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COMMISSION STAFF WORKING DOCUMENT

on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained

Document on the basis of Article 10 of Regulation (EC) No 141/2000

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1. INTRODUCTION

Orphan medicinal products are intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that are rare. While only a small number of patients suffer from one of the 5,000 to 7,000 orphan conditions that exist today, according to projections, rare diseases affect a total of some 30 million people in the 25 EU Member States[1].

On 27 April 2000, Regulation (EC) No 141/2000[2] of the European Parliament and of the Council and the implementing Commission Regulation (EC) No 847/2000[3] entered into force being the first Community-wide regulations on orphan medicines. The EU orphan legislation aims at providing **incentives for the research, development and marketing** of orphan medicinal products that the pharmaceutical industry would be unwilling to develop under normal market conditions.

Article 7 of Regulation (EC) No 141/2000 introduced the possibility of placing on the market an orphan medicinal product through a **Community procedure**. This so-called centralised procedure leads to a single marketing authorisation valid throughout the EU and granted in the form of a Commission decision based on the scientific evaluation of the European Medicines Agency (EMEA). The centralised procedure offers the advantage of the widest possible EU market with one single authorisation. Since November 2005, by virtue of Regulation (EC) No 726/2004[4], the centralised procedure has become compulsory for orphan medicinal products.

To be eligible for incentives, orphan medicinal products are identified through a Community **procedure of designation** laid down in Article 3 of Regulation (EC) No 141/2000. Designation can take place at any stage of development provided that the sponsor can establish that the criteria are met. The EMEA, through its Committee for orphan medicinal products (COMP) is responsible for reviewing designation applications. At the stage of the application for marketing authorisation the COMP works closely with the EMEA Committee for human medicinal products (CHMP). The CHMP is responsible for the assessment of quality, safety and efficacy data submitted as part of

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[1] Source: Background Paper on Orphan Diseases for the "WHO Report on Priority Medicines for Europe and the World". 7 October 2004.

[2] O.J. L 18, 22.1.2000, p.1

[3] O.J. L 103, 28.4.2000, p.5

[4] O.J. L136, 30.04.2004, p.1

an application for marketing authorisation for all human medicinal products, orphan or not, in the centralised procedures. Based on a scientific assessment, CHMP is responsible for giving the final recommendation to the Commission for the granting of centralised marketing authorisations.

When establishing the legislative framework on orphan medicinal products in Europe, it seemed appropriate to make sure that it could be evaluated in due course. Article 10 of Regulation (EC) No 141/2000 obliges the Commission to report on the experience acquired as a result of the application of that regulation, together with an account of the public health benefits which have been obtained. This Commission Staff Working Document responds to that obligation.

The document has been prepared in consultation with Member States, the European Medicines Agency and Interested parties. As major sources of information, the Commission has notably welcomed the COMP Report[5] presenting the views of the EMEA and COMP on the practical implementation of Regulation (EC) No 141/2000 and an independent study on the conditions for marketing of orphan medicines in Europe conducted on behalf of the European Commission[6].

[5] See http://emea.eu.int. COMP report to the Commission in relation to article 10 of Regulation 141/2000.

[6] See http://pharmacos.eudra.org/F2/orphanmp/index.htm. Study on the price of orphan drugs by Alcimed

2. EXPERIENCE ACQUIRED

2.1. Designation, authorisation and incentives

2.1.1. Designation

According to the procedure for designation laid down in Article 3 of Regulation (EC) No 141/2000, an orphan medicinal product should be intended to diagnose, prevent or treat a life-threatening or chronically debilitating condition. It should also be established that either the condition affects not more than 5 in 10 000 persons in the Community when the application is made ("prevalence criterion") or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment ("insufficient return on investment criterion"). Additionally, there should be no satisfactory method of diagnosis, prevention or treatment of the condition in question authorized in the Community ("no satisfactory method criterion") or, if such method exists, the medicinal product should be of significant benefit to those affected by that condition ("significant benefit criterion").

During the first five years of implementation (April 2000-April 2005), 458 applications for orphan designation were submitted resulting in 268 products being designated, relating to over 200 different rare conditions *(see Figure 1)*. Of all applications between April 2000 and April 2005, two were based on the insufficient return on investment criterion. All others were based on the prevalence criterion. For only one of the two applications based on the insufficient return on investment, a decision on designation has been issued; the other application resulted in withdrawal by the sponsor prior to COMP opinion.

Of those orphan medicinal products recommended for designation by COMP during that period, in 43% of cases the prevalence was below 1 in 10,000, in 47% between 1-3 in 10,000, and in 10% between 3-5 in 10,000 *(see Figure 2)*. Sixty-nine percent (69 %) of medicinal products recommended for designation fulfilled the significant benefit criterion. The majority of these opinions based on benefit were based on argumentation of potentially improved efficacy (78.8%), whereas a potentially improved safety profile and contribution to patient care were the unique criterion for benefit in only 5.2% and 5.7% of designations, respectively. In 10.4% of the designations the three criteria (improved efficacy, safety profile or greater contribution to patient care) were accepted in different combinations.

During the same period, the predominant therapeutic areas corresponding to the designated orphan medicinal products were cancer (36%), metabolic disorders (21%), immunology (11%), and cardiovascular and respiratory disorders (12%) *(see Figure 3)*. 54% of medicinal products designated have potential for paediatric use: 11% solely for paediatric use and 43 % for adult and paediatric use *(see Figure 4)*.

With 5 years of experience gained, the COMP has noted that the orphan legislation has been applied without any major difficulties. Although the COMP considers the data requirements for designation applications to be adequate and understandable, a number of practical points linked to the designation criteria have been highlighted.

Regarding the "insufficient return on investment criterion" the COMP has noted that there is very limited experience with this criterion as only two applications have been submitted on the grounds of insufficient return on investment.

