Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. *Revision 2005*

Introduction

Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products was adopted on 16 December 1999 and was published in the Official Journal of the European Communities on 22 January 2000[1]. It entered into force on 27 April 2000, the date of adoption by the Commission of the implementing regulation foreseen in Articles 3(2) and 8(4)[2]. Article 9 of the same regulation requires Member States to communicate to the Commission detailed information concerning any measure that have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. In addition, the Commission is required to publish a detailed inventory of all incentives made available by the Community and the Member States to support research into and availability of orphan medicinal products.

The first inventory was published in English in January 2001, and made available in all Community languages in June 2001. In November 2001, the Commission requested Member States to provide an update of the information available with a view towards preparing a 2002 version which was made public in August of that year.

In 2005, Member States were asked to communicate details on any measures introduced or in force since 2002. To complement the information collected by the Commission and to increase the level of information in the Inventory, the EMEA and Orphanet[3] contacted learned societies, patients' organisations, industry organisations, and other relevant stakeholders. Interested parties were requested to provide information on incentives for rare diseases at a national level. The information collected was then validated by the national competent authorities by the end of 2005. In addition, information on Community measures was requested from the different services of the Commission.

This third version therefore includes additional information received since the date of the second publication and represents the **status of such incentives as of end 2005**. Its publication follows the recently published general report on the experience acquired with the application of Regulation (EC) No 141/2000 on orphan medicinal products during the first five years of application[4].

The information in this inventory is intended to be updated on a regular basis.

---

[1] OJ L 18, 22.1.2000

[2] Commission Regulation (EC) No 847/2000 of 27 April 2000; OJ L 103, 28.4.2000

[3] Orphanet is an information site on rare diseases and orphan medicinal products for the general public. See http://www.orpha.net

[4] SEC (2006)832 of 20.6.2006, available at http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/orphan_en_06-2006.pdf

Aim of the Orphan regulation

The aim of the European Parliament and Council Regulation on Orphan Medicinal Products is to establish a Community procedure for designating orphan medicinal products and to introduce incentives for orphan medicinal products research, development and marketing, in particular by granting exclusive marketing rights for a ten year period[5].

In recent decades, medicine and medical research have made remarkable progress in saving lives, extending life expectancy and ridding the world of a number of diseases. The most spectacular successes of all have been in the use of vaccines to prevent childhood illnesses, in the use of antibiotics to combat infectious diseases and in the development of anti-viral medicinal products for the prevention or treatment of AIDS. Great strides have also been made in the diagnosis, prevention or treatment of cancer and cardiovascular diseases.

Nevertheless, there are still a great many diseases which cannot be treated satisfactorily and for which no medication or other diagnosis, prevention or treatment is available. In addition to the widespread and well-known diseases of this kind, there is also a whole series of diseases which affect relatively few people; approximately 5,000 such diseases have been identified. The pharmaceutical industry is reluctant to develop medicinal products to treat these diseases: pharmaceutical research and development are so expensive nowadays that there is practically no chance of any company making the effort to develop a medicinal product, to obtain authorisation for its use and to place it on the market if it is to be supplied at normal prices to the few patients who require it. That is why such medicinal products are known as "orphan medicinal products".

Society cannot accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. It is therefore up to the public authorities to provide the necessary incentives and to adapt their administrative procedures so as to make it as easy as possible to provide these patients with medicinal products which are just as safe and effective as any other medicinal product and meet the same quality standards.

In the United States, an incentive system for the development of orphan medicinal products (the "Orphan Drug Act") was introduced in 1983. All designated orphan products are eligible for a federal tax credit equal to 50 % of the clinical research expenditure; orphan products are exempted from the application fee for FDA approval, and the first product authorised for a specific indication gets a seven-year marketing exclusivity period. Congress also appropriates around $ 20 million for FDA for grants for orphan products. These measures have been very successful in stimulating the research and development of Orphan Medicinal Products, so much so that a number of other

[5] It is anticipated that a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 will be adopted and enter into force after the publication of this inventory. Article 37 of that Regulation, as it stands after the second reading in the European Parliament, provides that for medicinal products designated as orphan medicinal products, if specified criteria in the paediatric regulation are met, the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years.

countries have sought to emulate it. A similar regime was introduced in Japan in 1995, in Singapore in 1997 and in Australia in 1998.

In the European Union, in the course of the 1990's, a number of Member States adopted specific measures to increase knowledge on rare diseases and to improve their detection, diagnosis, prevention or treatment. In some cases, the relevant legislation or administrative provisions include a reference to the concept of "orphan drug" or "uneconomic drug". These initiatives, however, until recently have been few and far between and have certainly not led to any significant progress in research on rare diseases.

The objective of the Orphan Regulation is to advance this progress, by introducing a number of direct incentives, but also by encouraging Member States to adopt similar and/or complementary measures at a national level.

1. COMMUNITY MEASURES

1.1. The Regulation on Orphan Medicinal Products

The principal measure introduced by the Community is, undoubtedly, the Regulation on Orphan Medicinal Products. As of end 2005, 548 applications for designation as Orphan medicinal products were received by the European Medicines Agency (the Agency) and 350 positive opinions on the granting of designations had been adopted by the Committee for Orphan Medicinal Products. Of these, 342 had been translated into Community decisions. As of end 2005, 156 of applications were withdrawn by the sponsors before the adoption of opinions as the corresponding products were unable to successfully meet the criteria of the regulation.

A summary of the information as of end 2005 is provided in the table below:

Year	*Applications submitted*	*Positive COMP Opinions*	*Applications withdrawn*	*Final negative COMP Opinions*	*Designations granted by Commission*
2005	118	88	30	0	88
2004	108	75	22	4	72
2003	87	54	41	1	55
2002	80	43	30	3	49
2001	83	64	27	1	64
2000	72	26	6	0	14
Totals	**548**	**350**	**156**	**9**	**342**

Incentives

The principal direct incentives introduced by this Regulation are as follows:

(1) The introduction of a **designation procedure** for orphan medicinal products.

Designation as an orphan medicinal product may be applied for on the basis of an application to the Agency. Further details are available on the following web addresses:

http://www.emea.eu.int/htms/human/comp/orphapp.htm

http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm

The orphan medicinal products designated so far include possible treatments for conditions such as Fabry disease, agromegaly, myoclonic epilepsy, erythem nodusum leprosum, acute myeloid leukaemia, Gaucher disease. Approximately one third of all applications concern some form of cancer. The full listing can be found at the following web-address: http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm

On the basis of this designation, the possibility of **fee waivers** from the fees relating to the marketing authorisation procedure, including from fees for the provision of protocol assistance or scientific advice, marketing authorisation, inspections, renewals etc. In 2005, fee reductions granted to orphan medicinal products amounted to 6,842,900 EUR.

