for money.

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In addition, the DoH stated that it would continue to negotiate with industry on the PPRS, including how the results of a NICE value assessment will influence the price the NHS pays.

A Cancer Drugs Fund was introduced from April 2011, as an interim measure to give patients better access to drugs that their doctors recommend, whether or not these have been approved for NHS use by NICE.

**Orphan drug reimbursement**

In England, NICE is responsible for HTA. NICE generally considers each drug on a case-by-case basis, defining a cost-effective drug as one for which the incremental cost effectiveness ratio (ICER) per QALY, or the cost per life year gained is between £20,000 and £30,000 per year ($32,000 to $48,000).

This approach is difficult to apply to products for very small populations, so a subset of orphan drugs has been established where the prevalence of a disease in the UK is less than one in 50,000, with some exceptions. These are informally designated by NICE as “ultra-orphan drugs”.

Treatments for ultra-orphan conditions that present special difficulties meet all of the following criteria:

- High acquisitions costs and correspondingly high ICERs;
- Use in an ultra-orphan disease (no additional non-orphan indications);
- Use in ultra-orphan diseases that are chronic, severely disabling and/or life threatening; and
- Potentially for life-long use.

Ultra-orphan drugs marketed in the UK that fulfil these criteria include Cerezyme/Ceredase (imiglucerase) and Zavesca (miglustat) for Gaucher disease, Fabrazyme (agalsidase beta) for Fabry disease and Aldurazyme (laronidase) for mucopolysaccaridosis. With annual treatment costs of orphan drugs ranging from

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£50,000 to more than £300,000 per patient per year, estimates of the ICERs for ultra-orphan products invariably result in values that would not be considered cost-effective under NICE’s conventional criteria. Consequently, NICE would be most unlikely to recommend them for use by the NHS.

Scotland has its own system, the Scottish Medicines Consortium (SMC), which evaluates medicines and provides advice to the NHS in Scotland, in a similar way to NICE in England, Wales and Northern Ireland. The SMC analyses information supplied by the manufacturer on the clinical benefits of the drug and the justification of its price in order to assess whether or not a product represents value for money for NHS Scotland.111

According to the SMC, the assessment process for orphan drug submissions is the same as for all other drug submissions. However, “SMC may consider additional factors, such as whether the drug: treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; or bridges a gap to a “definitive” therapy.”112

111 Retrieved from Scottish Medicines Consortium website: http://www.scottishmedicines.org.uk/About_SMC/What_we_do/index

Send comments on this research to: feedback@fwreports.com
Orphan drug reimbursement in the US

Around 15 per cent of the US population is covered by Medicare. Access to orphan drugs falls mainly under Medicare Part D, which covers outpatient prescription drugs. Access to orphan drugs under Medicare depends partly on whether or not the drug is covered by the plan. Many orphan drugs are covered, but not all. The formulary tier on which the drug is placed is also a significant determinant, since different cost-sharing requirements are associated with each tier. For example, orphan drugs are often placed on the “specialty” tier, which is associated with high cost sharing. In addition, prior authorisation may be required, creating administrative barriers to treatment.

According to a report from the Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, Medicare prescription drug plan (PDP) coverage of orphan drugs is relatively extensive, in terms of the percentage of plans that cover drugs for rare diseases. The report states that the majority of drugs have either complete coverage (100 per cent) or high rates of coverage (more than 75 per cent) among PDPs. However, the report suggests, “The fact that many of these drugs are in protected classes (for either the orphan indication or another approved indication) may explain the high coverage rates of these drugs.”

The authors state that 26 orphan drugs were covered by fewer than 75 per cent of PDPs and four of these drugs were not covered by any PDP. Where a drug is not covered by a PDP, the full cost of the drug must be met by the patient out-of-pocket. It is also noted that there is higher coverage for orphan drugs in national PDP than in non-national plans, and among non-benchmark than benchmark plans. There was, however, “minimal use of quantity limits or step therapy, the latter of which was expected since there are often few, if any, therapeutic substitutes for these orphan drugs.”

In 2009, the Ryan Dant Health Care Opportunity Act of 2009 was introduced, amending title XIX (Medicaid) of the Social Security Act, as amended by the Children’s Health Insurance Program Reauthorization Act of 2009. This legislation permits “the option to disregard certain income in providing continued Medicaid coverage for certain individuals with extremely high annual lifelong orphan drug costs.”\textsuperscript{114}

The Affordable Care Act (ACA) was passed by congress and signed into law in March 2010. The June 2012, a final decision to uphold the healthcare law was rendered by the Supreme Court. From 2014, all private health insurance plans available through the Marketplace are obliged to offer a set of essential benefits, including prescription drugs. There are also schemes in place to cap out-of-pocket costs, depending on income. These new schemes may make healthcare more accessible to people with rare diseases.\textsuperscript{115}

\begin{quote}
\textsuperscript{115} More information is available on: \url{www.healthcare.gov}
\end{quote}
Availability and access to orphan drugs

Marketing authorisation (MA) for orphan drugs in the EU does not guarantee access for patients in all member states. Orphanet points out that the holder of the MA must decide on its commercialisation status and, the drug “will then go through numerous steps in each country in order to condition its management, and usually its price”.\(^\text{116}\) Despite efforts towards harmonisation, the time to market and availability of orphan drugs differs between EU member states.

Patient access schemes for specific treatments

Various patient access schemes (PAS) have been negotiated to improve access to rare disease therapies. PAS may provide an alternative route to market for some orphan drugs, whereby the manufacturer agrees to share the financial burden, particularly in the case of treatment failure. Various co-payment schemes are also in operation to assist patients for whom medicines would otherwise be unaffordable.

For example, Genzyme has a patient co-pay assistance programme for its enzyme replacement therapies in the US, in cases where patients’ prescriptions are not otherwise covered by state or federally funded healthcare programmes, such as Medicare or Medicaid.

Shire makes a number of specialty pharmaceuticals available to patients in the US through its Shire Cares patient assistance and support programme, for patients with limited financial resources who do not have prescription insurance or find difficulty in paying for their medicines. In addition, Shire Human Genetic Therapies (HGT) schemes provide co-pay assistance for eligible patients in the US who have commercial insurance. Shire’s OnePath programme offers co-pay assistance for certain patients who need help with paying for out-of-pocket medication costs.\(^\text {117}\)
A EURORDIS working paper\textsuperscript{118} discussed the variability of pricing and reimbursement decisions for a number of drugs approved for rare diseases. These were: Erbitux (cetuximab), Sutent (sunitinib), Lucentis (ranibizumab), Soliris (eculizumab), Fabrazyme (agalsidase beta), Replagal (agalsidase alfa) and Myozyme (alglucosidase alfa). Interestingly, the majority of these are no longer listed as orphan drugs in the EU, either because their period of market exclusivity has expired, or (in the case of Sutent) because the manufacturer has requested removal from the Community register.

\textit{Cetuximab and sunitinib}

In England, NICE recommends Merck KGaA’s Erbitux (cetuximab) in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), for the first-line treatment of metastatic colorectal cancer (MCC) under a PAS, whereby the manufacturer rebates 16 per cent of the amount of cetuximab used on a per patient basis.\textsuperscript{119}

In Scotland, there is a PAS for cetuximab in combination with chemotherapy for the treatment of MCC for a selection of patients, with an undisclosed discount on acquisition costs.\textsuperscript{120}

In Italy, AIFA has agreed a risk-sharing scheme for cetuximab for the treatment of MCC, whereby 50 per cent reimbursement applies in the case of therapeutic failure with eight weeks of treatment. For the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck, full reimbursement is applicable in the case of therapeutic failure within six weeks of treatment.