In the application for designation, a review of currently available diagnosis, prevention or treatment methods in the Community and an overview of all authorised medicinal products where applicable are required. The database on authorised medicinal products foreseen in Article 57 of Regulation (EC) 726/2004[7] will facilitate the validation of this information. This database will also increase visibility of those medicinal products authorised for rare diseases prior to the implementation of the orphan regulation and therefore without a formal orphan status.

With respect to the "significant benefit criterion", the sponsor is required to establish significant benefit in the EU population affected by the condition. As a consequence, applications which only concern diseases in developing countries will not be able to benefit from the EU orphan status.

2.1.2. Authorisation

Of the 268 designated orphan medicinal products between April 2000 and April 2005, 49 (19%) have applied for a marketing authorisation. Of these, 44 have filed through the centralised route and 5 via national procedures.

During the same period, twenty-two orphan medicinal products have received a marketing authorisation. Of those, twenty have been authorised via the centralised procedure and two through national procedures *(see Tables 1 and 2)*. As of April 2005, there were under evaluation 15 applications submitted to the EMEA against 2 applications submitted through the national procedures.

The number of orphan medicinal products authorised has increased each year since the entry into force of the EU orphan regulations. It is expected that the number of authorised orphan medicinal products will increase considerably in the years to come.

In order to assess the status of development of designated orphan medicinal products, EMEA conducted a survey and updated information was received for 170 medicinal products: 33 % of the medicinal products surveyed were in the final stage of clinical testing (Phase III) and a further 38% were in Phase II *(see Figure 5)*. Also, of the sponsors surveyed by EMEA, 50% plan to file an application for marketing authorisation in the next three years *(see Figure 6)*. Based on experience, it has been estimated that the number of products reaching the market will increase significantly in the next 3 years.

With the objective of ensuring full harmonisation of the internal market and in the interest of patients with rare conditions in the European Union, Article 3 of Regulation (EC) No 726/2004 has made the centralised procedure compulsory for orphan medicines from 20 November 2005. In light of the experience acquired with the orphan legislation since 2000, this measure has been widely welcomed.

[7] O.J. L 136, 30.04.2004, p.1

2.1.3. Incentives

The EU has chosen a policy for the research, development and placing on the market of orphan medicinal products primarily based on direct incentives granted by the Community but also by encouraging Member States to adopt similar and/or complementary measures at national level.

As required by Regulation (EC) No 141/2000, the Commission published in 2001 a detailed inventory of all measures made available by the Community and the Member States to support research into, and the development and availability of, orphan medicinal products. The inventory was updated in 2002[8]. 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, following an initiative of the COMP Working Group with Interest Parties, through the respective networks of its members, learned societies, patients' organisations, industry organisations and other relevant stakeholders were contacted. All these interested parties were requested to provide data on incentives at a national level. In addition, information on Community measures has also been requested from the different services of the Commission. Based on all the data collected, an update of the Inventory of Community and national incentive measures shall be published in 2006.

a) Community incentives

(1) Market exclusivity

A 10-year period of market exclusivity is given to orphan medicinal products designated by the Community and where either the Community or all EU Member States have issued a marketing authorisation in respect of the medicinal product concerned. During this period, similar products cannot be placed on the market for the same therapeutic indication unless one of the derogations in Article 8(3) of Regulation (EC) No 141/2000 applies:

– the holder of the marketing authorisation gives his consent,

– the holder of the marketing authorisation is unable to supply sufficient quantity of the product, or

– the second applicant can establish that the second medicinal product is clinically superior.

Market exclusivity is considered to be the main incentive given to companies for the development of orphan medicines.

Regulation (EC) No 141/2000 provides also for the possibility of reviewing the status of designated orphan medicinal products which may be triggered by a Member State at the end of the fifth year of market exclusivity. If maintenance of market exclusivity is no longer justified, the period of market exclusivity for the corresponding medicinal product will be reduced to six years.

[8] see http://pharmacos.eudra.org/F2/orphanmp/index.htm

(2) Fee reduction

The EU orphan legislation foresees a Community contribution to be allocated every year to the EMEA for orphan medicines. As a special contribution, it is used exclusively for the reduction of regulatory fees payable to the EMEA (e.g. protocol assistance, application for marketing authorisation, inspections and variations). Since 2002, a 100% fee waiver for request for protocol assistance and a 50% reduction for all other fees have been applied. Between April 2000 and April 2005, more than 12 M€ of Community funding has been used to support fee reductions for designated orphan medicinal products (see Figure 7).

(3) Incentives to support research

The EU supports research into rare diseases and orphan medicinal products through its multi-annual Framework Programmes (FP) for Research and Technological Development. 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 projects in various scientific fields such as genetics, neurology, immunology, metabolic diseases, oncology, mycology, infectious diseases, nephrology or dermatology. Different types of projects were supported: research, coordination of research, research infrastructures. A total of 47 projects were granted 64 M€ support in the FP5 Thematic Programme "Quality of Life and Management of Living Resources": 37 in the Generic Activities section, amounting at 48 M€; and 10 in the "Cell Factory" section, for a total budget of 16 M€. A list of these projects can be found in *Table 3*[9].

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 designed to provide new knowledge through multidisciplinary approaches and to durably integrate research activities of the participants. These broad projects, particularly suited to translational research, should allow tackling scientific issues relevant to groups of diseases, to develop tools that can be applied in ranges of diseases, or to answer more "horizontal" questions generally relevant to rare diseases. 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

[9] More information on the Quality of Life Thematic Programme can be found on: http://www.cordis.lu/life/.

delineated field of research. As in FP5, projects supported in FP6 address a variety of diseases and apply different approaches.

At mid-term of FP6, 27 projects were selected for support in Priority 1, representing a global budget of 96 M€. 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 M€. 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 M€[10]. A list of projects funded at mid-term of FP6 is provided in *Table 4*.

(4) Protocol assistance

The sponsor of an orphan medicinal product may request advice from the EMEA on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product. For rare diseases, which often raise complex developmental issues, this scientific support called protocol assistance is fully recommended.