The key incentive in the regulation is the 10 year **market exclusivity** provision. This is also based on the designation as an orphan medicinal product. Market exclusivity is unanimously regarded as crucial to any system of incentives for research and development work on orphan medicinal products. In the regulation, market exclusivity is granted only where the medicinal product has been designated as an orphan medicinal product by the Community and where either the Community or all 15 Member States have issued marketing authorisations in respect of the medicinal product concerned. The protection thus granted prevents the Community or a Member State from subsequently issuing a marketing authorisation for a similar medicinal product (e.g. the same active substance) and for the same indication. It does not prevent the marketing of another product for the same indication, which would constitute an unjustified restriction on therapeutic innovation, on the rights of third parties and on patient expectations. Moreover, it is anticipated that a Regulation of the European Parliament and of the Council on medicinal products for paediatric use will be adopted and enter into force after the publication of this inventory. Article 37 of that Regulation, as it stands after the second reading in the European Parliament, provides that for medicinal products designated as orphan medicinal products, if specified criteria in the paediatric regulation are met, the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years.

Protocol assistance refers to the provision of scientific advice to potential applicants for marketing authorisations on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the product. The development of an orphan medicinal product may present specific problems which must be taken into account. To take but one example, it may be difficult to find enough patients willing to take part in clinical trials for a medicinal product which might be of benefit only to a very few people. Therefore the facility to have scientific advice from experienced experts prior to making an application is an important incentive designed to aid the development of an orphan medicinal product. Uptake of protocol assistance by sponsors has been extensive and is increasing markedly over time. During the first five years of application of the orphan regulation over 80 protocol assistance procedures have been completed.

The regulation also provided for the possibility of a **Community marketing authorisation** for a designated orphan medicinal product. This Community marketing authorisation (issued by the Community under what is known as the "centralised procedure") is the simplest and quickest way of placing medicinal product on the market throughout the Community. Following the requirements set by Regulation (EC) No 726/2004 of the European Parliament and of the Council[6], as of 20 November 2005, the centralised procedure of marketing authorisation became mandatory for all designated orphan medicinal products. Up to December 2005, 24 designated orphan medicinal products had received marketing authorisation, 22 via centralised procedure and 2 via national procedures.

The regulation set up a **Committee for Orphan Medicinal Products (COMP)**. This committee is responsible for the scientific examination leading to designation of an Orphan Medicinal Product and has been in operation since April 2000. The COMP is composed of: a chairman, elected by serving COMP members; one member nominated by each EU Member States; three members nominated by the European Commission to represent patients' organisations; three members nominated by the European Commission on the EMEA's recommendation; one member nominated by each of the EEA-EFTA states (Iceland, Liechtenstein and Norway); one European Commission representative; and various observers. In the course of its designation work, the COMP has identified **experts on specific orphan diseases** and a database of these experts is being established. The aim of this exercise is to increase the European knowledge base about rare diseases, with the intention of being able to refer to these experts during subsequent evaluation of specific products or when providing scientific advice or protocol assistance. As of end 2005, more than 350 experts had been nominated.

On an international level, the COMP has developed international liaison with medicines agencies in North Amercia and Japan on orphan medicinal products. At the same time, the COMP has also cooperated with the World Health Organsiation (WHO) and other Non-governmental Organisations (NGOs) on neglected diseases.

In addition a **COMP working group with interested parties** (COMP-WGIP) composed of EMEA/COMP members and representatives of patient organisations and the pharmaceutical industry, established in 2001, meets 3-4 times per year. The mandate of the group encompasses transparency with regards to the designation procedure and preparation of policy proposals on orphan medicinal products.

1.2. The Rare Disease Task Force

The Rare Disease Task Force (RDTF)[7] is one of the main forums for discussion and exchange of views and experience in all issues related to rare diseases. It was set up in January 2004 by the Commission Services and it aims at giving advice and assisting the European Commission in promoting the optimal prevention, diagnosis and treatment of rare diseases in the EU, in recognition of the unique added value to be gained by rare diseases through European coordination. Members of the RDTF are current and past leaders of projects funded by Community public health and research programmes,

[6] OJ L 136, 30.4.2004

[7] http://www.rdtf.org

experts nominated by Member States and representatives of relevant international organisations (e.g. Euroepan Institutions, EMEA, WHO, OECD).

1.3. Specific Community research opportunities

The European Union supports research into rare diseases and orphan medicinal products through its multiannual Framework Programmes for Research and Technological Development (FP).

Support is granted to projects having successfully undergone a peer-review evaluation by independent experts in answer to call for proposals, issued regularly by the European Commission.

In Framework Programme 5 (FP5), which operated from 1998-2002, research on rare diseases and orphan drugs was conducted as disease-driven or technology-driven (tool-developing) projects in various scientific fields such as genetics, neurology, immunology, metabolic diseases, cancerology, mycology, infectious diseases, nephrology or dermatology. Different types of projects were supported: research, coordination of research, research infrastructures. A total of **47 projects** was granted **64 Million Euros** support in the FP5 Thematic Programme "Quality of Life and Management of Living Resources": 37 in the Generic Activities section, amounting at 48 Million Euros; and 10 in the "Cell Factory" section, for a total budget of 16 Million Euro. A list of these projects can be found in Annex 1. More information on the Quality of Life Thematic Programme can be found on: http://www.cordis.lu/life/.

Given the tremendous developments of the genome deciphering and its expected medical applications, the "Health" Thematic Priority of the current Framework Programme 6 (2002-2006) focuses on "Life Sciences, Genomics and Biotechnology for Health". In Priority 1, actions are undertaken to integrate clinical expertise and resources with relevant model systems and advanced tools in functional genomics to generate breakthroughs in the prevention and management of rare diseases. Emphasis is in particular put on translational research, aimed at bringing basic knowledge through to clinical application. The major support to rare diseases and orphan drugs development is provided through Priority 1.

FP6 has seen the introduction of new types of projects, Integrated Projects and Networks of Excellence, high-scale projects designed for the former to provide new knowledge through multidisciplinary approaches, or for the latter to durably integrate research activities of the participants. These broad projects, particularly suited to translational research, should allow to tackle scientific issues relevant to groups of diseases (for example, disorders of mitochondrial oxidative phosphorylation), to develop tools that can be applied in ranges of diseases (such as safe and efficacious retroviral transgenesis for gene therapy), or to answer more "horizontal" questions generally relevant to rare diseases, which need harmonisation (such as genetic testing).

In addition to these high-scale projects, smaller scale research, coordination and support projects are providing the rare diseases community with opportunities to answer focused needs, on disease-specific bases or to coordinate a delineated field of research.

As in FP5, projects supported in FP6 address a variety of diseases and apply different approaches (high-throughput screening, *in vitro* and animal models, structural chemistry etc.)

At mid-term of FP6, 27 projects were selected for support in Priority 1, representing a global budget of 96 Million Euros.

Among these, a project referencing national and European research projects, aiming at the identification of research projects at a near-to-the-market stage of development, and offering a platform for collaboration between academic and industrial partners, as well as allowing patients to signal their interest in participating in current/future research.

Besides Priority 1, other projects were funded within Research for Policy Support ("Priority 8") and the ERA-Net scheme of Coordination of Research Activities.

In Priority 8, a project should provide insight for future policies in primary immunodeficiencies.

The "ERA-Net" scheme supported a project to study the feasibility of coordinating national research programmes on rare diseases.

Altogether, 29 projects were contracted for a global budget around 100 Million Euros.

Several projects selected through calls for proposals issued in 2004 are currently being negotiated and contracted. The estimated total budget for these projects is 40 Million Euros.

More information on FP6 Priority 1 can be found on http://www.cordis.lu/lifescihealth/home.html.

