Inventory of Community and national incentive measures to aid the research, marketing, development and availability of orphan medicinal products, revision 2002

Background

Regulation (EC) No. 141/2000 of the European Parliament and of the Council on Orphan medicinal products was adopted on 16th December 1999 and was published in the Official Journal of the European Communities on 22nd January 2000.1 It entered into force on 27th 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. This second version therefore includes additional information received since the date of first publication and represents the status of such incentives at time of publication. Its publication follows the adoption of just over 100 orphan medicinal product designations by the Commission.

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

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.

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.

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1 OJ L 18, 22.1.2000
2 OJ L 103, 28.4.2000
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 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 last decade, 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.

The aim of this inventory is to collect together the measures that have been introduced both at Community level and at national level and to present this information in a transparent manner. To this end Member States have been asked to communicate details of any measures introduced or in force. In addition, information from the different services of the Commission has also been requested. This inventory is based on the information received as of end May 2002.
1. Community measures

1.1. The Regulation on Orphan Medicinal Products

The principle measure introduced by the Community is, undoubtedly, the Regulation on Orphan Medicinal Products. Since the entry into force of this regulation, 178 applications for designation as Orphan medicinal products have been received by the European Agency for the Evaluation of Medicinal Products (the Agency) and, as of end May 2002, 105 opinions on the granting of designations had been adopted by the Committee for Orphan Medicinal Products. 101 of these had been translated into Community decisions. 50 of the products discussed as of May 2002 were unable to successfully meet the criteria of the regulation and were withdrawn by the sponsors before the adoption of opinions. Of the five negative opinions adopted to date, two applications were subsequently withdrawn, two have resulted in final negative opinions and one has resulted in a final positive opinion following appeal. One negative decision has been adopted by the European Commission and a further negative decision is imminent.

A summary of the information as of May 2002 is provided in the table below:

<table>
<thead>
<tr>
<th>Year</th>
<th>Applications submitted</th>
<th>Applications withdrawn</th>
<th>Positive COMP Opinions</th>
<th>Negative COMP Opinions</th>
<th>Designations granted by Commission</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>72</td>
<td>3</td>
<td>26</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>2001</td>
<td>83</td>
<td>26</td>
<td>62</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>2002 (end May)</td>
<td>23</td>
<td>21</td>
<td>17</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Totals</td>
<td>178</td>
<td>50</td>
<td>105</td>
<td>2</td>
<td>101</td>
</tr>
</tbody>
</table>

Incentives

The principle direct incentives introduced by this regulation are as follows:

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 European Medicines Evaluation Agency (the Agency). Further details are available on the following web addresses: [http://www.emea.eu.int/htms/human/comp/orphapp.htm](http://www.emea.eu.int/htms/human/comp/orphapp.htm) and [http://pharmacos.eudra.org/F2/orphanmp/index.htm](http://pharmacos.eudra.org/F2/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. Further information on the amounts and procedure are available on the Agency web-site.

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.

**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 just 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. By April 2004, potential sponsors had made 4 requests for protocol assistance, and 3 follow up scientific advice requests concerning designated orphan medicinal products to the Agency.

The regulation also provides 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. The regulation gives Orphan medicinal products (easier) access to this procedure by exempting the sponsor from the requirement to show that the medicinal product meets the conditions set out in the Annex to Regulation (EEC) No 2309/93. As of May 2002, 4 orphan medicinal products had been authorised by the Commission; one of these has been authorised for use in two orphan indications.

<table>
<thead>
<tr>
<th>Name and EU number of medicinal product</th>
<th>Authorised Orphan indication</th>
<th>Date of authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FABRAZYME EU/1/01/188/001-003</td>
<td>Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency)</td>
<td>3 August 2001</td>
</tr>
<tr>
<td>REPLAGAL EU/1/01/189/001</td>
<td>Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency)</td>
<td>3 August 2001</td>
</tr>
<tr>
<td>TRISENOX EU/1/02/204/001</td>
<td>Induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.</td>
<td>5 March 2002</td>
</tr>
</tbody>
</table>
The regulation set up a **Committee for Orphan Medicinal Products (COMP)**. It is this committee which is responsible for the scientific examination leading to designation of an Orphan Medicinal Product. The COMP has been in operation since April 2000. 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 May 2002, 158 experts had been appointed by the COMP.

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://pharmacos.eudra.org/F2/register/orphreg.htm](http://pharmacos.eudra.org/F2/register/orphreg.htm)

**Activities of the COMP in other areas**

Article 4 of the Regulation assigns additional tasks to the Committee beyond its primary task of designation of orphan medicinal products. These tasks can be summarised as follows:

- To advise the Commission on the establishment and development of a policy on orphan medicinal products
- To assist the Commission in liaising internationally on matters relating to orphan medicinal products
- To assist the Commission in liaising with patient support groups
- To assist the Commission in drawing up detailed guidelines

In this context the COMP has organised several meetings with interested parties as follows:

A Workshop for Patient Organisations on Orphan Medicinal Products held on 21 March 2001.

A Workshop with Industry on Orphan Medicinal Products held on 11 April 2001.

A Workshop for Health Professionals and Academia on Orphan Medicinal Products held on 24 January 2002.
In addition a COMP working group with interested parties composed of EMEA/COMP members and representatives of patient organisations and the pharmaceutical industry, has been established, meeting for the first time in July 2001. This group will work on proposals for improving transparency on orphan activities, optimising the orphan designation procedure and delineating policy recommendations on orphan medicinal products.