For Pfizer’s Sutent (sunitinib), similar cost-sharing PASs have been agreed in England, Scotland and Italy. In England, for the treatment of advanced or metastatic renal cell carcinoma (RCC) or gastrointestinal stromal tumours (GIST) the manufacturer offers the first cycle of treatment with sunitinib free of charge to

\begin{itemize}
  \item \textsuperscript{120} EURORDIS (2013) Op cit
\end{itemize}
the NHS. In Scotland, a similar PAS is available for the treatment of GIST, whereby each patient receives one cycle free of charge.

In Italy, there is a cost-sharing scheme for sunitinib in the treatment of advanced or metastatic RCC, whereby the manufacturer provides the first treatment cycle free of charge. However, sunitinib is recommended by AIFA for the treatment of GIST, alleviating the need for a PAS for this condition.

**Ranibizumab**

NICE guidance for ranibizumab was reissued in May 2012, following a change to the PAS. Under the revised PAS, ranibizumab is recommended as an option for the treatment of wet age-related macular degeneration. Details of the PAS have not been made public. The guidance simply states that, “it is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations”.\(^\text{121}\) Under the first PAS agreement in 2008, the cost of ranibizumab beyond 14 injections in each treated eye was met by the manufacturer.\(^\text{122}\)

A PAS discount scheme is also in operation in Scotland, the details of which remain confidential.

In Italy, there is a payment by results scheme, where full reimbursement of the cost applies in the case of therapeutic failure within three months of treatment.

**Eculizumab**

Eculizumab is licensed for the treatment of atypical haemolytic uraemic syndrome, a chronic and rare disease that causes severe inflammation of blood vessels and the formation of blood clots, leading to organ damage in children and adults.

According to NICE, around 140 people in England have been diagnosed with this condition and at least a further 140 people remain undiagnosed. NICE is currently

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evaluating the benefits and costs of eculizumab for this condition for commissioning by the NHS. Results are expected in July 2014.\textsuperscript{123}

In Italy, a PAS scheme has been agreed for eculizumab, whereby the manufacturer pays for the first two packages.

In France, a budget-ceiling scheme operates, under which the company agrees to provide the medicine free of charge beyond this ceiling.\textsuperscript{124}

\textbf{Egalsidase alfa and egalsidase beta}

Genzyme’s Fabrazyme (egalsidase beta) and Shire’s Replagal (egalsidase alfa) are used in the treatment of Fabry disease. Both were approved in the EU as orphan drugs, although this status has since been withdrawn as the products have reached the end of their market exclusivity period.

Prior to Sanofi’s acquisition of Genzyme, manufacturing issues resulted in shortages of Fabrazyme. However, in October 2013, Sanofi announced an $80 million investment in a manufacturing site for Fabrazyme in order to increase production and support an anticipated increase in global demand over the next few years.\textsuperscript{125}

EURORDIS has identified various PAS for these therapies across Europe, outlined in table 5 below. For example, in Italy, these treatments are available under AIFA’s monitoring registry, while in the UK, NICE has not formally reported on either of these treatments and prescribing decisions are made at local level.\textsuperscript{126}

In the US, Genzyme operates a co-pay assistance programme for patients who have been prescribed Fabrazyme. Once enrolled in the programme, Genzyme

\begin{itemize}
  \item \textsuperscript{126} EURORDIS (2013). Op cit
\end{itemize}
covers 100 per cent of eligible drug and infusion-related out-of-pocket costs, up to the programme maximum. Shire HGT provides assistance to certain patients who need help with paying out-of-pocket medication costs.

### Table 5: Patient access schemes for Fabrazyme (egalsidase beta) and Replagal (egalsidase alfa)

<table>
<thead>
<tr>
<th>Country</th>
<th>Agreements</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>100 per cent reimbursed</td>
<td>Reimbursed under a specific hospital budget scheme known as MIGAC.</td>
</tr>
<tr>
<td>Germany</td>
<td>100 per cent reimbursed</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>No rebates</td>
<td>Included in AIFA monitoring registry, which guarantees the use of the medicine when prescribed.</td>
</tr>
<tr>
<td>Spain</td>
<td>No rebates</td>
<td>Treatment and its potential continuation is decided based on Expert Group discussions.</td>
</tr>
<tr>
<td>UK</td>
<td>Left to counties</td>
<td>NICE has never formally reported on Fabrazyme or Replagal.</td>
</tr>
<tr>
<td>USA</td>
<td>Co-payment scheme for Fabrazyme</td>
<td>Genzyme will reimburse 100 per cent of eligible out-of-pocket drug and infusion costs up to the maximum allowed by the scheme, where patients’ prescriptions are not covered under any state or federally funded healthcare programme.</td>
</tr>
</tbody>
</table>

Source: EURORDIS, Genzyme
Alglucosidase alfa

Genzyme’s Myozyme (alglucidase alfa) is an enzyme replacement therapy used to treat Pompe disease. EURORDIS has identified various PAS for alglucidase alfa across Europe, outlined in table 6 below. The majority of these are similar to the agreements in operation for egalsidase alfa and beta. As with Fabrazyme, Genzyme operates a co-pay scheme for patients in the US.

Table 6: Patient access schemes for Myozyme (alglucosidase alfa)

<table>
<thead>
<tr>
<th>Country</th>
<th>Agreements</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Reimbursed in practice</td>
<td>Reimbursed under a specific hospital budget scheme known as MIGAC.</td>
</tr>
<tr>
<td>Germany</td>
<td>100 per cent reimbursement</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>No rebates</td>
<td>Included in AIFA monitoring registry, which guarantees the use of the medicine when prescribed.</td>
</tr>
<tr>
<td>Scotland</td>
<td>Formally can be reimbursed but “not recommended for reimbursement”</td>
<td>Reimbursed in some patients on the basis of a risk-sharing scheme, through a central national fund.</td>
</tr>
<tr>
<td>Spain</td>
<td>No rebates</td>
<td>Treatment and its potential continuation is decided based on Expert Group discussions.</td>
</tr>
<tr>
<td>UK (except Scotland)</td>
<td>Left to counties</td>
<td>NICE has never formally reported on Myozyme.</td>
</tr>
<tr>
<td>USA</td>
<td>Co-payment scheme</td>
<td>Genzyme will reimburse 100 per cent of eligible out-of-pocket drug and infusion costs up to the maximum allowed by the scheme, where patients’ prescriptions are not covered under any state or federally funded healthcare programme.</td>
</tr>
</tbody>
</table>

Source: EURORDIS, Genzyme
Access to medicines for rare diseases in the US

NORD Patient Assistance Services

Patient Assistance Services in the US were pioneered by NORD, which has administered more than 380 patient assistance programmes since 1987, and provided $56 million in free drug and co-pay assistance.\(^{127}\) NORD’s Patient Assistance Services focus on the needs of patients with rare disease, while supporting the business objectives of its partners in the pharmaceutical and biotech industry.