A list of projects funded at mid-term of FP6 is provided in Annex 2.

2. MEMBER STATES MEASURES[8]

2.1. Austria

According to information collected for the publication of the first inventory in 2001, in Austria, the Austrian Drugs Act provided for the **waiving of fees** (e.g. for marketing authorisation or variations) for orphan drugs authorised through the national procedure. (applicable until 20 November 2005, date from which the centralised route of marketing authorisation of designated orphan medicinal product became mandatory). Austria has not notified any additional measures.

[8] The information regarding Member States Measures has been collected from various national stakeholders and validated by the relevant national competent authorities as of end 2005. The European Commission cannot take responsibility for the accuracy or completeness of this compilation.

2.2. Belgium

In Belgium, one of the most important measures has been the adoption of the Royal Decree of 8 July 2004 on the **reimbursement of orphan medicinal products** (*Moniteur Belge*, 20 July 2004).

This Decree, which entered into force on 20 July 2004, created a 'Committee of Doctors for Orphan Medicinal Products" within the Healthcare service of the INAMI (*Institut national d'assurance maladie invalidité* – National Invalidity Insurance Institute), the body responsible for issuing opinions on orphan medicinal products when an opinion is required, including with regard to evaluating individual rights to reimbursement. It also evaluates the existing reimbursement conditions for these products and draws up an annual activity report.

There is an accelerated review process for orphan medicines. In order to obtain reimbursement, a budgetary impact study is necessary and a Solidarity fund helps patients get reimbursement.

Several drafts for other legal acts relating to orphan medicinal products are currently under discussion:

– Draft law submitted to the Chamber of Representatives on 22 November 2005 - draft 51K2098. This draft is currently being examined by the Chamber of Representatives. Article 90 of this draft extends the definition of orphan medicinal products compared to the definition in the law on obligatory health care insurance and indemnities, coordinated on 14 July 1994, with a view to also taking into account orphan medicinal products registered in Belgium or for which an application for registration was submitted before 28 April 2000 and which satisfy the conditions set out in Article 3 of Regulation (EC) No 141/2000 and the criteria in Article 2 of Regulation (EC) No 847/2000. Article 92 of the draft provides that orphan medicinal products will be taken into account *inter alia* in the application of this Article, in order to create a **broader basis for reimbursement** for the flat rate reimbursement of medicinal products in hospitals.

– Draft **to extend the reimbursement of orphan medicinal products to self-employed workers.** One peculiarity of the Belgian health insurance system is that self-employed workers are insured only for what are known as "major health risks", mainly hospitalisation. With regard to "minor risks", including the need for medicines, self-employed workers who wish to may take out specific health insurance with a mutual society so as to be covered for "minor risks", upon payment of a specific contribution. The aim of this draft is to have the need for certain orphan medicinal products (FABRAZYME, REPLAGAL, TRACLMEER, ALDURAZYME) reclassified as a "major health risk", allowing self-employed workers to be reimbursed for them. The draft should be concluded in the first quarter of 2006.

– Draft **to have orphan medicinal projects excluded from the calculation basis for contributions, based on the turnover of pharmaceutical products for 2006**. Since 1995, the pharmaceuticals industry has had to contribute to the funding of social security by paying a contribution based on its turnover on the Belgian market for reimbursable pharmaceutical products. The aim of this draft law is to refine the system of turnover-based contributions and to better distribute the solidarity effort. This contribution on the basis of turnover will be scrapped for certain categories of

proprietary pharmaceuticals, such as orphan medicinal products. Reforming the turnover-based contribution system will also offer the opportunity to reduce the charges on pharmaceutical businesses making large investments in research and the development of new proprietary medicinal products, thus contributing to medical progress. It is therefore desirable to lower contributions for those enterprises conducting research into developing new medicines. The new system will provide for a modified system for small pharmaceuticals businesses. SMEs experience specific economic difficulties but continue to play an important role in the development of medicines. This draft law will be presented to Parliament in January 2006 for adoption. The law will apply to contributions due for 2006 and subsequent years.

Support for academic / industrial research on rare diseases is done via private funding for research through patients associations.

To foster **public information,** the National fund for scientific research (francophone) has created a contact group on rare diseases.

Clinical reference (integrated) centres for medical genetics: 8 centres for human genetics, each affiliated with major university and 6 publicly-funded, university hospital-based units in charge of patients with inborn errors of metabolism

2.3. Cyprus

Cyprus has not reported any national measures to support research into, or the development and availability of orphan medicinal products or medicinal products that may be designated as such.

2.4. Czech Republic

Under Act No 368/1992 Coll. on administrative fees as amended, **administrative fees are not charged** for applications for the registration of medicinal products or for an amendment, extension or transfer of registration of a medicinal product or for authorisations for parallel import of a medicinal product, if the application concerns a medicinal product included in the register of orphan medicinal products under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

Under §65(2)(b) of Act No 79/1997 Coll. on medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may **refrain from recovering costs where these concern operations which are in the public interest** or may have specially important implications for the wider population. These operations include applications for:

– authorisation/registration of clinical assessments of medicinal products and notification to the submitter of additions to the records in cases concerning the evaluation of an orphan medicinal product, and consultation and opinions on such applications;

– application for registration of an orphan medicinal product and application for amendment, extension or transfer of registration or application for authorisations for parallel import of an orphan medicinal product and consultation and opinions on applications concerning orphan medicinal products

Under §26d(1) of Act No 79/1997 Coll. on medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may, in the case of orphan medicinal products in justified cases meeting the conditions laid down by decree, allow **the registration of a medicinal product or the placing on the market of individual batches of a medicinal product even where the data are indicated on the packaging in a language other than Czech**.

2.5. Denmark

The Danish Medicines Agency provides **free scientific advice**.

In special cases and to a limited degree, the Danish Medicines Agency **can authorise the sale or dispensing of medicinal products that are not marketed in Denmark for other purposes than clinical investigations** (cohort or named patient supply).

Patients with life-threatening diseases for which there are no well-documented treatment options can be offered experimental treatment (named patient supply only).

Center for små handicapgrupper (www.csh.dk) holds a **public database on rare diseases** that gives information, provides guidance and contact with patient organisations.

Within the national health system, Denmark has a system of designation of **referral centres / highly specialised centres** for a number of different conditions, diseases or procedures, in the form of a catalogue from the National Board of Health made in dialogue with the local health authorities and the medical expertise. The general criteria for establishing such referral centres are rareness, complexity, multidisciplinarity and costly diagnosis and treatment. This catalogue is revised regularly. The catalogue as a whole contains lists of about 300 – 400 different conditions from groups of diseases as a whole to a single specific disease or procedure. About 100 different referral departments are located in one of the five university hospitals. As part of this general system the National Board of Health launched a special report in 2001 regarding rare diseases recommending that Denmark established two centres at university hospital level (one west, one east) for rare diseases, each covering approximately 14 specific diagnoses which did not already have a designated centre:

– Rigshospitalets Klinik for sjældne handicap (Rigshospitalets Clinic for Rare Disorders), Copenhagen (http://www.hosp.dk/rh.nsf/574e4fb13671535fc1256e9100413675/2dc63c3c0b7944bac1256f2a0048ddd4?OpenDocument)

– Centre for rare diseases at Aarhus University Hospital, Skejby Sygehus (http://www.auh.dk/sks/index_e.htm)

2.6. Estonia

On the basis of appropriate applications, Eesti Teadusfond (Estonian Science Foundation) supports at national level research on rare diseases, making no distinction between that and other scientific research (approx. EEK 600-800 over four years).