Apart from these workshops and working groups, representatives from associations and organisations dealing with issues related to orphan medicinal products are invited to present their activities to the COMP at regular intervals in order to increase overall knowledge and understanding in related areas. The following organisations have been invited to present relevant activities to the COMP:

The European Commission (representatives from DG Research and DG Health and Consumer Protection), Médecins Sans Frontières, Mission des Médicaments Orphelins, Ministry of Health in France, INSERM (Institut National de la Santé et de la Recherche Medicale) on the ORPHANET database, the Office for Orphan Product Development (OOPD) at the FDA, the Danish Epidemiology Science Centre, the Scientific Secretariat of the Dutch Steering Committee for Orphan Drugs.

In addition the EMEA staff supporting the COMP regularly liaise and share experiences with international bodies, including the US FDA on matters related to the designation of orphan medicinal products.

1.2 Proposal to review the pharmaceutical legislation

In November 2001, the Commission published a proposal to review the pharmaceutical legislation. The changes envisaged take account of the specific needs of orphan medicinal products and include specific labelling derogations, as well as possibilities for accelerated review of marketing authorisation applications, new rules for conditional marketing authorisations and a framework for availability of medicinal products on a compassionate use basis. While these latter measures are not exclusively intended to apply to orphan medicinal products, it is expected that applications for orphan medicinal products will be able to benefit from these new provisions.

1.3 Specific Community research opportunities

The Commission’s Research Directorate General is also active in its support for research into orphan medicinal products. The principal support is implemented through the Quality of Life and Management of Living Resources Programme of the 5th Framework programme. This support is provided in the form of research grants awarded on a competitive basis and selected by the Commission following an evaluation of independent experts.

As of 2002, the Quality of Life programme has supported a total of 25 projects with an overall budget of 39.2 Mio €. The first inventory covered the years 1999 and 2000 and comprised 17 contracts (13 from “Generic activities” and 4 from “Cell factory”. These are reproduced in Annex 1. For the year 2001, 8 new contracts from the key action “Cell factory representing an additional EC contribution of 15.7 Mio € have been awarded and are described in Annex 2.

These research contracts deal with a variety of diseases (cystic fibrosis, neurodegerative and metabolic disorders, autoimmune, inherited and viral diseases and apply different
approaches (high-throughput screening, gene therapy, peptide design. Two of the projects focus on preclinical testing of lead compounds.

Further information about the Quality of Life programme can be found on http://www.cordis.lu/life/home.html.

1.4. The Community Action programme on rare disease

A community action programme on rare diseases, including genetic diseases, was adopted by the Parliament and the Council for the period of 1 January 1999 to 31 December 2003. The aim of the programme is to contribute, in co-ordination with other Community measures, towards ensuring a high level of health protection in relation to rare diseases. Specific attention is given to improving knowledge and to facilitating access to information about these diseases. Four actions are specified in this decision:

1. The promotion of the development of, and access to, a coherent and complementary European information network on rare diseases

2. The contribution to training and refresher courses for professionals in order to improve early detection, recognition, intervention and prevention in the field of rare diseases.

3. The promotion of transnational collaboration and networking between groups of persons directly or indirectly affected by the same rare conditions

4. The provision of support at Community level for the monitoring of rare diseases with particular reference to clusters.

Further information is available on the web-site: http://europa.eu.int/comm/health/ph/programmes/rare/index_en.htm

As of April 2002, 7 new project proposals which come within the scope of the actions specified above have been identified supported by grants totalling about 1.295 m €. These projects are listed on the following page and are ongoing. One project was put on the reserve list.

The projects concerned encompass inter alia, the creation of information networks, alliances of patient groups, European databases on specific diseases, and the organisation of information and institutional networks. The projects are expected to contribute to ensuring a high level of health protection in the field of rare diseases and to facilitating the availability of information on rare diseases within the European Community.

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### Projects funded in 2002

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Project Title</th>
<th>Grant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Istituto Superiore di Sanità Roma, Italy</td>
<td>NEPHIRD: a European network for epidemiological and public health data collection on rare diseases</td>
<td>226,675.69 €</td>
</tr>
<tr>
<td>European Federation for Neurofibromatosis Associations St Niklaas, Belgium</td>
<td>Neurofibromatosis</td>
<td>132,011 €</td>
</tr>
<tr>
<td>ALZHEIMER EUROPE Luxembourg, Luxembourg</td>
<td>Rare forms of dementia</td>
<td>83,160 €</td>
</tr>
<tr>
<td>University Medical Center Utrecht – Dpt of Internal Medicine Utrecht, Netherlands</td>
<td>Metabolic Diseases Training Professionals Skills</td>
<td>145,603,05 €</td>
</tr>
<tr>
<td>Hospital Clinic i Provincial de Barcelona Barcelona, Spain</td>
<td>ENERCA (European Network for Rare Congenital Anaemias)</td>
<td>198,641 €</td>
</tr>
<tr>
<td>European Organisation for Rare Disorders Paris, France</td>
<td>EURORDIS</td>
<td>187,765 €</td>
</tr>
<tr>
<td>Institut National de la Santé et de la Recherche Médicale (INSERM) Paris, France</td>
<td>ORPHANET</td>
<td>300,000 €</td>
</tr>
</tbody>
</table>

### Reserve list 2002

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Project Title</th>
<th>Grant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regione Emilia-Romagna Assessorato Sanità Bologna, Italy</td>
<td>European Network on Inherited Bleeding Disorders</td>
<td>149,073 €</td>
</tr>
</tbody>
</table>