NORD’s range of services includes:

- **Medication Assistance Programs**, which provide drugs free of charge to financially eligible uninsured and underinsured patients.

- **Premium and Co-Pay Assistance Programs**, for patients with certain medical conditions who are unable to afford out-of-pocket costs associated with their plans.

- **Travel and Lodging Assistance for Clinical Trials**

- **Expanded Access/ Random Selection Program**, providing patients with information about clinical trials and also administers computerised random selection programmes when a limited amount of investigation drug is available.

- **Emergency or Limited Access Programs**, coordinating with manufacturers, prescribing physicians and regulatory agencies to register and screen patients for access to drugs that are outside the commercial distribution system.

- **Ancillary Access Programs**, offering additional support for diagnostic and laboratory testing.

Improving Access to Clinical Trials Act

In October 2010, the Improving Access to Clinical Trials Act became law, enabling patients with rare diseases to participate in clinical trials without losing eligibility for public healthcare. The law came into effect in April 2011. The bill was driven forward by the Cystic Fibrosis Foundation.\(^{128}\)

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Reporting on the new law, the National Hemophilia Association explained that the combination of a small number of potential participants for clinical trials, and the possible loss of Supplemental Security Income and Medicaid benefits for many who wish to participate, clinical “research for rare diseases and conditions becomes exceptionally difficult and may hinder research on new treatments and potential cures.”

Under the new law, the first $2,000 of compensation received annually by subjects for participation in clinical trials for rare diseases is no longer considered as income for when determining eligibility for Supplemental Security Income and Medicaid benefits. In some cases, money received as reimbursement for out-of-pocket costs, such as the cost of travel to the clinical trial, may also be excluded.

**Access to medicines for rare diseases in the EU**

**France**

Access to medicines that are either under development or approved in another country but do not have marketing authorisation in France is possible under a temporary authorisation for use (autorisations temporaires d’utilisation, or ATU) from the French national agency for medicines and health products safety (L’Agence nationale de sécurité du médicament et des produits de santé, or ANSM, and formerly AFSSAPS). According to the ANSM, ATUs may be granted in exceptional circumstances and on a temporary basis, providing the following conditions are met:

- Treatment, prevention or diagnosis of serious or rare pathologies;
- There is no suitable therapeutic alternative (medicinal product or other) available in France; and
- The benefit/risk ratio of the medicinal product is assumed to be positive.

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130 US Social Security Administration. Effect of money from clinical trials on SSI. Retrieved from: [http://ssa-custhelp.ssa.gov/app/answers/detail/a_id/2198](http://ssa-custhelp.ssa.gov/app/answers/detail/a_id/2198)

131 ANSM (2007) Notice to applicants for Temporary Authorisation for Use (ATU). Retrieved from: [http://ansm.sante.fr/var/ansm_site/storage/original/application/a211ad98e4e616212ae2d622f8f05488.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/a211ad98e4e616212ae2d622f8f05488.pdf)
In practice, there are two types of ATU: a nominative ATU, which concerns an individual named patient not taking part in biomedical research; and a cohort ATU, which concerns a group or sub-group of patients. A cohort ATU may be issued at the request of the holder of distribution rights of the drug, who must undertake to submit a marketing authorisation application within a stated time. It is important to note that the use of medicinal products subject to an ATU cannot replace a clinical trial and the aim is not one of investigation. In addition, an ATU must not be used for the purpose of continuing treatment of a patient who was previously treated as part of a clinical trial. In this case, continuity of treatment requires an extension of the clinical trial concerned by amending the protocol.

Nominative ATUs are available for single, named patients who are not participants in clinical trials. This type of ATU is issued at the request, and under the responsibility, of the prescribing physician. According to the ANSM, in 2010, around 15,000 patients were treated under the nominative ATU scheme.\footnote{ANSM. Autorisations Temporaries d’Utilisation. Retrieved (in French) from: \url{http://ansm.sante.fr/Activites/Autorisations-Temporaires-d-Utilisation-ATU/Autorisations-Temporaires-d-Utilisation/(offset)/0}}

In its 2009 annual report, the ANSM noted that, of the nine new marketing authorisations for orphan drugs in Europe during the year, six were already available in France under the ATU scheme.\footnote{ANSM. (2010, July) AFSSAPS Rapport Annuel 2009. Retrieved from: \url{http://ansm.sante.fr/var/ansm_site/storage/original/application/a40deaca3add3f9e767493ab831897e0.pdf}}

In order to allow off-label access to medicines, a temporary recommendation for use (recommandation temporaire d’utilisation, or RTU) may be granted. The conditions under which the ANSM may establish RTUs are specified in Decree 2013-742 of May 9, 2012. RTUs differ from ATUs in that they are only issued for medicines that are already commercialised in France for a different indication. However, like ATUs, RTUs are not substitutes for clinical trials. There are two qualifying conditions for an RTU:

\begin{itemize}
\item Qualifying condition 1: The medicine must be commercialised in France for an indication other than that for which it is being recommended.
\item Qualifying condition 2: The benefit-risk balance for the new indication must be demonstrated.
\end{itemize}
- There is an unmet therapeutic need, whereby there is no appropriate alternative medicine with an MA or a cohort ATU for the indication in question; and

- The benefit/risk ration of the medicine is assumed to be favourable, based on the available safety and efficacy data.\(^{134}\)

The guidance states that the ANSM will pay special attention to rare diseases. When a medicine is used to treat a rare disease for which there is a Centre of Expertise, it is possible for the pharmaceutical company to delegate patient monitoring to this centre, in whole or in part.

RTUs issued by the ANSM are designed to enable the use of medicines through the establishment of a patient-monitoring scheme organised by the pharmaceutical company concerned, and on a temporary basis, which may not exceed three years.\(^{135}\)

An Orphanet comparison of access to orphan drugs in Europe suggests access in France is rapid.\(^{136}\) Patients in France also have access to the vast majority of orphan drugs with EC marketing authorisation. A EURORDIS collaborative survey of access and prices of 60 orphan drugs across Europe in 2010 reported that 93 per cent of these were available in France, and 98 per cent of patients with rare diseases had potential access to orphan drugs.\(^{137}\)

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134 ANSM. (2012, October) Temporary Recommendation for Use (RTUs) Principles and information on the methods used by the ANSM for establishment and implementation. Retrieved from: http://ansm.sante.fr/var/ansm_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf


137 EURORDIS. (2011) Inventory of Access and Prices of Orphan Drugs across Europe: A Collaborative Work between National Alliances on Rare Diseases & Eurordis. Presentation retrieved from: http://www.eurordis.org/content/survey-patients’-access-orphan-drugs-europe
Germany
The off-label use of drugs is reimbursed by the statutory health insurance (GKV) under the following conditions:

- The drug will be used to treat a life-threatening or fatal disease;
- There is no alternative pharmaceutical therapy with a marketing authorisation in Germany; and
- There is scientific evidence of positive therapeutic effects. 138

The “compassionate use” of drugs was introduced into German legislation with the 14th amendment of the German Medicinal Product Act (AMG) and modified by the amendment of the AMG in July 2009. Under section 21, subsection 2, No. 6 of the AMG, a marketing authorisation is not required for medicinal products that are made available free of charge under the conditions specified in Article 83 of Regulation (EC) No. 726/2004 for administration to patients with a serious debilitating or life-threatening disease, who cannot be treated satisfactorily with an authorised medicinal product.