There is no concrete list of orphan medicines for reimbursement. Reimbursement of the price of medicines to patients is made from joint medical-insurance funds on the basis of *Eesti Haigekassa* (Estonian Health Insurance Fund)'s **medicine reimbursement budget in accordance with the diagnosis**, where the criterion for establishing the selection of corresponding diagnoses is not so much the incidence of the disease as its seriousness and mortality, the possibility of an epidemic, the need for alleviating the associated pain or other humane considerations, its chronic nature together with the impairment caused to the quality of life, and the match with the financial possibilities of the medical insurance scheme. There are also rare diseases in the catalogue of described diagnoses.

Measures for the **prevention, early detection or treatment** of rare diseases are constituted in particular by DNA diagnostics and screening programmes for newborn infants (see http://www.dnatest.med.ee).

Support for patients' associations comes from a national budget for *Eesti Patsientide Esindusühing* (Estonian Patients' Association). In addition there are plans to use funds arising from the gambling tax for project-based financing of patients' associations.

2.7. Finland

The National Agency for Medicines [*Lääkelaitos*] may grant **exemptions from marketing authorisation fees**. This rule applied to orphan medicinal products until 20 November 2005 when the centralised route of marketing authorisation became mandatory for designated orphan medicinal products.

The National Agency for Medicines gives **free administrative and scientific advice** to bodies developing orphan medicinal products. Furthermore, the special status of orphan medicinal products has been taken into account in inspection and authorisation procedures.

In terms of drug development, an important role is also played by **funding aimed at medical research**, which also includes research work into rare diseases and their medical treatment. For example, the National Technology Agency Tekes [*Teknologian kehittämiskeskus*] launched the Drug 2000 programme at the beginning of 2001 and finishing in 2006, the object of which is to bolster drug development in Finland, create new (and expand existing) research networks, enhance the competitiveness of service units and enterprises in the field of research and stimulate new international business in the medical field. The programme is also financed by the Finnish Academy and Sitra, annual funding totalling FIM 100-150 million. Medical research by the Ministry of Social Affairs and Health in the administrative sector is funded by means of a special State contribution for university hospitals, the total amount last year being around FIM 337 million. Part of this funding for research goes towards research on orphan medicinal products.

A **seminar** dealing with orphan medicinal products was held in Finland in Spring 2001

All medicines with a wholesale price approved by the Pharmaceuticals Pricing Board are automatically entitled to **reimbursement** under the basic refund category (50% reimbursement in 2005). A reasonable wholesale price refers to the maximum price at which the product may be sold to pharmacies and hospitals. The holder of marketing authorisation must be able to justify the reasonableness of the proposed wholesale price for a medicinal product that is to serve as a basis for the reimbursement payments. The application must include a detailed, comprehensive assessment of the cost of the drug therapy and the benefits expected to be gained thereby. Moreover, the application must include an evaluation of the product in relation to alternative drug treatments and other therapies. The application must also include the validity period of the pharmaceutical patent or a supplementary protection certificate, an estimate of the sales volume and number of users of the product over the next three years as well as the approved price and ground for reimbursement of the product in other EEA countries. Applications concerning medicinal products containing a new active substance must contain a health economic evaluation.

When considering the reasonableness of the proposed wholesale price, the Pharmaceuticals Pricing Board takes into account the cost of the drug therapy and the benefits to be gained from its use as regards both the patient and the overall health care and social costs. The Pricing Board will also consider the cost of the treatment alternatives, the prices of comparable medicinal products and the price of the medicine in question in other EEA countries. Manufacturing, research and development costs are also taken into consideration when making a decision on application, if they are considered relevant by the applicant, as are the funds allocated for reimbursement payments.

The evaluation criteria are the same for all medicinal products; no exceptions for orphan drugs are stated in the Health Insurance Act. However, the health economic evaluation is not always required from the marketing authorisation holder of orphan drug if justified by the applicant.

2.8. France

Rare diseases were included as one of the five major priorities of the 9 August 2004 Public Health law. Following this, in November 2004, the French government (Ministries of Health and of Research) launched a national plan (**National Plan for Rare Diseases 2005-2008**. http://www.orpha.net/docs/PMR-GB.pdf) which outlined ten major priorities for the management and treatment of rare diseases in France:

– Increase knowledge of the epidemiology of rare diseases

– Recognise the specificity of rare diseases

– Develop information for patients, health professionals and the general public concerning rare diseases

– Train professionals to better identify them

– Organise screening and access to diagnostic tests

– Improve access to treatment and the quality of healthcare provision for patients

– Continue efforts in favour of orphan drugs

– Respond to the specific needs of accompaniment of people suffering from rare diseases and develop support for patients' associations

– Promote research and innovation on rare diseases, notably for treatments

– Develop national and European partnerships in the domain of rare diseases

The GIS Maladies Rares (Institute for Rare Diseases) was created in 2002 to **coordinate and support research** into rare diseases. In the context of the National Plan, research projects on rare diseases will be financed over the period 2005-2008. In 2005, the call for proposals will support projects with an overall budget of 3 million euros (from the Ministries of Research and of Health, and the French Association for muscular dystrophy –AFM).

In addition, the GIS Maladies Rares in collaboration with the LEEM (French association of pharmaceutical companies) has set up a European initiative called ERDITI – European Rare Disease Therapeutic Initiative. This initiative aims at facilitating the access of researchers to molecules developed by the pharmaceutical industry and to evaluate their therapeutic potential.

Rare diseases are a priority in the call for proposals under the Hospital Programme for **Clinical Research** (PHRC). In 2003, 22 clinical research projects were selected for financing over three years with grants ranging from 75,000 to 640,000 euros per project (total budget 215,528 k€ for three years in 2003). In the context of the National Plan, 22.5 million euros will be available from 2005-2008.

Fee waivers can be granted in the case of drugs which fulfil the criteria for orphan drugs but do not have the designation ("medicament orphelin de fait")

Free scientific advice is available for orphan medicines from the French medicines agency (AFSSAPS).

Sponsors of orphan medicinal products are **exempted from the following taxes** to be paid under health and social legislation by enterprises promoting pharmaceutical specialities or wholesale distributors:

– the tax on the promotion of pharmaceuticals, based on the promotion costs of laboratories;

– the tax paid by the laboratories for the AFSSAPS;

– the safeguard clause for medicinal products;

– the tax on direct sales;

- the tax on the distribution of medicines.

Compassionate use for individual patients either for cohort use (given by the laboratory) or named patient supply (given by the French medicines agency). Approximately 20% of designated orphan drugs in France benefit from compassionate use and 14 out of 21 authorised orphan drugs were made available through compassionate use approximately 36 months before their marketing authorisation. Patients can also be treated with drugs before their authorisation through clinical trial and hospital preparations.

The **accelerated process for pricing** has been reduced to 15 days.

Particular prescribing conditions are in place for:

– drugs for hospital use

– drugs with hopsital prescription

– drugs with initial hospital prescription

– drugs with prescription only by specialists

– drugs with a particular follow up during the treatment

Reimbursement measures are in place for compassionate use.