* Estimated amount
<table>
<thead>
<tr>
<th>Organisation</th>
<th>Project Title</th>
<th>Grant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute of Pathology University of GRAZ - Austria</td>
<td>Rare pulmonary diseases; establishment of diagnostic criteria and reference/training centers</td>
<td>62,982,80 €</td>
</tr>
<tr>
<td>SENSE INTERNATIONAL United Kingdom</td>
<td>CAUSE (Charge Association and Usher Syndrome in Europe)</td>
<td>129,602,17 €</td>
</tr>
<tr>
<td>Istituto di Ricerche Farmacologiche Milan, Italy</td>
<td>A European educational programme on rare diseases</td>
<td>98,473,77 €</td>
</tr>
<tr>
<td>MEDIZINISCHE HOCHSCHULE Hannover, Germany</td>
<td>European Network on the Epidemiology, Pathophysiology and Treatment of Severe Chronic Neutropenia</td>
<td>131,677,00 €</td>
</tr>
<tr>
<td>UNIVERSITY OF ULSTER Coleraine, Northern Ireland</td>
<td>EUROCAT: Surveillance of congenital anomalies in Europe</td>
<td>383,280,00 €</td>
</tr>
<tr>
<td>INSERM Paris, France</td>
<td>ORPHANET</td>
<td>280,000,00 €</td>
</tr>
<tr>
<td>EURORDIS European Organization for Rare Disorders Paris, France</td>
<td>New communication technologies (website) to the service of the rare disorders network and sharing of good practices in different help services to patients, already existing in Europe (hot line)</td>
<td>90,000,00 €</td>
</tr>
<tr>
<td>IRCCS - San Matteo - Pronto Pavia, Italy</td>
<td>A European information network on paediatric rheumatic diseases</td>
<td>142,670,00 €</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Project Title</th>
<th>Grant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Interest Group London, UK</td>
<td>Creating a European Alliance of Patient and Parent Groups for Genetic Services and Innovation in Medicine</td>
<td>110,000 €</td>
</tr>
<tr>
<td>Schlosspark Klinik Berlin, Germany</td>
<td>Muscle diseases – prototype of rare and disabling disorders: creation of a European Information network”.</td>
<td>128,000 €</td>
</tr>
<tr>
<td>University Medical Centre Utrecht, The Netherlands</td>
<td>Transfer of expertise on rare metabolic diseases in adults</td>
<td>120,000 €</td>
</tr>
</tbody>
</table>
2. Information from Member States

Incentives available at Community level need to be supported by complementary national initiatives, particularly in areas such as fiscal incentives and national research projects. At the time of publication of the first inventory, in accordance with Article 9 of the Orphan Regulation, information on measures adopted had been received from 12 out of 15 Member States. Finland subsequently provided some information. Not all Member States had taken specific measures.

By end of May 2002, in response to a second request by the Commission, updated responses were received from all countries with the exception of Greece and Italy. UK and Spain provided some information for the first time. These responses have been integrated into this second publication of the inventory.

The information provided to the Commission is presented according to the information received from each Member State. Where updates have been provided, this is indicated accordingly.

2.1. Austria

In Austria, the Austrian Drugs Act provides for the waiving of fees (e.g. for marketing authorisation or changes) for orphan drugs, which have not been authorised according to the Central authorisation procedure. In this case an official application should be made to the Austrian authorities for the activity concerned. The public health interest of the marketing authorisation application must be shown to be far greater than that of the individual applicant. This information has not changed since publication of the first inventory.

2.2. Belgium

<table>
<thead>
<tr>
<th>Institution</th>
<th>Project Details</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institut de Pathologie et de génétique de Loverval</td>
<td>EDDNAL : European Directory of DNA Laboratories</td>
<td>85,000 €</td>
</tr>
<tr>
<td>INSERM Paris, France</td>
<td>ORPHANET : an European database on rare diseases and orphan drugs</td>
<td>220,000 €</td>
</tr>
<tr>
<td>University of Tampere Tampere, Finland</td>
<td>Information network for Immunodeficiencies</td>
<td>105,000 €</td>
</tr>
<tr>
<td>University of Ulster Coleraine, Northern Ireland</td>
<td>EUROCAT: Surveillance of congenital anomalies in Europe</td>
<td>260,000 €</td>
</tr>
<tr>
<td>EURORDIS Paris, France</td>
<td>Orphan Medicinal Products to the service of patients affected by rare diseases</td>
<td>130,000 €</td>
</tr>
<tr>
<td>Istituto Superiore di Sanita Rome, Italy</td>
<td>NEPHIRD : Network of Public Health Institutions on Rare Diseases</td>
<td>60,000 €</td>
</tr>
</tbody>
</table>
Since publication of the first inventory, Belgium has continued its activities in the framework of the working group created under the aegis of the Prime Minister in order to determine which actions are possible. Two separate aspects are in the process of being addressed.

The establishment of exemptions for national fees for marketing authorisations for orphan medicinal products was published in the Official Journal of July the 9th. The Royal Decree of 3 July 1969 on the registration of medicinal products has been revised. Amendments concerning orphan medicinal products include the incorporation of the definition of medicinal products as laid down in Regulation 141/2000 and an indication that the national fees for registration is to be reduced by half.

In addition the new decree adds a new concept for medicinal products already authorised and for which a request for orphan status has been submitted to and accepted by the Committee for medicinal products and agreed on the basis of the criteria laid down in the orphan regulation. These medicinal products can benefit from a reduction of up to one quarter of the maintenance fees.