In July 2010, the Ordinance on Medical Products for Compassionate Use (AMHV) came into force. The AMHV introduce the “confirmed notification procedure” for compassionate use programmes, for which the federal institute for drugs and medical devices (BfArM) is the higher federal competent authority. A list of confirmed compassionate use programmes is available on the BfArM website, in German. 139

Patients with rare diseases have relatively easy access to orphan drugs in Germany, according to Orphanet. 140

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140 Orphanet. Early access to orphan drugs in Europe. Retrieved from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_EUR#Ava

www.fwreports.com
Italy

In 2012, consumption of orphan drugs in Italy, expressed in defined daily doses (DDDs), amounted to 5,905,112 at a cost of €671.2 million and accounting for 8.04 per cent of the total pharmaceutical spending of the public health system. According to AIFA, the five principal active ingredients in terms of having major impact on spending were: lenalidomide (19 per cent), bosentan (13 per cent), deferasirox (nine per cent), eculizumab (eight per cent) and alglucosidase alfa (six per cent), which together represented almost 56 per cent of total spending on orphan drugs. With regard to consumption, 63 per cent of the total DDDs were of the following active ingredients: bosentan (16 per cent), sildenafil (14 per cent), lenalidomide (13 per cent), deferasirox (12 per cent) and anagrelide (eight per cent).\(^{141}\)

A EURORDIS collaborative survey of access and prices of 60 orphan drugs across Europe in 2010 reported that 67 per cent of these were available in Italy.\(^{142}\) This percentage is broadly in line with a 2012 EUCERD report,\(^{143}\) which stated that 47 out of 66 orphan drugs authorised in the EU, had been launched on the Italian market. Among these, the cost of 44 was fully paid by the SSN, while three were reimbursed under Law 648/96. The report’s authors noted that, at the time of writing, the other approved orphan drugs had a pending request at AIFA with respect to pricing and reimbursement. A list of approved orphan drugs, containing the designated indication and date of listing in the official gazette is available from the national institute of health (Istituto Superiore di Sanità, or ISS).\(^{144}\)


\(^{142}\) EURORDIS. (2011) Inventory of Access and Prices of Orphan Drugs across Europe: A Collaborative Work between National Alliances on Rare Diseases & Eurordis. Presentation retrieved from: [http://www.eurordis.org/content/survey-patients’-access-orphan-drugs-europe](http://www.eurordis.org/content/survey-patients’-access-orphan-drugs-europe)


**Fondo AIFA**

Article 48 of Law 326 of 2003 established an innovative funding scheme for orphan drugs. Pharmaceutical companies in Italy are required to donate five per cent of their annual expenditure on promotional activities to a national fund for orphan drugs (Fondo AIFA). The fund is split equally between:

(i) The acquisition of orphan drugs for rare diseases that are not yet authorised, but which represent a hope of cure for serious diseases (allowing patients access to these drugs under the SSN). For the year 2012, the AIFA fund dispersed €901,130 for the treatment of 19 patients;

(ii) Independent research on the use of drugs. AIFA claims to be the first medicines agency in Europe to include among its tasks the promotion of independent research on drugs aimed at public institutions and non-profit organisations. Between 2005 and 2007, AIFA's fund was dedicated to rare diseases and orphan drugs, in order to undertake studies of efficacy and safety and to improve the treatment options for this particular subset of patients. Specific issues were the benefit/risk profile of orphan drugs approved by the EMA, and the benefit/risk profile of off-label treatment for rare diseases. Total funding provided by AIFA for rare diseases amounted to €13 million for 64 projects over this three-year period.

In addition to this, in 2008, AIFA contributed €3 million for 12 studies on rare diseases that were announced by the ministry of health.

**Law 648/96**

Under Law 648/96 patients may be able to access specified drugs under the SSN for which there is no available alternative therapy. These include innovative products that are marketed elsewhere but not authorised in Italy, medicines undergoing clinical trials but not yet authorised, and off-label use of products authorised for a different condition.

To be available under Law 648/96, drugs must be included in an official list, regulated by AIFA's technical and scientific advisory committee (CTS). For those

drugs on the list, prescription is available on a named patient basis. The full list of medicines as of December 2008 is available for download from AIFA's website. AIFA (2008) List of drugs that are available through the national health service under Law 648/96. Available (in Italian) from: http://www.agenziafarmaco.gov.it/sites/default/files/elenco1_farmaci_l648_rev.pdf

More information on the medicines included in the scheme is available on AIFA’s website (in Italian), including some additional medicines that have been added to the scheme since December 2008. AIFA, Special use of drugs: http://www.agenziafarmaco.gov.it/it/content/uso-speciale-dei-farmaci

A subsequent ministerial decree, published in the official gazette on May 8, 2003, provides therapeutic access to drugs that are undergoing clinical trials in cases where there is no therapeutic alternative available. This provision covers access to the medicine outside of the trial clinics to named patients who have not received the treatment as part of the trial, or for continued access for patients who have received the drug as part of a trial that has demonstrated an efficacy and tolerability profile. Under this decree, the medicine is provided free of charge by the manufacturing company. Ministry of Health Decree of May 8, 2003. Uso terapeutico di medicinale sottoposto a sperimentazione clinica (Therapeutic use of medicines undergoing clinical trials). Retrieved (in Italian) from: http://gazzette.comune.jesi.an.it/2003/173/2.htm

Spain

In Spain, the AEMPS can facilitate access to medicines that do not have marketing authorisation for compassionate use on an individual, named patient basis, or to groups of patients under a temporary authorisation of use protocol. Royal Decree 1015/2009, which was published in the official bulletin of the state in July 2009, sets out criteria for the provision of medicines in special situations.


147 AIFA, Special use of drugs: http://www.agenziafarmaco.gov.it/it/content/uso-speciale-dei-farmaci
(EC) 726/2004. Temporary authorisations enable compassionate use of medicines in the hospital setting.

Under the Decree, the compassionate use of drugs undergoing clinical trials may be authorised to patients who are not part of the trial. The procedure for access to investigational drugs is either via an authorisation for individual access, or an authorisation for temporary use. The Decree also provides access to drugs approved in countries other than Spain, and off-label use. As in other EU states, the use of a medicine under these rules cannot be for research purposes.

According to a 2012 EUCERD report, 83 per cent of orphan drugs authorised by the EC had been launched in Spain.\textsuperscript{150} Previously, a EURORDIS collaborative survey of access and prices of 60 orphan drugs across Europe in 2010 had reported that only 33 per cent of these were available in Spain.\textsuperscript{151} The results of this study also suggested that 49 per cent of patients with rare diseases had access to orphan drugs in Spain.

\textbf{UK}

Patients with rare diseases in the UK may be able to get access to developmental drugs for compassionate use on an individual, nominative basis. However, generally speaking, access to orphan drugs is considered to be slow in the UK.\textsuperscript{152}

During 2010, Rare Diseases UK (RDUK) undertook a survey of patients and families affected by rare diseases,\textsuperscript{153} the results of which indicated that a significant proportion of people with rare diseases do not receive an adequate response to their needs from the NHS. The survey represented 119 different rare and “ultra-rare” conditions, with respondents from all parts of the UK. Among the findings reported were inconsistencies in access to treatments and, while some patients

\textsuperscript{150} Aymé, S. and Rodwell, C. eds. (2012, July) 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases, 167.