In terms of **public information measures**, support for the Rare Diseases Platform, and most particularly for the Orphanet portal on rare diseases has been reinforced under the National Plan. In addition, the French medicines agency internet site has a list of clinical trials for rare diseases, a list of compassionate use authorisations (cohort use) from 1994 onwards and other general information on hospital preparations.

In the context of the National Plan, the Ministry of Health has launched a call for proposals for University Hospitals for complex **diagnostic analysis** through molecular genetic testing for metabolic and endocrine diseases and for non-malignant hereditary blood disorders, with the aim of improving access to these tests.

The National Plan also foresees an annual call for proposals for clinical **centres of reference** for rare diseases. In 2004, 34 individual centres of reference were designated and received total funding of 10 million euros. Each centre is designated for five years with a mid-term evaluation after three years and at the end of five years.

2.9. Germany

The Bundesministerium für Bildung und Forschung (BMBF) supports a **Network for research** of rare diseases (5 million euros in 2004) which started in 2003. Currently, ten networks for national academic groups, clinical centres, specialised laboratories and patients organisations for basic and clinical research have been funded for an initial three years with a possible extension of two years after a mid-term evaluation.

Other regional sources of funding exist e.g. the Bavarian municipality of Wiesfeld for the University of Münster funded a project on Carbohydrate-deficient Glycoprotein (CDG)-Syndrome in 1999 (100,000 DM).

The 14th amendment to the German drug law, which came into force in September 2005, allows for **pre-authorisation access** to orphan drugs.

All medicinal products, including orphan drugs, are included in a database called AMIS, run by the German Institute of Medical Documentation and Information (DIMDI) ensuring **public information**.

2.10. Greece

Greece has not reported any national measures to support research into, or the development and availability of orphan medicinal products or medicinal products that may be designated as such.

2.11. Hungary

The Hungarian Government promotes the use of orphan medicinal products for specific patients by means of **special financial arrangements**.

In the case of some rare conditions (such as Fabry disease or adult-type chronic myeloid leukemia (CML)), the National Health Insurance Fund [*Országos Egészségbiztosítási Pénztár – OEP*] provides standard price-support for the medicinal products in a predetermined manner. In this case the patient's contribution is negligible or 0%.

In other cases, support for the orphan medicinal product imported for the patients' treatment can be provided on application under a special equity procedure laid down by law. The *OEP* pays the price-support for the necessary medicinal products from amounts earmarked in the outpatients' equity fund.

The holders of marketing authorisations for orphan medicinal products (or their representatives in Hungary) cooperate fully with the medical profession and the OEP.

In Hungary, a **committee on the treatment of rare conditions** has been set up within the Scientific Health Council [*Egészségügyi Tudományos Tanács*]. It ensures, *inter alia*, that in all cases people suffering from such conditions receive adequate care. People suffering from rare conditions in Hungary are registered at the various treatment centres.

Research into medicinal products and developing and marketing them are also facilitated by the fact that Hungary is affiliated to the Orphanet Program for the diagnosis and treatment of rare conditions, and the Orphanet Hungary database is to be set up in the near future.

2.12. Ireland

Ireland has not reported any national measures to support research into, or the development and availability of orphan medicinal products or medicinal products that may be designated as such.

2.13. Italy

In 2001 a governmental decree (279/2001) set up a **national network for rare diseases** including a national registry for diagnostic and epidemiological purposes. In addition, there is co-ordination of research between the regions, the Ministry of Health and the Instituto Superiore di Sanità.

Other projects in support of rare diseases include the **Italian National Project for standardisation and quality assurance of genetic testing** (coordinated by Istituto Superiore di Sanità - ISS) which received 500,000 euros from 2000-2002, and a number of other smaller projects financed by the Ministry of Health.

A national call for proposals for scientific projects related to rare diseases is being funded in 2005-6 in collaboration with the USA. The Italian contribution is 5 million euros.

The Italian drug agency is to launch **a call for proposals to fund projects** on orphan drugs (from research to clinical trials) at the end of 2005.

10% of the annual tax on the promotional activities of pharmaceutical companies is invested by the Ministry of Health in research on rare diseases and clinical trials using orphan drugs.

A **compassionate use** programme is regulated under law 648/1996

After diagnosis in a designated hospital, patients can obtain **free treatment** (Government Decree 279/2001).

Reimbursement is granted for all orphan drugs which follow centralised procedure of marketing authorisation

The Italian **National Centre for Rare Diseases** was established at the Istituto Superiore di Sanità in 1998 provides information to patients, families and health workers; education of health workers; elaboration of specific guidelines; elaboration of a database containing Orphan Drugs available in the country; collaboration with patients' associations (quality of life, access to social and health services, etc.).

Regional Centres for rare diseases are available in many Italian Regions; for example: the Information Centre for Rare Diseases at the Mario Negri Institute, located in Ranica (Bergamo)

The **Interregional Coordination** for Rare Diseases involves the Ministry of Health, the Istituto Superiore di Sanità (ISS), and all Italian Regions. This Committee has several aims, which include harmonisation of the regional networks for rare diseases, implementation of the National Registry for rare diseases and management of the list of rare diseases for which patients can obtain free diagnosis and treatment.

Since 2001, 228 regional **centres of reference** have been established by official regional decisions following the governmental regulation on rare disease. The criteria used by the 21 Regions to identify centres were not homogeneous and each region has adopted a different model for the organisation of the regional network. In each Region a Coordination Centre has been (or should have been) created in order to coordinate the initiatives of regional centres.

2.14. Latvia

The State Agency of Medicines is entitled, due to considerations of health protection, to make a decision (after co-ordination with the Minister for Health) regarding the **fee**

exemption or reduction for activities associated with the evaluation, registration or re-registration of a medicinal product if the medicinal product, although without orphan designation pursuant to Regulation 141/2000, is intended for the treatment of a rare disease.

The State Agency of Medicines may **issue importation and distribution authorisation for medicinal products not registrered in Latvia if the medicinal product is intended for treatment of a rare disease** (for an individual patient on the basis of prescription or for use in a health care institution on the basis of a written request).

1% of reimbursement budget is intended for reimbursement of medicinal products used for treatment of rare diseases (not always those drugs have orphan designation).

2.15. Lithuania

Compensation for orphan medicinal products and medicinal products for rare diseases and conditions is paid for out of the funds earmarked for that purpose in the budget of the compulsory health insurance fund (Ministry of Health Decree No 151 of 20 March 1998; Official Gazette, 1998, No 33-894; 1999, No 7-159).

Individuals are compensated for expenditure on the purchase of medicinal products for rare diseases and conditions on presentation of specialist doctors' reports, following a decision by the committee, set up by the Health Ministry's State Patient Fund, responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions and on cases for which no provision has been made (Decree of the Health Ministry's State Patient Fund Directorate No 1K-149 of 22 November 2005; Official Gazette, 2005, No 139-5037).

2.16. Luxembourg

The Government of Luxembourg collaborates closely with and actively supports the Engelhorn Foundation for rare diseases, the headquarters of which is located in Luxembourg. The Engelhorn Foundation has set up a **research database** available to all persons interested in orphan medicinal products.