2.2.2 Reimbursement measures
As already mentioned in January 2001, Belgium proposes to take account of the special nature of orphan medicinal products when a request for reimbursement is introduced. The possibility of taking special account of likely volumes of use during pricing and reimbursement negotiations, with the intention of arriving at contracts with pharmaceutical firms based on the most appropriate price/volume relationship continues to be under examination. In the meantime it will be possible for requests for reimbursement of orphan medicinal products to take account of their special nature during the examination of such requests. In addition, special rules may be determined with a view towards continuing the availability and reimbursement of orphan medicinal products.

2.3. Denmark

Similarly, in Denmark, reduced fees\(^4\) are charged for the marketing approval of orphan medicinal products.

In addition the Danish Medicines Agency has communicated to interested parties, such as patients organisations, pharmaceutical companies and research organisations that the orphan medicinal product regulation is currently operational. The Danish Medicines Agency already gives specific advice to both pharmaceutical companies and researchers concerning both design of clinical trials and development plans. Specific taskforces have been created nationally to ensure information about genomics and gene therapy with a special focus on rare diseases.

An operational collaboration also exists between the Centre for Rare Disorders and Disabilities and the Danish Medicines Agency.

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\(^4\) Ministry of Health Order 123 of 22 February 2000
This information remains valid for 2001.

2.4. France

2.4.1. Genomic research and Genome network projects

In addition to the work done by charitable organisations, the French government has prepared a broader strategy to address the study of genetic diseases, including the study of rare diseases. The measures to stimulate the supply of orphan medicinal products are part of this overall strategy, which covers all stages from genetic research to the development of drugs.

Accordingly, the French Ministry for Research runs three synergistic programmes:

- **The Biological Resources Centre (BRC)** mission is to acquire, validate, study and distribute biological collections, some of which are of strategic importance for research into genomics and functional genomics. The Minister for Research, in partnership with research bodies, provided 7.6 million € in 2001, to which should be added another 1.5 million € from the Hospital Tumour Banks Invitation to Tender issued by the Ministry for Health. These actions will continue in 2002.

**Concerted action to foster genomics** is being undertaken with the aim of supporting major research programmes into genomics and functional genomics in France. 69 million € were provided in 2001. The National Genotyping Centre (CNG) is financed by this programme and has developed high-bandwidth platforms linked with quality control systems which make it possible to study the linking sites typical of genetic diseases over the entire genome. Over the last three years, active cooperation has been built up between academic laboratories and the CNG, with over 30 rare diseases having been or currently being studied.

**The Genhomme network**, a national network for research and technical innovation in human genomics. Its objective is to develop the tools that are crucial for functional genomics and its applications. Action taken in 2000 and 2001 was focused more particularly on supporting bioinformatics, nanobiotechnology and post-genome technology, which are relevant to both rare diseases and multi-gene diseases.

More specifically, perfecting therapeutic tools and developing orphan medicinal products falls within two main subject areas: (1) new drugs (from the therapeutic target to the candidate molecule to the validation of the active principle) and (2) cell therapy and gene therapy which make it possible to provide specific therapies, particularly for rare diseases.

This network is co-financed by the Ministry for Research (15 million € per year), the Ministry for the economy, finance and industry (15 million € per year), for a five year period, that means 150 million € in public funds over five years and an equal amount by the private sector (150 million € over five years). In order to foster the transfer of technology and the emergence of new therapies, all the research contracts involve both private and public partners.
The Genhomme network includes in its functioning, and particularly in its strategic orientation committee, the charitable organisations which are entrusted with overseeing the balance of financing between common multifactorial diseases and rare diseases.

In 2001, as part of the Genome programme, the French National Institute for Health and Medical Research and the French Association against Myopathies, with support from the Ministry for Research, have issued a call for proposals intended to promote the emergence of research networks focusing on rare diseases. These would bring together theoretical researchers, biologists and clinicians in order to make advances in our knowledge of the physiopathology of rare diseases and propose new therapeutic approaches. 32 projects have been chosen to receive financing totalling 2.5 million € over two years.

The Hospital Programme for Clinical Research, instituted in 1993, is an annual call for projects by the Ministry for Health. As part of the programme, the Ministry annually issues the subjects that are to take priority. The call for projects is addressed to clinician-researchers in the French hospital system, particularly at university hospitals. “Rare diseases” was among the priorities in 2001. Thanks to this, 15 research projects were selected for financing totalling 2.5 million € over several years. The circular launching the 2002 call for projects has just been published and, once again, “rare diseases” are a priority.

2.4.2. Tax provisions

Article 48 of the Social Security Financing Law for 2001 exempted sponsors of orphan medicinal products 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 French Health Products Safety Agency (AFSSAPS);
  - the safeguard clause for medicinal products;
  - the tax on direct sales;
- the tax on the distribution of medicines.

This measure will come into force as the taxes are collected (between December 2001 and March 2002) and as the designated medicinal products are added to the list of medicinal products which are eligible for reimbursement or the list of medicinal products authorised for use by public authorities.

Currently about 75 medicinal products are included in the orphan register. New incentives will foster the entry of these products into the French market during 2002. Turnover and distribution costs could quickly reach 15 to 30 million €, which will be covered by social security. Additional health insurance expenses and loss of income due to the exemptions from tax would then come to over 15 million €.

2.4.3. Support for organisations linked to rare diseases
The Ministry for Health also supports the **Rare Disease Platform** (76 000 €). This includes four bodies:

- the **Rare Disease Alliance**, a national group which includes approximately 80 associations of rare disease patients and their families;

- **Orphanet**, an internet server providing information on rare diseases and orphan medicinal products;

- **Allo-gènes**, a telephone service providing information on genetic diseases;

- **Eurordis**, a European network of association and national bodies concerned with rare diseases.