Uptake of protocol assistance by sponsors has been extensive and is increasing markedly over time *(see Figures 8-10)*. The experience gained so far indicates that using scientific advice/protocol assistance increases the probability of approval *(see Figure 11)*. During the first 5 years of application of the EU orphan regulations, over 80 protocol assistance procedures have been completed. The number of requests for protocol assistance received progressively increased from 5 in 2001 to 35 in 2004.

b) Member States measures

Incentives available at Community level should be supported by complementary national initiatives. At the time of the publication of the 2002 update of the Inventory of Community and Member States measures, 14 Member States provided a report. Of these, not all had taken specific measures for the marketing and development of orphan medicinal products. Initiatives at national level include fiscal incentives, national research projects, fee reductions, scientific/administrative advice and fast track authorisation procedures.

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

2.2. Public Health benefits and access to treatment

2.2.1. Public health benefits

The ultimate benefit of Regulation (EC) No 141/2000 would be an increase in the survival, the life expectancy and / or the quality of life of patients affected by rare disorders.

Altogether, the first 22 orphan medicines have been authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. Prior to the authorisation of these medicines, for 8 out of 20 corresponding rare conditions (40 %) there were no satisfactory treatment options authorised in the Community. This in itself is a major benefit.

For the remaining 12 rare diseases targeted, the authorised orphan medicinal products are expected to bring a significant benefit to patients via improved efficacy over authorised treatments, improved safety and/or major contribution to patient care.

As a consequence, more than 1 million patients suffering from these orphan diseases in the Community may potentially benefit from the availability of these new treatments authorised since Regulation (EC) No 141/2000 came into force. The preliminary conclusion is therefore that the orphan regulations have delivered on the fundamental objective of improving public health in the EU.

It is, however, still too early to assess in full the benefits of the regulation. The period of time that has elapsed since the orphan regulations entered into force is too short for the full public health impact of the orphan medicines on the key parameters, such as survival, life-expectancy and quality of life, to be assessed thoroughly.

2.2.2. Access to treatment

The major incentive for placing orphan medicinal products on the market, the 10-year period market exclusivity is granted by a Community decision. Nevertheless, orphan medicinal products like other authorised medicines are subject to national laws governing pricing, reimbursement and distribution. Different national policies across the Community help explain differences in the access to treatment for patients in different EU Member States or in different regions within the same country. Although Directive 89/105/EEC[11] lays down precise deadlines for national decisions on pricing and reimbursement, orphan medicinal products for which a marketing authorisation has been granted are not available in several Member states beyond the mentioned deadlines. In addition, when orphan medicinal products are made available in a Member State, it is difficult to determine their real accessibility because the delivery of these medicines, often in hospitals, is not well recorded.

European patients' organisations have indeed reported very different levels of access to treatment across the European Union. This was also highlighted by the Report on the first 3-year mandate of the Committee for Orphan Medicinal Products (April 2000 - April 2003). It was noteworthy that, for the first five orphan medicines authorised in the EU, the number of days elapsed between marketing authorisation and commercialisation in

[11] O.J. L40, 11.2.1989, p.8

pharmacies varied considerably among EU Member States. On average the shortest delay was of 35 days and the longest of 212 days. In many cases, orphan medicinal products were not available at all.

A regular survey is performed by European patients' organisations. The latest survey analysed the availability of the 12 orphan medicinal products which received an EU marketing authorisation before 31 December 2003. The results of this study showed that in December 2004, thus one year after the authorisation of the 12th product, only one Member State could demonstrate the availability of all 12 orphan medicinal products. Only in 12 of the 25 EU Member States, at least six of the 12 analysed orphan medicinal products were available[12].

2.3. Economic impact

2.3.1. Growth, jobs and innovation

According to preliminary findings of an economic assessment carried out by an Industry Task Force[13], Regulation (EC) No 141/2000 has had a distinctive positive economic impact in the EU. Given that the time frame since the Regulation came into force is short, reliable statistics related specifically to orphan medicinal products investments and their economic benefits are not available yet. However, some preliminary indications of broad trends can be provided.

There is general consensus that the EU orphan legislation has contributed to create the right financial and political environment in which the attention of the sector can turn to rare diseases. Since its implementation, a significant number of start-ups have been created and many existing companies have begun research on rare diseases. According to the above-mentioned economic assessment, about one-third of the companies surveyed are start-ups created in or after 2000. An additional 20% of the companies surveyed were set up in the period 1997-99, a time when the efforts to create the European orphan regulation were under way or known to industry. Finally, over half of the sampled companies started developing orphan medicinal products in or after 2000. The level of assets and turnover has also grown and companies have consistently approached their activities on a global scale.

According to the same study, jobs related to orphan medicinal products seem to have increased at a quicker pace than general industry trends, both those relating to R&D positions and, especially, those around and beyond R&D, as companies producing orphan medicines get ready to bring their products to the market. All the companies surveyed have increased their total number of employees in the European Community between 2000 and 2004 (43% increase on average). Moreover, R&D expenditure on rare diseases has grown faster than general medicinal R&D investment. The companies surveyed increased R&D investment in orphan medicinal products more than two-fold on average between 2000 and 2004.

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[12] See results of the Eurordis' study on orphan drug availability at http://www.eurordis.org.

[13] Economic impact assessment of Regulation (EC) No 141/2000. Joint EuropaBio (the European Association for BioIndustries) and EBE (Emerging Biopharmaceutical Enterprises) Task Force. August 2005.

To ascertain the "innovativeness" of the medicinal products seeking orphan designation, the EMEA reviewed all products that have been subject of a designation application over the period 2000-2004. From this review, it is noteworthy that novel/innovative products[14] constitute 53% of all applications for orphan designation. The orphan initiative would, thus, appear to have already made a positive impact on research into rare diseases.

Moreover, approximately 21% of the products that have been subject of a designation application over the same period are biotechnology products (e.g. monoclonal antibodies or recombinant enzymes) and emerging therapies such as anti-sense, gene therapy and cell therapy. This figure is expected to further increase as more and more innovative biotech products are presented for orphan designation *(see Figures 12-14)*.