In addition, the Government of Luxembourg supported and co-hosted the EURORDIS/RDTF **European Conference** on Rare Diseases, held in Luxembourg on 21 and 22 June 2005 (http://www.rare-luxembourg2005.org/).

2.17. Malta

Incentives for orphan medicinal products are not yet established in Malta and are still being considered. Incentives with regards to fees concerning pharmaceutical activities related to orphan medicinal products will be taken into consideration in the process.

As of end 2005, no measures have been taken in Malta targeting exclusively the increase in availability of orphan medicinal products. Measures, however, are being taken to

promote Research and Development in Malta. Enterprises carrying out Research and Development are entitled to various tax credits according to the nature of the specific investments. These tax credits are in addition to the standard 100 % deductions allowed under the Income Tax Act (Cap. 123). These credits are granted under a general framework, which applies to all Research and Development initiatives and not exclusively to the pharmaceutical sector.

2.18. Poland

Poland is contemplating a return to the concept of specialist drugs in the *Act on healthcare services financed from public funds*. The draft of the Act, which will go before Parliament in the first quarter of 2006, will introduce a specialist drugs category which will allow very expensive therapies (including treatments involving orphan drugs) to be covered by the reimbursement system.

The National Health Plan (2004-2012) put in place by the *Act on general insurance in the National Health Fund* covers reparative and preventive medicine. It provides for access to the latest diagnostic and treatment techniques and is open-ended, i.e. it can be amended and supplemented. For that reason, it can be extended to include a programme encompassing patients suffering from rare diseases that takes account of the policy on orphan drugs.

Data on orphan drugs should also include drugs purchased direct by hospitals from the responsible body (producer) under contracts for medical services between hospitals and the National Health Fund, and under so-called drugs programmes.

The ***National Forum on the Treatment of Orphan Diseases*** (www.chorobysieroce.pl) was created at the beginning of 2005 and groups together associations that for many years have been seeking to ensure care and treatment are provided for those suffering from orphan diseases. The members of the *Forum* are: *Stowarzyszenie Rodzin z Chorobą Gauchera* (Association of Families affected by Gaucher's disease), *Stowarzyszenie Rodzin z Chorobą Fabry'ego* (Association of Families affected by Fabry's disease), and *Stowarzyszenie Chorych na Mukopolisacharydozę* (Association of Families affected by Mucopolysaccharidosis and related diseases). As announced by the Ministry of Health on its webpages, on 13 July 2005 a meeting was organised by the Minister of Health with national non-government organisations representing patients. At that meeting, the Forum presented its demands regarding deficiencies in the operation of the National Health Fund from the viewpoint of patients suffering from orphan diseases.

Regarding measures to promote innovation in pharmaceuticals, the Minister of Health commented on the draft amendment of the *Act of 29 July 2005 on a number of forms of innovation support*, proposing an extension of technology loans to cover the development of orphan drugs, but the Minister of the Economy failed to back the proposal.

2.19. Portugal

According to information collected for the publication of the first inventory in 2001, in Portugal, INFARMED sent the office of the State Secretary for Health a draft Order for

the **waiving of 50% of the fees** for orphan drugs authorised through the national procedure (applicable until 20 November 2005, date from which the centralised route of marketing authorisation of designated orphan medicinal product became mandatory). Portugal has not notified any additional measures.

2.20. Slovakia

Support for **academic research** exists for specific projects eg: VEGA grant for project on prognostic parameters of chronic myeloproliferative diseases and myelodysplastic syndrome in biopsy of bone marrow (158,000 SKK over three years) and APVT grant for project on immunophenotypisation of human glioma via flowing cytometry in diagnostic and study of multiple drug resistance and gliomagenesis (779 000 SKK over three years).

2.21. Slovenia

Slovenian measures concerning national incentives for orphan medicinal products were:

– allowing **labelling** in any EU language with stickers in Slovenian language

– **negotiation on drug prices**

– **reduced fees** for marketing authorisation procedure (if centralised procedure was not followed).

2.22. Spain

The following institutions give support for **academic / industrial research** on rare diseases:

– Instituto de Investigación de enfermedades raras – IIER (National Research Institute for Rare Diseases): Promotion of Basic and clinical research. Funded since 2003 (9 million euros in 2004).

– Institute of Health Carlos III – Fund for Health Research (FIS): Single and multi-centre research projects and research projects on technology assessment. Funded since 2001. 35 projects in 2003; 2.14 million euros granted in 2004; Co-operative Research Networks (RTICS). Funded since 2002. 12 networks funded; 6.68 million euros granted in 2004;

– Federación Española de Enfermedades Raras – FEDER (Spanish Federation of Rare Diseases): Federation that includes all Spanish patient associations for rare diseases and orphan drugs. Provides funding for research. In the future there should be some priority given to research on Rare Genetic diseases in the National R&D Plan.

There are specific **scientific advice procedure** foreseen for potential orphan medicinal products in the Spanish Agency of Medicines and Medical Devices (AEMPS). A Plan to

identify these products in early stages and help to develop them (within the EMEA context) will be set up at the Spanish Agency.

There is an authorisation procedure within the **Compassionate Use** system (AEMPS).

Public information measures include:

– Sistema de información sobre enfermedades raras en España – SIERE (Information system on rare diseases in Spain). There are plans to update the system and to complement it with epidemiologal information.

– Specific web pages from Research networks such as REpIER, INERGEN, GIN; ORGEN, REDEMETH, REC-GEN, etc.

– Rare Diseases Research Institute belonging to Institute of Health Carlos III.

– List of available orphan drugs in the REpIER website.

Measures for prevention / early diagnosis / management of rare diseases are National neonatal screening programmes. In addition, there is a Directory of Diagnosis centres on genetic and metabolic diseases (INERGEN website).

Support for patients associations is given by private and public (Labour Ministry) funds.

National coordination measures are provided by the Ministerial steering committee, the IIER and a national ethics committee for rare diseases was set up in December 2002.

There are plans to establish national **centres of reference** for rare diseases by 2007.

2.23. Sweden

In the context of Orphan Drugs, the Medical Products Agency (MPA) adheres to the prevalence criteria stated in Regulation (EC) No 141/2000. However, the knowledge database of the Swedish National Board of Health and Welfare defines rare diseases as "Disorders or injuries resulting in extensive handicaps and affecting no more than 100 individuals in one million inhabitants”.

The Swedish Research Council is a government agency under the Ministry of Education and Science. The scientific council for medicine evaluates and prioritises research in medicine, pharmacy, odontology and care sciences and, on behalf of the Swedish Research Council, decides on project grants in these fields. Project funding is based on quality criteria (bottom-up procedure) and not subject to prioritisation based on research areas, with a few exceptions. The Swedish Research Council for medicine has an annual budget of around 47 million euros. It sponsors mainly individual research projects and funding is in the response mode. Project grants usually cover 10-20% of total project costs. Junior research positions are also funded. The Swedish Research Council for medicine also makes decisions to provide financing of principal investigators in areas of research where directed support is of strategic value.

The Swedish Research Council Medicine supports **research on rare diseases**. This funding includes project grants and salaries for principal investigators in areas that

relates to rare diseases (1,1 million euros/ 2005). Because research projects are only partly funded by the SRC, the total amount of funding for research in rare diseases in Sweden is greater than what is funded by the research council.