\textsuperscript{151} EURORDIS. (2011) Inventory of Access and Prices of Orphan Drugs across Europe: A Collaborative Work between National Alliances on Rare Diseases & Eurordis. Presentation retrieved from: http://www.eurordis.org/content/survey-patients’-access-orphan-drugs-europe

\textsuperscript{152} Orphanet. Early access to orphan drugs in Europe. Retrieved from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_EUR#Ava

were informed of the availability off-label or unlicensed medicines, some patients and families often had to inform their doctors.

According to the report, around 35 per cent of responders were aware of an authorised treatment for their rare disease. Among these, 89 per cent stated they were in receipt of this treatment. Around 34 per cent of responders stated that there was no licensed treatment available for their rare disease, while the remaining 31 per cent did not know whether or not there was a licensed treatment available for their condition. Possible reasons suggested for this lack of knowledge included patients simply being unclear as to whether or not their treatment was licensed, or a potential reflection of a lack of information being available to the patient regarding their condition and treatment options.

Changes to drug funding are a cause concern for rare disease patients in England

In October 2013, a new campaign report was presented to the Health Minister by the All Party Parliamentary Group (APPG) for Muscular Dystrophy, warning that people with muscle-wasting conditions could be denied cutting-edge therapies owing to drastic changes to the way drugs are funded and assessed for rare diseases.

The report followed a six-month inquiry by the APPG, which was supported by the Muscular Dystrophy Campaign. According to the report - Access to high-cost drugs for rare diseases - parents of children with Duchenne muscular dystrophy fear that unnecessary delays, funding issues and bureaucracy may result in the “race against time” for their children to be treated being lost.

Members of the APPG “are particularly concerned that funds previously earmarked for rare disease drugs, have now been merged into the overall budget for NHS services commissioned across England. This leaves expensive therapies for rare conditions competing for funds with medications for prevalent conditions, such as diabetes or heart disease.” 154 According to the Muscular Dystrophy Campaign, the Members of Parliament (MPs) on the APPG also reported serious concerns over the NICE’s approval process for new drugs, which “they fear may delay cutting-edge therapies or prevent them reaching children and young people entirely”.

Trends in orphan drug development

Orphan drugs in the US

As of October 2013, the cumulative total of drugs with FDA orphan drug designation stands at 2,925. Of these, 446 have been approved for marketing, while 420 have been withdrawn. During the 30 years since the Orphan Drug Act was introduced in the US, the number of orphan drug designations has generally followed an upward trend. Between 1983 and 1992, 83 drugs received orphan designation. Over the following ten years, from 1993 to 2002, 151 drugs were granted orphan designation. Between 2003 and 2012, 188 drugs were granted orphan designation, while a further 24 achieved orphan drug status between January and October 2013.

While it is possible to apply for orphan drug designation at any stage during drug development, the majority of drugs are designated prior to clinical trials. The length of time between orphan drug designation and marketing authorisation is illustrated in figure 5 below, which shows the percentage of orphan drugs that have subsequently been approved, by year of designation. The more recently designated orphan drugs have a much lower rate of marketing approval, simply because a large proportion remain in development.
Although the number of designated orphan drugs has been following an upward trend, the number of orphan drugs that attain marketing approval each year has declined, particularly during the last decade. During the first ten months of 2013, 188 developmental drugs were granted orphan designation, while just three orphan drugs were approved over the same period. Since 2010, the number of orphan drugs approved for marketing in the US has been in single figures each year, suggesting it may be becoming more difficult to gain approval for orphan indications. By comparison, of the 40 drugs that were granted orphan designation in 1984, 23 were subsequently approved for orphan indications; equivalent to 57.5 per cent of the total.
### Table 7: Orphan drug designations and approvals in the US, 1983-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Designated</th>
<th>Of which approved</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1984</td>
<td>40</td>
<td>23</td>
<td>12</td>
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<tr>
<td>1985</td>
<td>50</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>1986</td>
<td>33</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>1987</td>
<td>58</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>1988</td>
<td>73</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>1989</td>
<td>76</td>
<td>19</td>
<td>30</td>
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<tr>
<td>1990</td>
<td>89</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>1991</td>
<td>81</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>1992</td>
<td>55</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>1993</td>
<td>65</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>1994</td>
<td>59</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>1995</td>
<td>57</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>1996</td>
<td>57</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>1997</td>
<td>54</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>1998</td>
<td>68</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>1999</td>
<td>78</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>2000</td>
<td>70</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>2001</td>
<td>79</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>2002</td>
<td>64</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>2003</td>
<td>96</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>2004</td>
<td>133</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>2005</td>
<td>124</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>2006</td>
<td>142</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>2007</td>
<td>118</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>2008</td>
<td>165</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>2009</td>
<td>165</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>2010</td>
<td>195</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>2011</td>
<td>203</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>189</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2013 (Jan-Oct)</td>
<td>188</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,925</strong></td>
<td><strong>446</strong></td>
<td><strong>420</strong></td>
</tr>
</tbody>
</table>

**Source:** FDA
The first orphan drugs were approved in the US in 1984. By October 2013, the cumulative number of marketing approvals had reached 446. Numerous companies operate in the diverse orphan drug market; more than 250 companies have drugs approved for one or two orphan indications. The leading companies in terms of the number of orphan drugs approvals are: Novartis, with 26 approved orphan indications; Roche, which has 22 approvals, mainly via Genentech; and GlaxoSmithKline, which has approvals for 18 orphan indications. In joint fourth place are Pfizer and Sanofi, with 14 approvals each. Sanofi gained most of its orphan drug approvals through its acquisition of Genzyme in 2011.
Table 8: Number of orphan drug approvals in the US, by company

<table>
<thead>
<tr>
<th>Company</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>26</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>22</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>18</td>
</tr>
<tr>
<td>Pfizer</td>
<td>14</td>
</tr>
<tr>
<td>Genzyme (Sanofi)</td>
<td>14</td>
</tr>
<tr>
<td>Bayer</td>
<td>10</td>
</tr>
<tr>
<td>Amgen</td>
<td>10</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>10</td>
</tr>
<tr>
<td>Celgene</td>
<td>9</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>8</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>6</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>6</td>
</tr>
<tr>
<td>Merck &amp; Co</td>
<td>5</td>
</tr>
<tr>
<td>Eisai</td>
<td>5</td>
</tr>
<tr>
<td>Cangene</td>
<td>4</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>4</td>
</tr>
<tr>
<td>Baxter Healthcare</td>
<td>4</td>
</tr>
<tr>
<td>Biomarin</td>
<td>3</td>
</tr>
<tr>
<td>Gilead Sciences</td>
<td>3</td>
</tr>
<tr>
<td>Lundbeck</td>
<td>3</td>
</tr>
<tr>
<td>Millennium Pharmaceuticals</td>
<td>3</td>
</tr>
<tr>
<td>Shire</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>256</td>
</tr>
</tbody>
</table>

*Source: FDA*
Figure 7: FDA orphan drug approvals, by company

Source: FDA
Almost one quarter of orphan drugs approvals are for oncology indications (23.1 per cent). By October 2013, the cumulative total of oncology approvals had reached 105. This far exceeds all other therapy areas. Immunology is in second place, with 41 orphan drug approvals, while 37 approvals have been granted for systemic hormones for orphan indications and 32 approvals have been granted for rare metabolic indications.