The variety of approaches and action taken by the Platform complement one another. The services that make up the **Orphanet database**, funded by the National Institute for Health and Medical Research, the Directorate-General for Health, and the *Mutualité Française* and *Caisse Nationale d’Assurance Maladie*. They are crucial for professionals and patients, as are the personalised advice available by telephone or by post, the national representation of all the associations concerned with rare diseases and European enlargement in order to develop the most effective strategies.

### 2.4.4. Specific funding

Since 2001, **funding** for **medical advances** has been set aside in hospital financing to enable them to cope with **therapeutic innovations**.

In 2002, this amounts to 229 million €, part of which is dedicated to orphan medicinal products which have received European marketing authorisations in 2001.

### 2.5. Finland

#### 2.5.1 Fee exemptions for national applications

The National Agency for Medicines [*Lääkelaitos*] may grant exemptions from marketing authorisation fees. This rule also applies to orphan medicinal products.

#### 2.5.2 Scientific advice and inspections

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.

#### 2.5.3 Scientific Research Measures

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, 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.

2.5.4 Seminar on Orphan Medicinal Products
A seminar dealing with orphan medicinal products was held in Finland in spring 2001.

2.6. Germany

In Germany, there are currently two main applicable measures which can be expected to facilitate the availability of Orphan medicinal products. These measures are aimed at the simplification of the placing on the market of medicinal products for orphan diseases. In addition a specific measure to promote targeted research on rare diseases has also been introduced.

2.6.1. Rapid Authorisation

German legislation on medicinal products provides for the rapid authorisation of medicinal products of great therapeutic use. This also applies to medicinal products intended for the treatment of orphan diseases.

2.6.2. Reduced Documentation to support marketing authorisation

If it is in the public interest to bring a medicinal product onto the market because of its great therapeutic use, the documents on the analytical, pharmacological, toxicological or clinical tests carried out may be expanded on even after the medicinal product has been authorised, and further tests may be carried out if such tests appear necessary for a full evaluation of the product.5

2.6.3. Research measures

A special measure to promote research into orphan diseases has been drawn up under the Federal Government's health research programme and came into effect in December 2000. This concerns the promotion of the creation of a national network for groups of rare diseases, including, in exceptional cases, individual rare diseases. Further information can be found on the web-site address: http://www.dlr.de/PT/.

In this framework, a project under the aegis of the Federal Ministry of Health is being funded for the creation of a model network of patients with rare retinal degenerative diseases, especially Usher Syndrome and choroideremia (PushNet). The main objective of this project is to create a model patient network which can be copied by other groups

5 Para. 28(3) of the Law on Medicinal Products
to give them a common voice and strengthen their position in dealings with health institutions.

The project is due to finish at the end of 2003.

2.7 Italy

Italy has not introduced any specific national initiatives to promote and/or facilitate “national” research and development of medicinal products “designatable” as orphan medicinal products. No new information has been provided since the publication of the first inventory. However a number of initiatives in the field of rare diseases have been taken through targeted research financed by the national Health Fund6.

2.7.1 Research targeted towards rare diseases

Financing has been granted to a number of research projects which are conducted by research institutes (Istituti di Ricovero e Cura a Carattere Scientifico, Istituto Superiore di Sanità) and which concern potential innovative therapies for rare diseases, notably:

in 1998:

– Development of new gene therapy approaches to Tay-Sachs Disease (Istituto per l’Infanzia Burlo Garofalo, Trieste);

– New therapies for coelia disease (Ospedale Bambino Gesù, Rome);

– Biotechnology in the diagnosis and experimental treatment of Hirschsprung Disease (Istituto per l’Infanzia Giannina Gaslini, Genoa);

in 1999:

– Biological-molecular characterisation of the neuroblastoma with reference to the optimisation of existing treatments and the development of innovative therapies (Istituto Giannina Gaslini, Genoa);

– Gene therapy approaches to adrenoleuco dystrophy (Istituto per l’Infanzia e Pie Fondazioni Burlo Garofalo, Trieste);

– Rare diseases: national register and study models aimed at improving prevention, aetio-pathogenesis, diagnosis and therapy (Istituto Superiore di Sanità, Rome);

– Inflammatory, oxidative and autoimmune mechanisms in disabling diseases of the nervous system and research into new therapeutic methods (Istituto Superiore di Sanità, Rome).

– Italian National Registry on Rare Diseases (Istituto Superiore di Sanità, Rome): besides the organisation of the National Registry as a basis for epidemiological studies, the objectives include the organisation of a National inventory of orphan medicinal products available in Italy.

6 Article 12(2)(a) of Legislative Decree 502/92, as amended
in 2000:

- Network of Public Health Institutions on Rare Diseases (NEPHIRD) funded by the European Commission. This project is co-ordinated by Italy (Istituto Superiore di Sanità, Rome) and include 15 Countries (EU and EU-associated). The main aim is to develop and implement an international network among public health Institutions, in order to produce valid and comprehensive epidemiological data on selected rare diseases.

2.7.2. Improving the availability of orphan medicinal products

The Italian National Health Plan provides for generic ways of improving the availability of pharmaceuticals. The draft regulation on the national rare diseases network and exemption from contributing to costs, now in the process of being issued, does not provide for any particular initiatives: the current “rules” on the supply of medicinal products to patients will continue to apply. However, it would be reasonable to imagine that appropriate measures will be adopted to ensure wider availability of pharmaceuticals under the national health service.

2.8. Luxembourg

The Government of Luxembourg has not taken any independent measures to stimulate the availability of orphan medicinal products, but 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 it co-organised a meeting within the European Agency for the Evaluation of Medicinal products as a workshop with academia and health professionals on orphan medicinal products.