The Swedish Cancer Society is a non-profit organisation whose task is to collect money and distribute it for cancer research, information about cancer and lend/give support to activities which in different ways contribute to improvements within cancer treatment and care. The Swedish Cancer Society is the major source for cancer research in Sweden and provides support for high quality research projects in all types of cancer as well as to various types of academic research positions. Based on the current project catalogue, it is estimated that the support to **clinical research into rare cancer** types, fulfilling the orphan drug criteria, amounts to 27 million SEK in 2004 (approx. 3 million euros). This support probably varies only slightly from year to year.

It has not been possible to dissociate the support to research into the disease itself from that oriented towards orphan drug development as these research efforts are often mixed but probably very little is used to directly support drug development.

The MPA adheres to the EMEA **fee waiving rules**, i.e. 100% for scientific advice and 50% for all other fees.

Clinical trial application fees to the MPA: Non-commercial sponsors lacking industry support can apply for a 100% fee waiving which is usually granted.

Providing IMP free of charge by the sponsor in clinical trials: Swedish law allows exemptions, should an obligation to perform a trial post-marketing have been linked to the granting of the marketing authorisation for an Orphan Drug.

2.24. The Netherlands

The Dutch **registration fee for a medicinal product may be waived** if the medicinal product is already registered in one or several other EU member states and the prevalence of the indicated disease is less than 1 in 150.000 inhabitants in The Netherlands.

The Innovative Research Incentives Scheme (a programme started in 1996 and funded until 2011), has a bottom-up approach and consists of several subsidy schemes e.g. directed to excellent researchers in specific phases of their scientific careers or clinical fellows who want to combine their education as a medical specialist with clinical research. 50 out of 729 projects supported between 1998 –2004 were for rare disease research (7%, resulting in an estimated budget of 9-10 million euros).

Four projects in the new grant scheme in Gene Therapy started in 2005. Two of these were in rare diseases, with a budget of about 2 million euros. The programme will run until 2013.

Thr programme BioPartner FSG/STIGON (1998 – 2007) had as its goal **to establish high-tech businesses and entrepreneurship** in life sciences, including medicinal products for chronic and rare diseases. The total budget for the STIGON programme (including rare diseases) is about 9 million euros and is funded by several ministries and scientific institutions. There is no involvement of private money.

A **new programme specific to rare diseases** and orphan drugs is being developed in 2005/6. The Ministry of Health, Welfare and Sport has provided funds (maximum 250,000 euros) to the Netherlands Organisation for Health Research and Development (ZonMw) to prepare this programme. A formal decision on the funding of such a programme is not yet available.

The Steering Committee on Orphan Drugs has funded and will continue to fund some rare disease projects (2001-2007; 50,000 euros per project per year).

There are **tax reductions** for R&D of high-tech start-ups (WBSO measure) that orphan drug companies can also use.

In 2005 an **orphan business developer** is starting to stimulate Dutch academic researchers and pharmaceutical industries to develop orphan drugs. This project is paid for by the Ministry of Health over four years.

There are also several programmes from the Ministry of Economic Affairs to **facilitate start-ups** (Innovation Subsidy Collaboration projects (IS), Subsidy programme on exploiting knowledge and Technostarters) that orphan drug companies can use.

Free advice is available from the Dutch Steering Committee on Orphan Drugs

In the case of orphan medicinal products for a rare disease for which no alternative treatments exist, there is **no obligation for companies to show pharmaco-economic data**. In individual cases this may also be the case for orphan medicinal products for a disease with a prevalence that is less than 5:10,000 for which an alternative treatment does exist.

For the care of patients suffering from organ diseases, special funding is available. For the use of orphan drugs in university hospitals, a **new reimbursement method** will be introduced from 1 January 2006. By this method, the concentration of the use of orphan drugs (i.e. the treatment of certain particular rare disorders with orphan drugs – designated as such according to Regulation (EC) No 141/2000 and with a market authorisation within the EU) will be stimulated. The costs of the orphan drugs in hospitals will be almost totally refunded (95%). In contrast, general pharmaceuticals are not specifically refunded but are covered by the general hospital budget.

With regard to these costs an extra € 24 million will be available for university hospitals only. An amount of € 10 million will be yearly available for out-of–hospital treatment with orphan medicinal products whose costs cannot reimbursed - because of insufficient data on added therapeutic value - via the current reimbursement system.

On the Dutch website www.orphandrugs.nl **general information** on rare diseases and orphan drugs is available. On the Dutch website www.erfocentrum.nl **information is available on specific rare diseases**.

The Steering Committee on Orphan Drugs functions as an **information centre** for rare diseases and orphan drugs. The Dutch patient alliance VSOP started a Working group for rare diseases in 2000 and functions as an information centre for patients with a rare disease.

A foundation funded by the Ministry of Health (Stichting Fonds PGO) **subsidises national patient organisations**, including specific and umbrella patient organisations for rare diseases.

The Steering Committee on Orphan Drugs was established in 2001 by the Minister of Health and has as its mission to encourage the development of orphan drugs and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases.

The Netherlands supports the opinion that the care for patients suffering from rare diseases should be concentrated in a **limited number of centres**, in order to guarantee expert care and the possibilities for research.

The eight academic medical centres in The Netherlands function as the main clinical reference centres for specific rare diseases. However, other hospitals may also function as well-coordinated centres. The number of clinical reference centres for rare diseases varies considerably in The Netherlands, e.g. there are 16 haemophilia centres, 6 centres for cystic fibrosis, 2 for MPS, and one each for Gaucher disease and Fabry disease. In the section on Reimbursement measures it is explained that funds for the reimbursement of orphan medicines are only available for university hospitals.

2.25. United Kingdom

The definition of rare disease, used by the National Specialist Commissioning Advisory Group, is much rarer than for the EU definition of rare diseases; 2 per 100,000 or lower, which covers 30 conditions, diagnoses or procedures (mostly genetic diseases of children).

Patients with rare disease receive drugs on a named patient basis.

All licensed drugs are eligible for reimbursement in the UK. Decisions are taken by relevant funding bodies at local level, not nationally, in the light of available funds. There is not a separate budget for 'orphan drugs'.

Home delivery is available for various products, for example enzyme replacement therapies.

The National Specialist Commissioning Advisory Group provides a special mechanism for care of patients with a selected list of very rare disorders in England. There are similar mechanisms in Scotland and Wales.

Grants are available to support patients' organisations.

Within the national health system, a separate system exists for providing funding to specialised **centres of reference** (around fifty) for particular conditions (not necessarily rare diseases), diagnoses or procedures. The centres are reviewed constantly and there has been a strong emphasis on defining patient outcome measures, and publishing these data. Some Regional specialist services also exist for genetic diseases but these are funded separately.