2.3.2. Public health-care expenditure

Due to the rarity of the conditions for which orphan medicines are intended for, it is very difficult to establish an appropriate price level, especially if they target a condition for which there is no alternative treatment. Nevertheless, according to the report conducted by Alcimed[15], the cost of treating a patient with an orphan medicinal product seems, in most cases, not to be higher than that of other treatments with the same therapeutic target.

There is no clear data to assess the overall impact of the orphan regulations on public expenditure. However, Alcimed has estimated that, based on analyses conducted in France and Netherlands in 2004, the total cost of orphan medicinal products per country accounted for 0.7-1% of the national budgets earmarked for medicines.

Most EU Member States have either one competent national authority or several decentralised authorities that publish reference guidelines for pricing and reimbursement negotiations for medicines. Criteria for evaluating price level and reimbursement may include the prices practised in other European countries, the extent of investment by the company and the level of innovation, the medical benefit and the level of cost-effectiveness.

2.4. Experience with the new Committee and Transparency

2.4.1. COMP

COMP has taken on an important role in stimulating the development of orphan medicinal products and in implementing the legislation. This legislation has been applied without any major difficulties, achieving outstanding results and public health benefits. The COMP, together with the Commission and in consultation with stakeholders and interested parties, has developed appropriate guidance to establish a sound EU process to designate orphan medicinal products eligible for incentives as provided by the legislation.

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[14] medicinal products classified under the following headings: Gene therapy; Human cell therapy; Xenogeneic therapy; Tissue engineering; Monoclonal antibody; Micro-organisms; Antisense; Recombinant enzymes; Blood products; Novel chemicals.

[15] See http://pharmacos.eudra.org/F2/orphanmp/index.htm. Study on the price of orphan drugs

Expert network

Since 2000, a network of experts has been established to assist the COMP in its review of designation applications. To date more than 350 experts (clinicians specialised in rare disorders, representatives of patients' organisations with first hand experience of the conditions, pharmacologists, research scientists, and epidemiologists) have been nominated.

The expert network has not only provided invaluable expertise for the COMP in its evaluation of designation applications, it has also enhanced the interest of the scientific community in rare diseases and increased awareness of the medicinal products that are being designated.

Role of patients

The COMP is the first scientific committee in the EU to include representatives of patients' organisations as full members. Three seats of COMP have been assigned to patients' organisations since its creation in 2000. This has not only stimulated dialogue with patient groups but has also had positive impact on triggering the committee's work from the patients' need and public health perspectives, structuring patient groups' work at EU level and has supported patients' demands for greater transparency in decision-making.

International cooperation

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

2.4.2. Communication and transparency

There is a general agreement that Regulation (EC) No 141/2000 on orphan medicinal products has provided a legal frame that fosters better communication and collaboration between stakeholders for the development and marketing of orphan medicinal products. This adds up to more general initiatives in the field of rare diseases.

COMP Working Group with Interested Parties

The EMEA has set up a COMP Working Group with Interested Parties (COMP-WGIP) in which representatives of industry, patients and health professionals participate. The mandate of the group, which meets 3-4 times a year, encompasses transparency with regard to the designation procedure and preparation of policy proposals on orphan medicinal products.

Public Summary of COMP Opinions and EMEA/COMP press releases

Following a recommendation of COMP-WGIP, the need to provide patients with summarised information on COMP Opinions in lay-man language for ease of comprehension was identified. To address this need, release of the first *Public Summary of Opinions* by EMEA commenced in January 2002. Public summary of opinions are written by the EMEA Secretariat and validated by the concerned sponsors and European patient group representatives.

A press release is also published by the EMEA after each COMP meeting and provides an overview of the orphan medicinal products recommended for designation by the Committee, any new guidance documents and the key topics discussed.

Community Register of Orphan Medicinal Products

As required by Regulation (EC) No 141/2000, the orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products[16].

The Rare Diseases Task Force

The Rare Diseases Task Force (RDTF)[17] 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 for rare diseases through European co-ordination. Members of the RDTF are current and past leaders of projects funded by Community public health and research programmes, experts nominated by Member States and representatives of relevant international organisations (e.g. European Institutions, EMEA, WHO, OECD).

2.4.3. Scientific and public awareness

Regulation (EC) No 141/2000 and the gradual introduction of authorised orphan medicines have generated an increase in both scientific and public awareness regarding rare disorders and orphan medicines. EMEA has estimated that there has been an increase of around 70 % in the number of scientific publications comparing the periods 1995-1999 with 2000-2004 and an increase of 85% when the search is narrowed to those publications specifically referring to ‘Europe’ and ‘European Union’. A similar search carried out in the general press in five Member States indicates that the number of newspaper articles in each Member State has also increased[18].

3. CONCLUSIONS

The response to the orphan legislation in the EU has far exceeded initial expectations; more than 450 applications for orphan designation have been submitted in the period between April 2000 and April 2005. Of those, more than 260 have been designated and 22 have gone on to receive a marketing authorisation.

Although more than 5 years of experience with the Regulation has now been gained, the true impact of the EU orphan initiative on public health will only be revealed progressively as longer term experience is accumulated. Already, more than 1 million patients suffering from orphan diseases in the Community may potentially benefit from these new 22 orphan medicines authorised during the first five years of application of Regulation (EC) No 141/2000. In addition, there is good ground to assume that the

[16] See http://pharmacos.eudra.org/F2/register/index.htm

[17] See http://www.rdtf.org

[18] See http://emea.eu.int. COMP report to the Commission in relation to article 10 of Regulation 141/2000.

legislation has stimulated industrial activity leading to company creation with promising high-tech potential.

The full benefits of the EU orphan regulations require optimal synergies between action on Community and on Members State level. Incentives at the European Union level need to be translated into rapid access of patients to the new products throughout the entire Community and they need to be supplemented by incentives at Member States level. In this regard, the past experience was not entirely satisfactory.