2.9. Netherlands

Measures taken in the Netherlands - and forthcoming measures - are based on three recommendations of the Health Research Council (Raad voor Gezondheidsonderzoek) which were presented to Minister Els Borst-Eilers of Health, Welfare and Sport.

1. Establishment of a national structure for orphan medicinal products within an existing scientific institution.

2. Giving priority, in conjunction with other European countries, to a number of rare diseases and subsequently encouraging large European concerns to direct their research effort precisely towards these priority diseases.

3. Promoting the development of medicinal products by means of tax incentives and subsidy schemes.

An outline is given below of the policy measures taken by the Ministry for Health, Welfare and Sport. Reference is also made to promotional measures taken earlier in the Netherlands, and still in force, which are also of major significance to the development of orphan medicinal products.

2.9.1. Development of a national co-ordination structure for orphan medicinal products
Following a request from the Minister for Health, Welfare and Sport the Medical Branch of the Netherlands Organisation for Scientific Research (MW-NOW) set up a national organisational structure for orphan medicinal products and rare diseases on 6 April 2001. This structure is made up of a Steering Committee in which involved parties (umbrella organisations of a.o. patients’ support groups, doctors, pharmaceutical companies and also the Medicines Evaluation Board and the Care Insurance Council) participate and a secretariat for support and co-ordinating activities.

One of the first tasks of this structure will be the collection of information on rare diseases and orphan medicinal products, an inventory of various diseases and numbers of patients in the Netherlands thus continuing and extending the work initiated by the Health Research Council and creating thereby, an inventory of research and a national and international forum for contact and exchange.

This will be followed by the co-ordination and promotion of basic and patient-related research by institutions, small biotechnology-based businesses and also bigger pharmaceutical companies and patients' organisations.

The new structure is a contact point for questions concerning the European regulation and for consultation in connection with the pre-registration stage and issues concerning the central European register. The Netherlands hopes that this co-ordination and incentive organisation will give a better overview of developments in order to avoid wasting manpower and resources. In this way the Netherlands is also combining the Community action programme on rare diseases with the development of orphan medicinal products. The aim of this action programme is to strengthen existing networks of patients' organisations and to create new networks. Indirectly this programme is also of importance to the development of orphan medicinal products. Recital 19 of the action programme states that "a programme of action on rare diseases must form part of a coherent overall policy that includes initiatives regarding orphan medicinal products which are possibly not sufficiently profitable in commercial terms and medical research".

The Netherlands also advanced this point in the negotiations on the action programme. A special role is provided for patients' organisations in patient-related research. A pharmaceutical company cannot deal with the respective disease without a minimum number of patients. For a clinical study of a new medicinal product for common diseases a company can find what it needs in many hospitals or doctors' surgeries. In the case of a rare disease, this is clearly more difficult: the number of patients is small and often it is not known how many patients are actually involved, where they live or how they can be reached. Patients' organisations can obviously play a significant intermediary role in this instance.

The Ministry for Health, Welfare and Sport has made available an annual budget of maximum 450, 000 € for this new national structure for a period of four years, after which the Ministry will decide whether to continue up to a maximum of ten years. In so doing the Minister for Health, Welfare and Sport will, as usual, assign tasks to Zelfstandige Bestuurs Organen-ZBOs (independent bodies), in this case the Netherlands Organisation for Scientific Work-MW-NWO, on the basis of outlines. Most of the budget is destined for the continued functioning of the new structure and the rest will go on subsidies for scientific research and awareness-building of rare diseases among patients above all.
The secretariat of the steering committee (see section 2.8.1) has an office in the MW-NWO.

2.9.2 Prioritising certain rare diseases in collaboration with other European bodies

The Minister for Health, Welfare and Sport will ask the new organisational structure to work together with its European counterparts and possibly with the European Committee for Orphan Medicinal Products to make an inventory of the state of epidemiological and scientific research into rare diseases in the Netherlands and in Europe and in the process to link up with activities developed as part of the Community action programme on rare diseases. Prioritising rare disorders per se is not yet foreseen as a task for the steering committee in the near future, but might be - for pragmatic reasons - unavoidable in the long term.

2.9.3. Tax incentives and subsidies at a national level

In the context of tax incentives the Netherlands refers to existing legal rulings for high-tech companies. An important aspect in this context, for example, is tax reductions for research and development work (R&D). This ruling offers persons liable to taxes (i.e. company-owners) tax reductions on labour costs for their R&D workers. Parties other than companies (e.g. universities and scientific institutions) can also qualify for this reduction where their employees perform research and development work for a company. There is also the possibility of a general tax-reducing ruling for persons who are self-employed.

Experience in the initial years of this ruling has shown that a number of companies geared to developing biotechnological medicinal products will not make any profit and may even suffer losses. It is also possible to debit losses to the profits of the three previous years (retro-compensation), following which unlimited forward loss accounting applies. It might also be said in this connection that development costs often do not have to be entered in the books but can be set off directly against profits.

In the year 2000 and 2001 voluntary writing-off of new laboratories built primarily for research and development work was possible to a limited extent.

In conjunction with the Ministry of Finance, the Ministry of Health, Welfare and Sport has come to the conclusion that supplementary tax incentives are not needed at present.