Annex 1: FP5 Quality of Life projects supporting research into rare diseases and orphan medicinal products

Generic Activities

Structural Studies on the Mechanism of DNA Excision Repair
Ultraviolet-Sensitive Genetic Disorders Associated with Defects in DNA Repair and Transcription
Molecular and Biochemical Pathogenesis of Friedreich's Ataxia: Search for Treatments
Genetic Resolution of MYOpathies: European CLUSTER
Multidisciplinary Approach to Understanding the Pathophysiology of the Wiskott-Aldrich Syndrome Towards Improved Healthcare
A Systematic Approach Towards the Understanding, Diagnosis and Treatment of CDGS, a Novel Group of Inborn Metabolic Disorders Caused by Defects of Glycosylation
Development of a Genomic DNA Bank of Iga Nephropathy (Igan) Patients and Family Members. New Trends in Genetics for the Early Diagnosis of Familial Igan
Evolving Evidence Based Treatment Strategies for Infantile Hyperinsulinism Using Clinical, Genetic and Cell Biological Insights into a Heterogenous Disease
Coresets of Outcome Measures and Definition of Improvement for Juvenile Systemic Lupus Erythematosus and Juvenile Dermatomyositis
Nephrin in Proteinuric Diseases: Development of Diagnostics, Prognostic and Treatement Modalities
Molecular Characterization and Identification of Biological Risk Factors in Mantle Cell Lymphoma
European Collaboration on Craniofacial Anomalies
Neuroprotection and Natural History in Parkinson Plus Syndromes: a Clinical Trial of the Efficacy and Safety of Riluzole in Parkinson Plus Syndromes
European Network for Fetal Transplantation
Concerted Action on Mitochondrial Biogenesis and Disease
Cystic fibrosis: rescue of the function and of the processing of CFTR mutants by pharmacological agents and by interacting proteins
Peroxisomal diseases: elucidation of the pathogenesis and evaluation of treatments by using mouse models
The European Initiative for Primary Immunodeficiencies

European network on GENetic DEAFness: pathogenic mechanisms, clinical and molecular diagnosis, social impact
Improved healthcare for patients with primary antibody deficiencies through new strategies elucidating their pathophysiology.
The pemphigoids, autoimmune blistering diseases of the skin and mucosae: immunopathogenic mechanisms, prognostic and diagnostic markers.
An integrated Research and Diagnostic Network for skeletal dysplasias
Molecular mechanisms of disease progression and renoprotective pharmacotherapy in children with chronic renal failure
Clinical features associated with tropheryma whipplei infection in a European setting - pathogenesis, diagnosis and treatment of Whipple's disease
Early diagnosis and analysis of the genetic causes of primary pulmonary hypertension (PPH), a rare and life-threatening disease
Novel methods for predicting preventing and treating attacks in patients with hereditary angioedema
Twin to twin transfusion syndrome and monochorionic twinning European network
European network for vascular disorders of the liver
European registry of severe cutaneous adverse reactions (SCAR) to drugs and collection of biological samples
Paraneoplastic Neurological Syndromes (PNS): clinical and laboratory aspects
Human Hereditary Deafness - Identification of Genes, Molecular Diagnostic Tests, Epidemiologycal Data, Understanding Pathogenesis and Search for Therapies
Alpha-1 International Registry
Development of ultrasensitive methods for proteome: Application to cystic fibrosis.
Oculopharyngeal muscular dystrophy: a paradigm to investigate new pharmaco-therapeutic approaches to trinucleotide-expansion diseases and muscular dystrophies.
European society of paediatric oncology neuroblastoma research network
European cytogeneticists association register of unbalanced chromosome aberrations
European network of DNA, cell and tissue banks on rare diseases

Key Action Cell Factory

Thematic network around cystic fibrosis and related diseases

Development of high throughput PNA-based molecular diagnostic systems
Pre-clinical evaluation of delivery systems for neuroprotective gene therapy in neurodegenerative diseases
Innovative therapeutics for the prototype autoimmune disease, myasthenia gravis
Integrated in vitro and in vivo testing of drugs in prion diseases: screening, development and mechanisms of novel therapeutics
Gene Therapy of Hematopoietic Stem cells for Inherited Diseases
Novel genechip technology for simplified detection of molecularly heterogeneous genetic diseases: Detection of cystic fibrosis as a model.
Development of a rapid high-throughput assay for sensitive and specific detection and strain typing of Creutzfeldt-Jakob disease based on fluorescence correlation spectroscopy
A systematic and multidisciplinary approach towards understanding and therapy of the inborn lysosomal storage disease alpha-mannosidosis
Neuropeptides for lung treatment of rare lung diseases, primary and secondary pulmonary hypertension (Neuropeptide Lung Therapy)

Annex 2: FP6 projects supporting research into rare diseases and orphan medicinal products

Priority 1 (Health), section Combating Major Diseases

Type	Title
IP	Rational treatment strategies combating mitochondrial oxidative phosphorylation (OXPHOS) disorders
STREP	European genomics initiative on disorders of plasma membrane amino acid transporters
CA	Wilson disease: creating a European clinical database and designing multicentre randomised controlled clinical trials
SSA	Platform of information services for the coordination of rare disease research with various stakeholders from research, SMEs and patient organisations and the coordination of early clinical trials
IP	European integrated project on spinocerebellar ataxias (EUROSCA): Pathogenesis, genetics, animal models and therapy
STREP	X-linked Adrenoleukodystrophy (X-ALD): pathogenesis, animal models and therapy
STREP	Cell biology of rare monogenic neurological disorders involving KCNQ channels
STREP	Dissecting neuronal degeneration: Neuronal ceroid lipofuscinoses from genes to function
STREP	Genetic Models of Chronic Neuronal Degeneration Causing Hereditary Spastic Paraplegia
STREP	Prognosis and Therapeutic Targets in the “Ewing” Family of Tumours
STREP	Autoimmune polyendocrine syndrome type I - a rare disorder of childhood as a model for autoimmunity
STREP	From Immune Responses in Rare Autoimmune Diseases to novel Therapeutic Intervention Strategies-a personalized Medicine approach
STREP	Prader-Willi Syndrom: a model linking gene expression, obesity and mental health
CA	Rare genetic skin diseases: advancing diagnosis, management and awareness through a european network
CA	Congenital Disorders of Glycosylation: a European network for the advancement of research, diagnosis and treatment of a growing group of rare disorders

Priority 1 (Health), section Advanced Genomics and its Applications for Health

Type	Title
STREP	Development of new methodologies for low abundance proteomics : application to cystic fibrosis
IP	Integrated project to decipher the biological function of peroxisomes in health and disease

IP	DNA damage response and repair mechanisms
NoE	Genetic testing in Europe - Network for test development harmonization, validation and standardization of services
STREP	Genetics of coenzyme Q deficiency in humans
STREP	Mitochondrial diseases: From bedside to genome to bedside
IP	Concerted Safety & Efficiency Evaluation of Retroviral Transgenesis in Gene Therapy of Inherited Diseases
STREP	Improved precision of nucleic acid based therapy of cystic fibrosis
STREP	Gene therapy for Epidermolysis Bullosa: a model system for treatment of inherited skin diseases
STREP	Ex vivo gene therapy for recessive dystrophic epidermolysis bullosa : pre-clinical and clinical studies

Actions across thematic Priority 1 (Health)

Type	Title
SSA	International Conference on Rare Diseases and Orphan Drugs
SSA	European Network for research on alternating hemiplegia in childhood for promoting SMEs integration

Research for Policy Support

Type	Title
STREP	Policy-oriented and harmonising research activities in the field of primary immunodeficiency diseases (PIDs)

Coordination of Research Activities

Type	Title
SSA	ERA-Net for research programmes on rare diseases