**Table 9: Orphan drug approvals in the US, by therapy area**

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>105</td>
</tr>
<tr>
<td>Immunology</td>
<td>41</td>
</tr>
<tr>
<td>Systemic hormones</td>
<td>37</td>
</tr>
<tr>
<td>Metabolism</td>
<td>32</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>32</td>
</tr>
<tr>
<td>Haematology</td>
<td>31</td>
</tr>
<tr>
<td>CNS</td>
<td>28</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>21</td>
</tr>
<tr>
<td>Antiprotozoals and anthelmintics</td>
<td>16</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>13</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>73</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>448</strong></td>
</tr>
</tbody>
</table>

*Source: FDA*
Figure 8: Orphan drug approvals in the US, by therapy area (%)

- Oncology: 23.4%
- Immunology: 9.2%
- Systemic hormones: 8.3%
- Metabolism: 7.1%
- Anti-infectives: 7.1%
- Haematology: 6.9%
- CNS: 6.3%
- Cardiovascular: 4.7%
- Musculoskeletal: 2.9%
- Antiprotozoals and anthelmintics: 3.6%
- Other: 20.5%

Source: FDA
Orphan drugs in the EU

As of October 2013, 66 orphan drugs are authorised by the EMA for marketing in the EU. Since 2002, the number of marketing authorisations (MAs) granted annually has been in single figures for most years. The exceptions are 2007, when 13 orphan drugs were approved, and 2012, when ten orphan drugs were approved. The MAs for two drugs that originally held orphan drug designation have since been withdrawn from the EU market: Pfizer's Onsenal (celecoxib) and Regeneron’s rilonacept.

Table 10: Orphan drugs approved in the EU, 2002-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Authorisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>2</td>
</tr>
<tr>
<td>2003</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>5</td>
</tr>
<tr>
<td>2005</td>
<td>3</td>
</tr>
<tr>
<td>2006</td>
<td>7</td>
</tr>
<tr>
<td>2007</td>
<td>13</td>
</tr>
<tr>
<td>2008</td>
<td>6</td>
</tr>
<tr>
<td>2009</td>
<td>6</td>
</tr>
<tr>
<td>2010</td>
<td>3</td>
</tr>
<tr>
<td>2011</td>
<td>5</td>
</tr>
<tr>
<td>2012</td>
<td>10</td>
</tr>
<tr>
<td>2013</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
</tr>
</tbody>
</table>

Source: EMA
There are more than 40 companies with MAs for orphan drugs, 30 of which each hold a single MA. The leading companies in the orphan drug space include Novartis with six MAs, while Shire, Pfizer, Celgene and Orphan Europe each have four MAs.
Figure 10: Orphan drugs authorised in the EU, by company

Source: EMA
Oncology indications account for 23 of the 66 orphan drugs approved for marketing in the EU, equivalent to 34.8 per cent of the total. A further 13 drugs are approved for metabolic conditions, seven are immunotherapies, and six are for the treatment of rare cardiovascular diseases, including pulmonary arterial hypertension. Among the six orphan drugs authorised for CNS disorders, two are approved for the treatment of rare forms of epilepsy.

Table 11: Orphan drugs authorised in the EU by therapy area

<table>
<thead>
<tr>
<th>Therapy area</th>
<th>Authorisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>23</td>
</tr>
<tr>
<td>Metabolism</td>
<td>13</td>
</tr>
<tr>
<td>Immunology</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>6</td>
</tr>
<tr>
<td>CNS</td>
<td>6</td>
</tr>
<tr>
<td>Hormones</td>
<td>3</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>66</strong></td>
</tr>
</tbody>
</table>

Source: EMA

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155 EMA, marketing authorisations for orphan drugs as of October 2013.
Figure 11: Orphan drugs authorised in the EU, by therapy area

![Bar chart showing orphan drugs authorised in the EU by therapy area.](chart)

Source: EMA

156 Op cit
Orphan drug commercial success stories

Orphan drug regulation was initialised to encourage companies to develop innovative therapies for rare diseases that were unlikely to be commercially viable. With a handful of notable exceptions, orphan drugs rarely become blockbuster products. However, companies are emerging as specialists in the orphan drug space and the combined sales of a portfolio of orphan drugs can realise revenues in the millions, or in some cases billions, of dollars.

According to a recent study, the commercial success of 18 orphan drugs in ten disease states indicated an 84 per cent approval rate from Phase II forward, compared with 35 per cent for non-orphan drugs.157

The companies featured in this section of the report have all achieved notable commercial successes in the rare diseases market. This list is not intended to be representative of all the players in the orphan drugs market; it simply highlights examples of successes that some companies have achieved in this sector.

157 Bernstein Research (2010, April). The long view: doing well by doing good – the advantages of adopting a family of orphans.
Table 12: Selected key therapies for rare diseases, by 2012 sales ($ million)

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>2011</th>
<th>2012</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glivec, Gleevec (imatinib)¹</td>
<td>Novartis</td>
<td>4,659</td>
<td>4,675</td>
<td>0.3</td>
</tr>
<tr>
<td>Tracleer (bosentan monohydrate)²</td>
<td>Actelion</td>
<td>1,722</td>
<td>1,600</td>
<td>-7.1</td>
</tr>
<tr>
<td>Soliris (eculizumab)</td>
<td>Alexion</td>
<td>783</td>
<td>1,134</td>
<td>44.8</td>
</tr>
<tr>
<td>Tasigna (nilotinib)</td>
<td>Novartis</td>
<td>716</td>
<td>998</td>
<td>39.4</td>
</tr>
<tr>
<td>Exjade (deferasirox)</td>
<td>Novartis</td>
<td>850</td>
<td>870</td>
<td>2.4</td>
</tr>
<tr>
<td>Afinitor, Votubia (everolimus)³</td>
<td>Novartis</td>
<td>443</td>
<td>797</td>
<td>79.9</td>
</tr>
<tr>
<td>Cerezyme (imiglucerase)⁴</td>
<td>Sanofi</td>
<td>441</td>
<td>633</td>
<td>43.5</td>
</tr>
<tr>
<td>Myozyme (alg glucosidase alfa)</td>
<td>Sanofi</td>
<td>429</td>
<td>594</td>
<td>38.5</td>
</tr>
<tr>
<td>Revatio (sildenafil)</td>
<td>Pfizer</td>
<td>535</td>
<td>534</td>
<td>-0.2</td>
</tr>
<tr>
<td>Replagal (agalsidase alfa)²</td>
<td>Shire</td>
<td>475</td>
<td>498</td>
<td>4.8</td>
</tr>
<tr>
<td>Elaprase (idursulfase)</td>
<td>Shire</td>
<td>465</td>
<td>498</td>
<td>7.1</td>
</tr>
<tr>
<td>Letairis (ambrisentan)</td>
<td>Gilead</td>
<td>376</td>
<td>429</td>
<td>14.1</td>
</tr>
<tr>
<td>Fabrazyme (agalsidase beta)²</td>
<td>Sanofi</td>
<td>152</td>
<td>375</td>
<td>146.7</td>
</tr>
<tr>
<td>Vpriv (velaglucerase alfa)</td>
<td>Shire</td>
<td>256</td>
<td>307</td>
<td>19.9</td>
</tr>
<tr>
<td>Volibris (ambrisentan)</td>
<td>GlaxoSmithKline</td>
<td>273</td>
<td>201</td>
<td>-26.2</td>
</tr>
<tr>
<td>Ventavis (iloprost)²</td>
<td>Actelion</td>
<td>120</td>
<td>118</td>
<td>-2.4</td>
</tr>
<tr>
<td>Firazyr (icatibant)</td>
<td>Shire</td>
<td>11</td>
<td>116</td>
<td>954.5</td>
</tr>
<tr>
<td>Mozobil (plerixafor)</td>
<td>Sanofi</td>
<td>82</td>
<td>103</td>
<td>25.6</td>
</tr>
<tr>
<td>Arzerra (ofatumumab)</td>
<td>GlaxoSmithKline</td>
<td>71</td>
<td>95</td>
<td>34.7</td>
</tr>
<tr>
<td>Zavesca (miglustat)</td>
<td>Actelion</td>
<td>77</td>
<td>90</td>
<td>16.9</td>
</tr>
<tr>
<td>Ilaris (canakinumab)¹</td>
<td>Novartis</td>
<td>n/a</td>
<td>72</td>
<td>~</td>
</tr>
<tr>
<td>Jakafi (ruxolitinab)³</td>
<td>Novartis</td>
<td>n/a</td>
<td>30</td>
<td>~</td>
</tr>
<tr>
<td>Veletri (epoprostenol)⁵</td>
<td>Actelion</td>
<td>17</td>
<td>26</td>
<td>52.9</td>
</tr>
</tbody>
</table>