ANNEXES

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ANNEX I – Figures

(Source : COMP Report to the Commission in relation to article 10 of Regulation 141/2000)

Figure 1: **Overview of Orphan Designation Procedures - Outcomes April 2005**

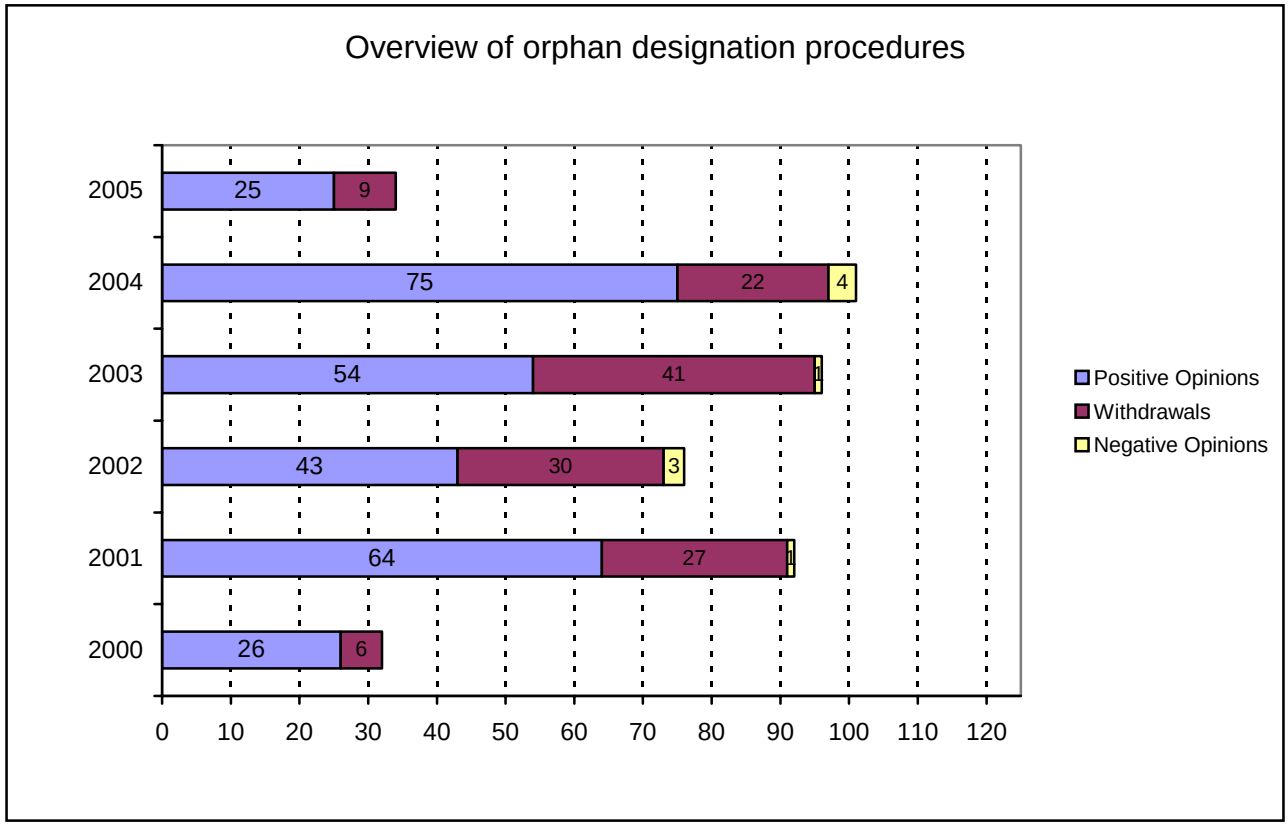


Figure 2: **Prevalence Range of Designated Orphan Conditions - April 2005**