2.9.4. Activities of the Dutch Foundation for Care Research (ZON)

In its annual programme for the year 2000 the organisation "Dutch Foundation for Care Research (ZON)" intended to focus on rare diseases in respect of the chronically ill. The Ministry of Health, Welfare and Sport will consult ZON on how best to spend structural government subsidies already in place. In 2001 ZON integrated with MW-NWO (see section 2.8.1 section ) and its new name is ZONMW. One advantage of this is the integration of basic and applied research in healthcare. The Ministry will also look at the financial support of scientific research and projects in the area of better provision of

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7 This reduction amounts to 40% to the limit of a wage of 68 000 € and 13% on higher wages. The condition for this reduction is the performance of R&D. In order to qualify for this reduction companies have to apply for a certificate from the Ministry of Economic Affairs.
information. The Netherlands will advocate continuation of measures within the European Union regarding rare diseases in the 6th Framework Programme.

2.9.5 Orphan medicinal products – implications for social insurance

Because of the special problem of rare diseases and orphan medicinal products, the Ministry of Health, Welfare and Sport has begun consultation with the Care Insurance Council (College Voor Zorgverzekeringen-CVZ) on how to regulate access to the social insurance package. It is particularly important to establish whether medicinal products which are registered via the central European procedure and have the status of orphan medicinal products can be included in the social insurance package without any further conditions. This also raises the question as to whether the (yet to be implemented) pharmaco-economic guidelines have to be applied before orphan medicinal products can be admitted to the social insurance package. Early co-ordination of the CVZ and the Steering Committee for orphan medicinal products is facilitated since CVZ fully participates in the steering committee. In 2001 three orphan medicinal products were market authorised in the Community, Fabrazyme® and Replagal® for Fabry’s disease and Glivec® for the treatment of chronic myeloid leukaemia. In the Netherlands access to these products is assured for patients with one of the afore-mentioned diseases. Glivec® is fully reimbursed under the existing regulations, but in the case of Fabrazyme® and Replagal® a subsidy for five years pursuant to a policy on subsidies for new and expensive medicinal products has been developed by the Care Insurance Council at the Ministry’s request. An encompassing issuing of instructions for the reimbursement of market authorised orphan medicinal is due later this year.

2.9.6 Subsidies and Incentives

As regards subsidy and incentive programmes, 9 million € has already been made available in the Netherlands for the programme initiated by the Ministry of Economic Affairs for innovative drug research and entrepreneurship (STIGON). In addition to contributions from the Ministries of Economic Affairs and Education, Culture and Science, there have also been contributions from the Netherlands Organisation for Scientific Research (NWO) and from various scientific institutions. This has made for a total of 9 € million over four years. This programme is geared towards the establishment of high-tech businesses and entrepreneurship in medicinal products for chronic and rare diseases. The STIGON programme is a continuation of an innovative drug research incentive that began in autumn 1999 for a period of four years.

The Ministry of Health will consult the Organisation for Applied Scientific Research (TNO) on whether orphan medicinal products can be included as a sub-theme in the theme of diagnostic and medication.

2.9.7 Dutch activities with respect to the Programme of Community action on rare diseases

The Community action programme on rare diseases (with a relatively limited budget of 6.5 million €) draws to a close at the end of 2003. This will be followed by a new co-ordinating action programme in the field of public health integrated in the 6th Framework Programme.
2.10. Portugal

To date, no national measures have been approved to support the research, development and marketing of orphan medicinal products, or any designated as such.

On 15 November 2001, however, INFARMED sent the Office of the State Secretary for Health a draft Order which aims to reduce by 50% the charges payable by applicants for authorisations to market (or to take other action) concerning orphan medicinal products or medicinal products which can be designated as such. If this draft is approved, it will be an incentive for developing and marketing the medicinal products in question.

2.11 Spain

2.11.1 Rapid Authorisation.

The Spanish legislation on medicinal products provides for the rapid authorisation of medicinal products of great therapeutic use, which also applies to medicinal products intended for the treatment of orphan diseases.

2.11.2 Research measures

Clinical research:

The Spanish Medicines Agency gives special advice to researchers and companies about the design of clinical trials of this kind of drug and a special consideration is taken into account when authorising clinical trials.

The National Plan of Research, Profarma, of the Directorate General of Policy on Technologies, of the Ministry of Science and Technology, in co-operation with the Spanish Medicines Agency and the Directorate General of Pharmacy and Medical Devices (Ministry of Health and Consumer Affairs), is including research/work on these important areas for Public Health as a plus in research and development programmes submitted by pharmaceutical companies.

The Instituto de Salud Carlos III, of the Ministry of Health and Consumer Affairs: "Research Programme for Rare Diseases": There is a Group of Coordination of this Programme at national level at the Institute, in co-operation with several National Medical Societies and Associations of Patients.

Among the objectives of this Programme are:

- To get a general view of the Rare Diseases problem.
- To know the present situation of these diseases in Spain.
- To develop an information system.
The Universidad Autónoma de Barcelona is leading a research Programme to compile registers and data bases on existing resources, reference centres and patients suffering rare diseases with the aim of fostering precocious treatment and clinical development. Among their activities:

- Regulations and rules on clinical trials and foreign medicines for compassionate use.
- Opinion polls among patients and care-takers on the supply and financing of medicines.
- Co-operation with pharmacists at hospitals and dispensing pharmacies to study the use, availability and cost of medicines.
- Creation of a web site on legislation on orphan medicines that presents information on 3 levels: patients and care-takers; health and social care professionals; pharmaceutical industry.

2.12 Sweden

The Medical Products Agency (MPA) has communicated to interested parties including patient and pharmaceutical industry organisations the information that the orphan regulation has come into force and information, including the possibility of obtaining funding, on the Programme of Community action on rare diseases (1999 to 2003). As part of this communication the MPA has invited proposals for actions which Sweden could take to support research into and development of orphan medicinal products. No additional measures were taken in 2001.