Source: Company reports
1. Product was approved for orphan indication(s) but has been removed from the EC orphan drug register at the company’s request.
2. Product has been removed from the EC orphan drug register following expiry of ten years’ market exclusivity.
3. Votubia retains orphan drug status but Afinitor has been removed from the EC orphan drug register.
5. Product not approved for marketing in EU.
Actelion

Actelion is a world leader in the treatment of pulmonary arterial hypertension (PAH) and aims to sustain this position with its portfolio of approved and potential treatments. Actelion developed and launched Tracleer (bosentan), the gold standard in PAH with more than 44,000 patients on therapy. In 2012, sales of Tracleer amounted to CHF 1,500 million ($1,600 million). The company has two other products currently approved for PAH: Ventavis (iloprost) and Veletri (epoprostenol). Actelion markets Ventavis in the US, while Bayer Schering Pharma markets the drug outside the US. In 2012, Actelion reported sales of CHF 110 million ($118 million). Veletri was launched in the US in April 2010. This improved formulation of epoprostenol is stable at room temperature, alleviating the need for ice packs at most commonly used concentrations. Sales in 2012 were CHF 24 million ($26 million).

Actelion’s Zavesca (miglustat) is approved for Niemann-Pick type C (NP-C) disease in the EU and other markets outside the US. NP-C is a rare neurological disorder for which there is no cure. Zavesca is also approved in the US, EU and elsewhere for the treatment of adult patients with Type 1 Gaucher disease for whom enzyme replacement therapy is not an option. In 2012, Actelion reported sales worth CHF 85 million ($90 million).

Alexion Pharmaceuticals

Alexion is a biopharmaceutical company that focuses on the development of drugs for severe, life-threatening, ultra-rare disorders, including haematological, kidney and neurological diseases, transplant rejection, cancer and autoimmune diseases. The company’s first marketed product, Soliris (eculizumab), a first-in-class terminal complement inhibitor received its initial approval from the FDA in 2007 for the treatment of paroxysmal nocturnal haemoglobinuria (PHN). Soliris has subsequently been approved in the US and EU as a treatment for patients with atypical haemolytic uremic syndrome (aHUS). In 2012, sales of Soliris increased to $1,134 million, compared with $783 million in the previous year.

Alexion continues to investigate Soliris for additional indications, including Shiga toxin E. coli-related haemolytic uremic syndrome (STEC-HUS); pre-sensitised kidney transplant (acute humoral) rejection; severe and refractory myasthenia gravis; and severe and refractory neuromyelitis optica. Phase II trials are ongoing.
In February 2012, Alexion expanded its pipeline through the acquisition of Enobia Pharma, gaining asfotase alfa, a highly innovative, late-stage compound with the potential to treat hypophosphatasia (HPP). Due to a genetic defect, patients with HPP are deficient in an enzyme known as tissue non-specific alkaline phosphatase. Without this enzyme, patients can face severe outcomes, including progressive damage to multiple vital organs, destruction and deformity of bones, profound muscle weakness, impaired renal function, and respiratory failure. Asfotase alfa was awarded orphan drug designation in the US and EU in 2008 and Fast Track status in the US in 2009. A Phase II/III trial is ongoing, with expected completion in 2014.

GlaxoSmithKline

GlaxoSmithKline (GSK) has a number of products with orphan drug designation and, in 2012, the company created a separate 'rare diseases' therapy area. GSK’s total sales of rare diseases products amounted to £495 million ($784 million) in 2011.

GSK’s leading rare diseases products in terms of revenue are Flolan (epoprostenol) and Volibris (ambrisentan), both of which are indicated in the treatment of PAH. Flolan is an old product and is subject to generic competition in major markets. In 2012, GSK reported global sales of Flolan at £135 million ($214 million), a overall decline of 25 per cent from the previous year. At the same time, sales of Volibris increased by 35 per cent to reach £127 million ($201 million). Volibris is marketed by GSK outside the US. Gilead Sciences markets ambrisentan in the US as Leitairis.

Novartis

Although Glivec/Gleevec (imatinib) is no longer included on the EC orphan drug register, Novartis' rare diseases offering includes Tasigna (nilotinib), Afinitor/Votubia (everolimus) and Exjade (deferasirox). The company’s rare diseases portfolio achieved combined revenue of around $7.4 billion in 2013.

Glivec was initially approved for the orphan indication of chronic myeloid leukaemia in 2001, both the EU and US. It was subsequently approved for additional orphan oncology indications, including gastrointestinal stromal tumours (GIST), acute lymphoblastic leukaemia, dermatofibrosarcoma protuberans, chronic oesinophilic
leukaemia, hypereosinophilic syndrome, and treatment of myelodysplastic/myeloproliferative diseases. In order to ensure patient access to Glivec, “where needed and possible” for patients with rare cancers who cannot afford the drug, Novartis operated a patient access programme, which has reached some 52,300 patients. In 2012, Novartis reported sales of Glivec worth $4,675 million.

Novartis has also achieved significant commercial success with Tasigna (nilotinib), which is indicated for the treatment of adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia. In 2012, Novartis reported sales of Tasigna at $998 million. Novartis operates an expanded access scheme to Tasigna for patients with rare cancers.

Exjade (deferasirox) is also among Novartis’ top 20 products in terms of sales. Exjade is an iron chelator with orphan drug designation, used for the treatment of chronic iron overload. Sales of Exjade amount to $870 million in 2012.