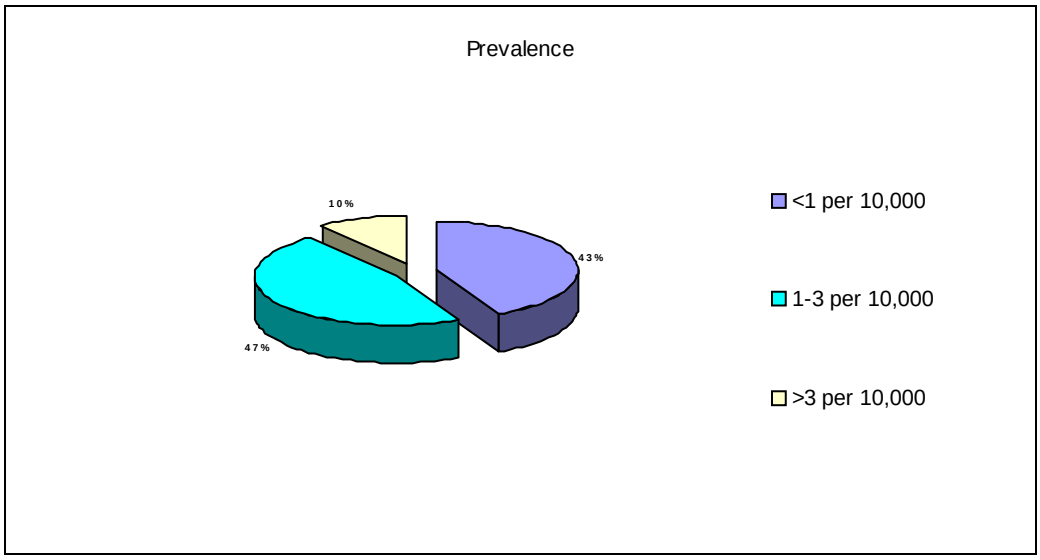


Figure 3: **Distribution of Orphan Designations by ATC code (April 2005)**

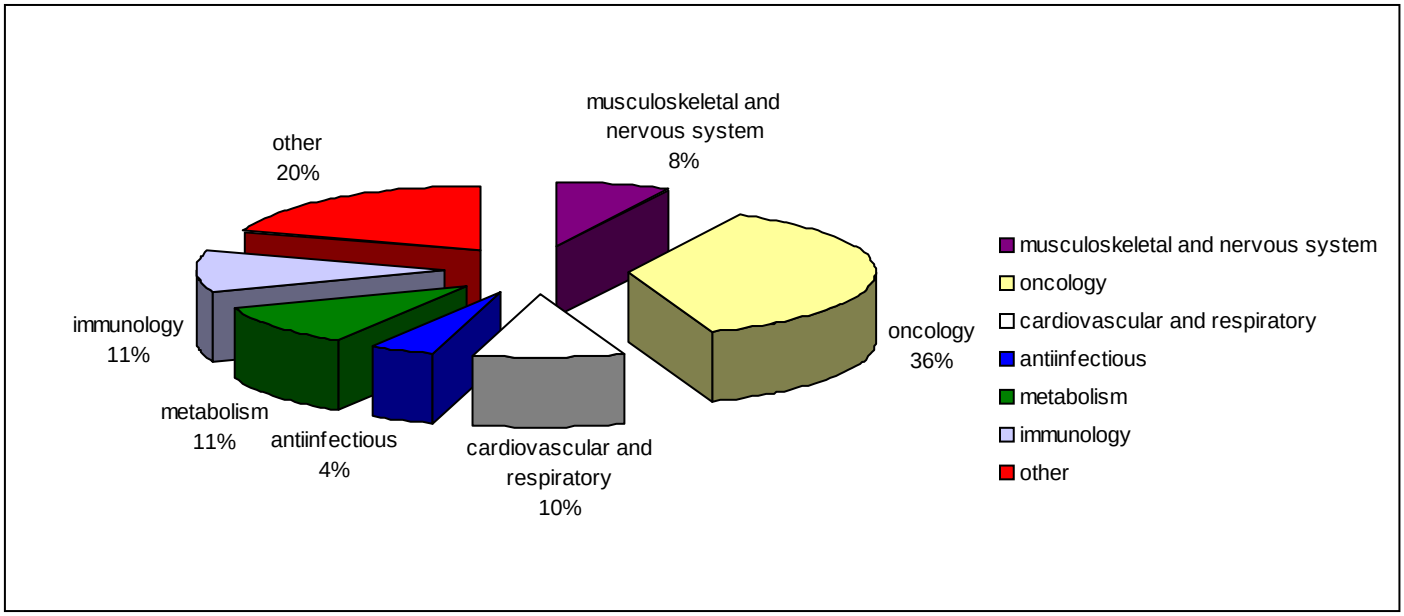


Figure 4: **Paediatric Use of Orphan Medicinal Products (April 2005)**

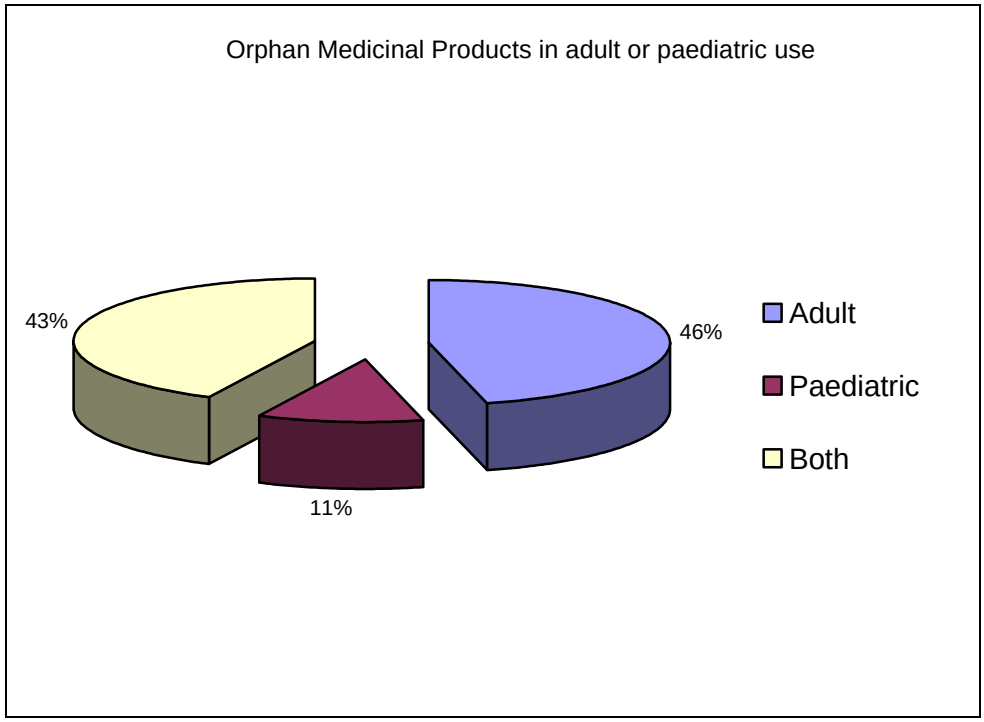