In September 2000, the Medical Products Agency organised an Orphan Drug meeting with the participation of Marlene Haffner from the FDA and representatives from the Swedish Board of Health and Welfare, EURORDIS, clinicians, geneticists, research societies and industry.

The objective of the meeting was primarily to increase the awareness of the Orphan Regulation and to form a national platform for interaction.

2.12.1 Fee exemptions for national applications

The Medical Products Agency applies the same fee reduction policy as that of the EMEA for sponsors of designated orphan medicinal products.

2.12.2 Database on rare conditions

The Swedish Board of Health and Welfare is building a database for rare conditions.

2.13 United Kingdom
The Medicines Control Agency has taken a number of measures to simplify the licensing process to help get medicines for rare diseases on to the market. These measures include:

- the provision of free national scientific advice to sponsors of orphan medicinal products
- accelerated marketing authorisation applications
- acceptance of a reduction in documentation, provided that efficacy, safety and quality are not compromised
- a substantial fee reduction for marketing authorisation applications processed under the mutual recognition procedure
- a substantial reduction in service charges.

2.13.1 Orphan Drugs Conference

The UK Department of Health organised a conference in September 2000 which brought together clinicians, patients, and representatives from the pharmaceutical industry to explore ways to help stimulate research and encourage the development and production of orphan medicinal products. The conference promoted awareness of the Orphan Medicinal products Regulation, and encouraged partnerships between relevant bodies.

2.13.2 Tax Credits

The Government has announced in its April 2002 Budget, tax credits for all pharmaceutical companies which spend money on research and development – orphan medicinal products included. Additional incentives are being offered to companies which undertake research into vaccines and medicines for the treatment of TB, malaria and HIV/AIDS.

2.14 Countries which have taken no specific national measures

Apart from the implementation of the provisions of the regulation on Orphan medicinal products and the nomination of a Member of the Committee for Orphan Medicinal Products, Ireland, and Greece have to-date taken no national measures to support research into, or the development and availability of, orphan medicinal products or medicinal products that may be designated as such.
Annex 1: List of Projects (1999-2000) under the Quality of Life Programme supporting research into orphan medicinal products fund

**Generic Activities**

<table>
<thead>
<tr>
<th>Project Description</th>
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<tbody>
<tr>
<td>Structural studies on the mechanism of DNA excision repair</td>
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<tr>
<td>Ultraviolet-sensitive genetic disorders associated with defects in DNA repair and transcription</td>
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<tr>
<td>Molecular and biochemical pathogenesis of Friedreich's ataxia: search for treatments</td>
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<tr>
<td>Multidisciplinary approach to understanding the pathophysiology of the Wiskott-Aldrich syndrome towards improved healthcare</td>
</tr>
<tr>
<td>A systematic approach towards the understanding, diagnosis and treatment of CDGS, a novel group of metabolic disorders caused by defects of glycosylation</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Evolving evidence-based treatment strategies for infantile hyperinsulism using clinical, genetic and cell biological insights into a heterogeneous disease</td>
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<tr>
<td>Coresets of outcome measures and definition of improvement for juvenile systemic lupus erythematosus and juvenile dermatomyositis</td>
</tr>
<tr>
<td>Nephrin in proteinuric diseases. Development of diagnostics, prognostic and treatment modalities.</td>
</tr>
<tr>
<td>Molecular characterisation and identification of biological risk factors in mantle cell lymphoma</td>
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<tr>
<td>European collaboration on craniofacial anomalies</td>
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<tr>
<td>Neuroprotection and natural history in Parkinson's plus syndromes: a clinical trial of the efficacy and safety of riluzole in Parkinson's plus syndromes</td>
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<tr>
<td>European network for fetal transplantation</td>
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**Key Action Cell Factory**

<table>
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<tr>
<th>Project Description</th>
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<tr>
<td>Thematic network around cystic fibrosis and related diseases</td>
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<tr>
<td>Development of high-throughput PNA-based molecular diagnostic systems</td>
</tr>
<tr>
<td>Pre-clinical evaluation of delivery systems for neuroprotective gene therapy in neurodegenerative diseases</td>
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<tr>
<td>European cell therapy in the nervous system</td>
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</table>
Annex 2: List of contracts (2001) under the Quality of Life Programme supporting research into orphan medicinal products related projects

**Key Action Cell Factory**

<table>
<thead>
<tr>
<th>Project Description</th>
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<tbody>
<tr>
<td>Novel genechip technology for simplified detection of molecularly heterogeneous genetic diseases: Detection of cystic fibrosis as a model.</td>
</tr>
<tr>
<td>Development of a rapid high-throughput assay for sensitive and specific detection and strain typing of Creutzfeldt-Jakob disease based on fluorescence correlation spectroscopy.</td>
</tr>
<tr>
<td>Early Diagnosis of Alzheimer's Disease and Related Dementia</td>
</tr>
<tr>
<td>A Systematic and Multidisciplinary Approach Towards Understanding and Therapy of the Inborn Lysosomal Storage Disease Alpha-Mannosidosis</td>
</tr>
<tr>
<td>Innovative therapeutics for the prototype autoimmune disease, myasthenia gravis</td>
</tr>
<tr>
<td>Integrated in vitro and in vivo testing of drugs in prion diseases: screening, development and mechanisms of novel therapeutics</td>
</tr>
<tr>
<td>Gene Therapy of Hematopoietic Stem cells for Inherited Diseases</td>
</tr>
<tr>
<td>Research, selection and mechanism of action of potential therapeutic agents against Flaviviridae (hepatitis C virus, dengue virus, west nile virus,)</td>
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