Pfizer

In terms of revenue generation, Pfizer’s leading orphan drug is Revatio (sildenafil). Revatio has orphan drug designation in the EU, although it is not protected as an orphan drug in the US. Revatio is indicated for the treatment of patients with PAH, to improve exercise capacity. In 2012, Pfizer reported global sales of Revatio at $534 million, a similar level to the previous year. The expiry of the US patents in September 2012 for oral Revatio and May 2013 for the injectable formulation are likely to result in a significant reduction in revenue from this product over the coming years as it becomes vulnerable to generic competition.

The most recent addition to Pfizer orphan drug portfolio is Bosulif (bosutinib), which was approved by the EC in March 2013 for the treatment of adults with chronic myeloid leukaemia who are Philadelphia-chromosome-positive. Bosulif also has orphan drug designation in the US, where it was approved by the FDA in September 2012.

Vyndaqel (tafamidis) was approved in the EU in November 2011 for the treatment of transthyretin (TTR) amyloidosis in adult patients with Stage I symptomatic polyneuropathy to delay peripheral neurologic impairment. This product has yet to be approved by the FDA.
In the US, Pfizer has been granted orphan drug status for Xalkori (crizotinib), which received FDA approval in August 2011, for the treatment of patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test. Xalkori has been conditionally approved in the EU, but does not have orphan drug designation.

In May 2012, Pfizer received FDA approval for Elelyso (taliglucerase alfa) for injection for long-term enzyme replacement therapy in patients with Type I Gaucher disease. Marketing authorisation for this product was refused in the EU, where an existing therapy, Shire’s Vpriv (velaglucerase alfa) has orphan exclusivity for this indication.

Shire

In November 2013, Shire announced an agreement to acquire ViroPharma for around $4.2 billion, which will significantly strengthen the company’s rare disease portfolio. In a company press releases announcing the agreement, Shire Chief Executive Officer, Flemming Ornskov MD commented that the “acquisition is expected to create a $2 billion rare disease revenue base” in 2014, representing around 40 per cent of Shire’s total product sales.

ViroPharma’s Cinryze (C1 esterase inhibitor [human]), which is approved for the prophylactic treatment of hereditary angioedema (HAE), will complement its own HAE therapy Firazyr (icatibant). ViroPharma generated revenues of $428 million in 2012, with Cinryze posting US sales in the year of $321 million. Shire believes there is significant opportunity for future revenue growth for Cinryze in the US and other markets, as new HAE patients are identified and treated, and additional physicians gain experience with the therapy. ViroPharma also markets Plenadren (hydrocortisone) for adrenal insufficiency in adults and Buccolam (midazolam) for prolonged seizures in infants, children and adolescents, while its pipeline includes maribavir for the treatment of cytomegalovirus infection in transplant patients.

Shire has several approved orphan drugs targeting rare genetic diseases, including lysosomal storage disorders, such as Fabry disease, Gaucher disease and Hunter syndrome; and mucopolysaccharidosis II (MPS II). In addition to Firazyr, Shire’s Human Genetic Therapies (HGT) portfolio includes a number of enzyme replacement therapies: Replagal (agalsidase alfa), Elaprase (idursulfase), and
Vpriv (velaglucerase alfa). In 2012, the combined sales of these HGT products amounted to $1.4 billion. In addition to these, Shire’s Specialty Pharmaceuticals division markets Xagrid (anagrelide), which has orphan drug status in the EU.

**Sanofi**

Sanofi gained much of its rare diseases portfolio through the acquisition of Genzyme, which was completed in April 2011. Genzyme has particular expertise in rare genetic disorders, particularly enzyme replacement products to treat lysosomal storage diseases (LSDs), such as Gaucher disease, Fabry disease and Pompe disease. In 2012, Sanofi reported sales of rare disease products worth $1.7 billion.

Among Genzyme’s flagship products is Cerezyme (imiglucerase), an enzyme replacement therapy for the treatment of Gaucher disease. Cerezyme was approved by the FDA in May 1994 and by the EMA in November 1997. In 2012, Sanofi reported sales of Cerezyme at €633 million ($814 million).

Other principal enzyme replacement therapies for rare diseases are: Fabrazyme (agalsidase beta) for the treatment of Fabry disease, with sales of €292 million ($375 million) in 2012; and Myozyme/Lumizyme (alglucidase alfa), for the treatment of Pompe disease, with sales of €462 million ($594 million). Genzyme also developed Mozobil (plerixafor), which is used in combination with granulocyte colony-stimulating factor (G-CSF) in the treatment of lymphoma and multiple myeloma. Sales of Mozobil amounted to €96 million ($103 million) in 2012.
Conclusions

Rare diseases are a global problem. While each identifiable rare disease may affect only a small number of patients, rare diseases en masse affect millions of people around the world. This report highlights the need for drug developers and stakeholders to work together towards a common goal of ensuring access to appropriate healthcare for all patients with rare diseases.

There have been concerted efforts by regulatory agencies to harmonise certain aspects of orphan drug regulation, which are designed to make it easier for sponsors to successfully navigate regulatory requirements, particularly in the US and EU. There are also various incentives available to orphan drug developers in the US, EU and elsewhere. Among these, market exclusivity is particularly attractive, although the length of this exclusivity varies between countries.

International alliances of patient organisations are also helping to create significant knowledge pools about rare diseases that are useful to patients, doctors and drug developers alike. Among these, EURORDIS play a significant role, representing more than 500 rare disease patient organisations and over 4,000 rare diseases in more than 50 countries.

There is evidence to suggest that industry and patient organisations should work together to successfully develop innovative treatments for rare diseases. For example, the collaboration between Vertex Pharmaceuticals and the Cystic Fibrosis Foundation resulted in the development and approval of Kalydeco (ivacaftor) for a subset of CF patients with a rare genetic mutation. This example highlights the potential benefits of for companies working closely with patient organisations at an early stage of development in raising awareness of an innovative therapy, well in advance of marketing authorisation.

The US Office of Rare Diseases Research (ORDR) efforts to develop a Global Rare Diseases Patient Registry and Data Repository (GRDR) of anonymous, aggregated patient data should also help to unite drug developers with diagnosed, rare disease patients for clinical trials.
Marketing authorisation does not guarantee patient access to innovative drugs for rare diseases. While many countries have national health schemes that provide reimbursement for pharmaceuticals, there may be additional barriers or delays in getting high-cost orphan drugs added to reimbursement lists in some countries. However, it is possible for manufacturers and national agencies to successfully negotiate patient access schemes, whereby the manufacturer agrees to bear some or all of the cost of the drug, particularly in cases where treatment fails in an agreed timeframe. As healthcare providers continue to face budgetary constraints, it is likely to become increasingly important for industry and other stakeholders to work together to ensure patient access to innovative treatments.

However, scientific and technological advances have enabled significant progress in the development of innovative therapies for sub-groups of cancer patients in particular and there have been notable commercial success stories for drugs that were initially approved for orphan indications. While the number of orphan drugs reaching blockbuster status is likely to remain small, the total value of the orphan drugs market has been forecast to grow to more than 15 per cent of the global pharmaceutical market over the next five years. Several factors combine to make the orphan drugs market an attractive prospect for the pharmaceutical industry over the coming years, not least of which is the continued unmet medical need in a large number of rare diseases, and scientific advances that are making the development of innovative, targeted therapies to treat some of these conditions an achievable goal.