Figure 5: **Status of Development of Orphan Sponsors (April 2005)**

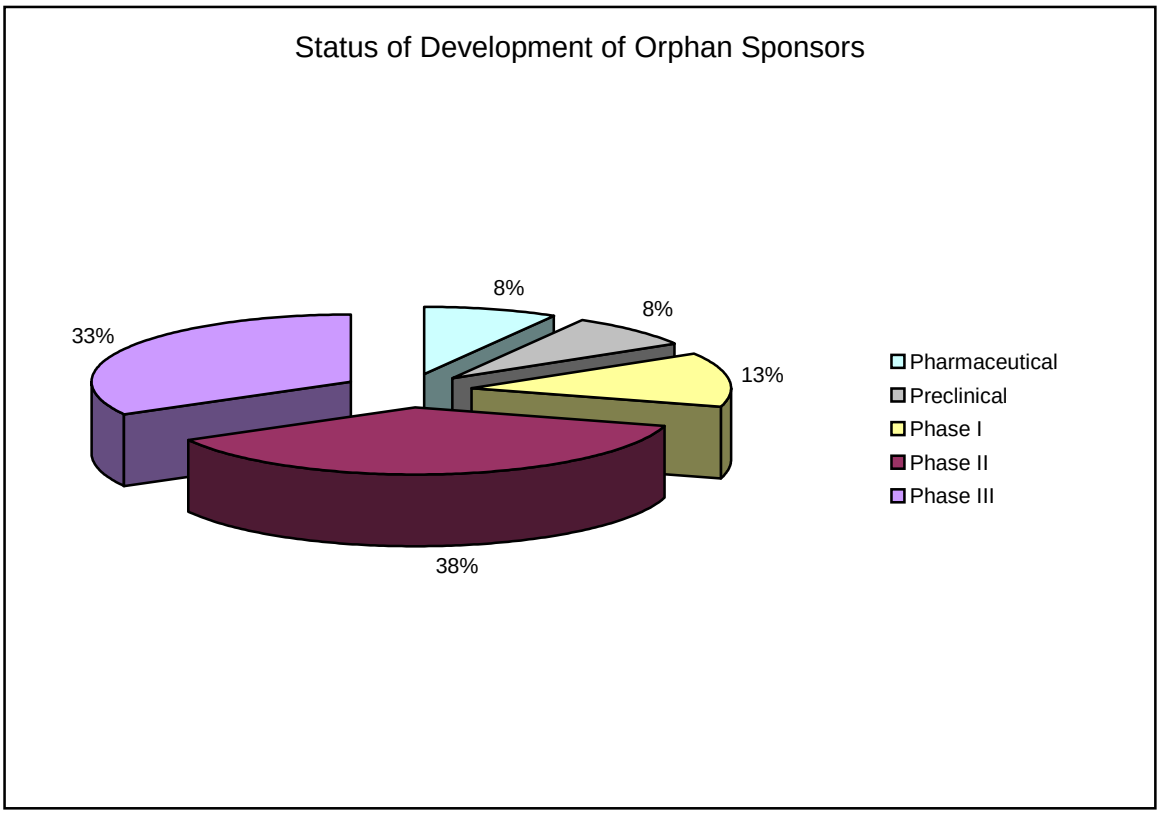


Figure 6: **Planned Applications for Marketing Authorisation for Designated Orphan Medicinal Products (April 2005)**

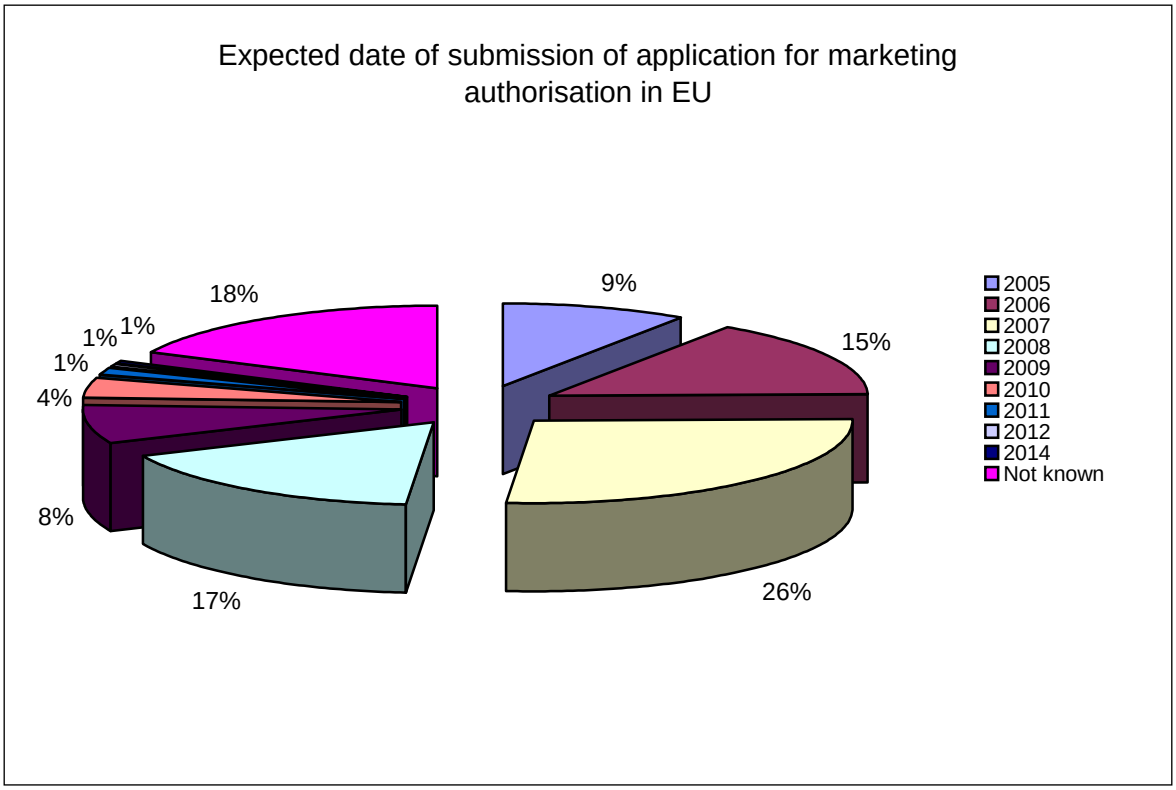


Figure 7: **Overview of Fee Reductions Granted to Orphan Medicinal Products – Status (April 2005)**

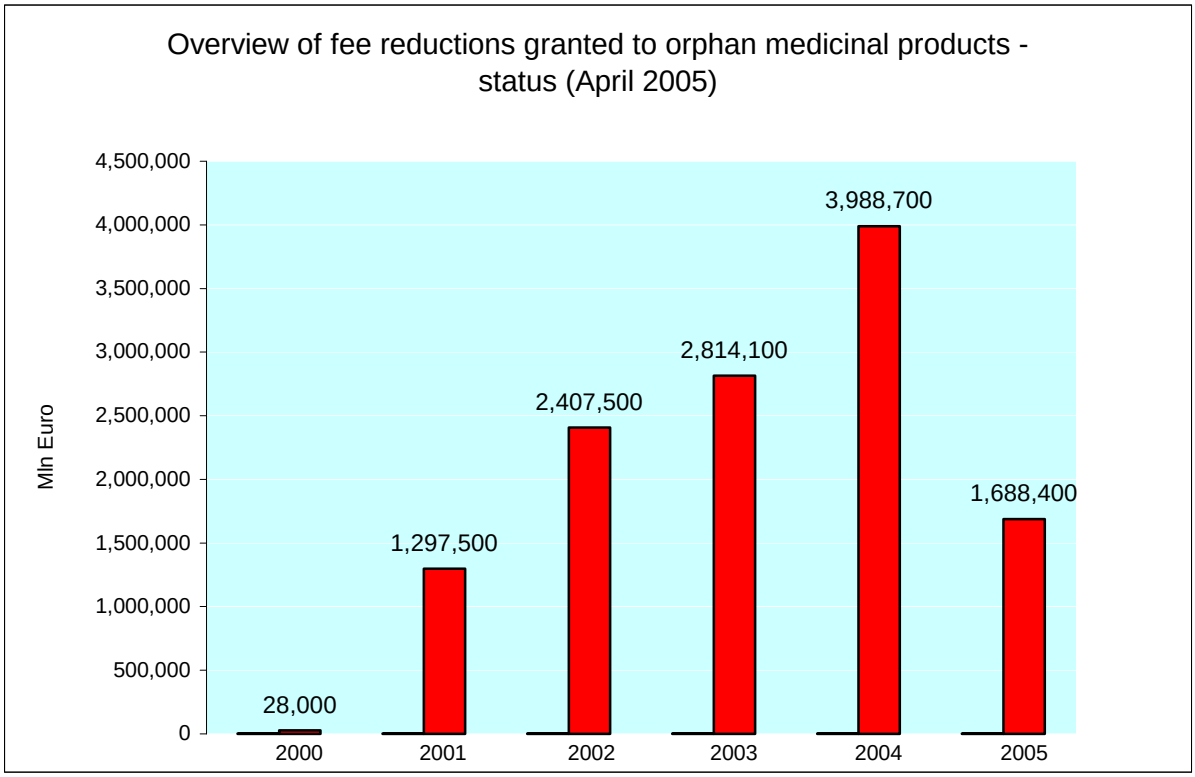


Figure 8: **Number of Protocol Assistance Requests, Oral Explanations and Pre-submission Meetings: 2001-2004**

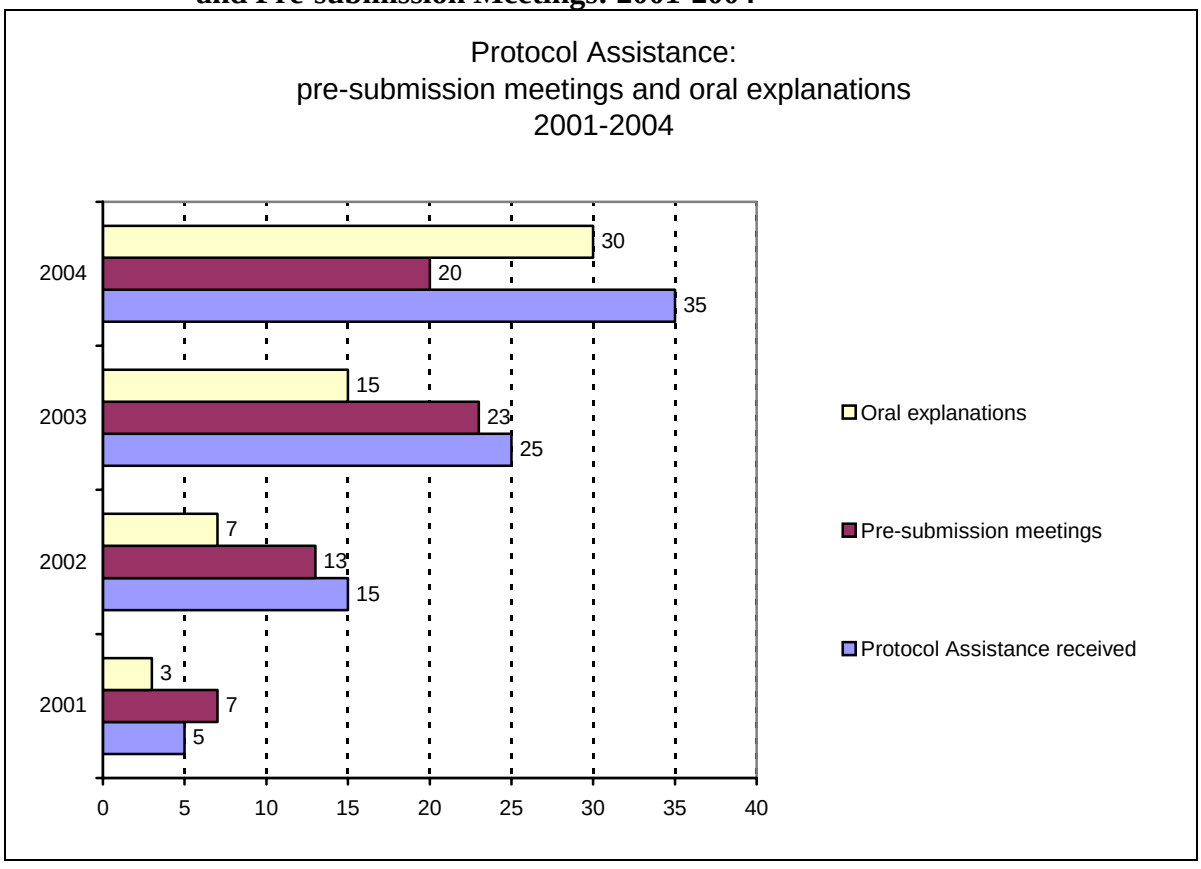


Figure 9: **Number of Protocol Assistance finalised per year: 2001-2004**

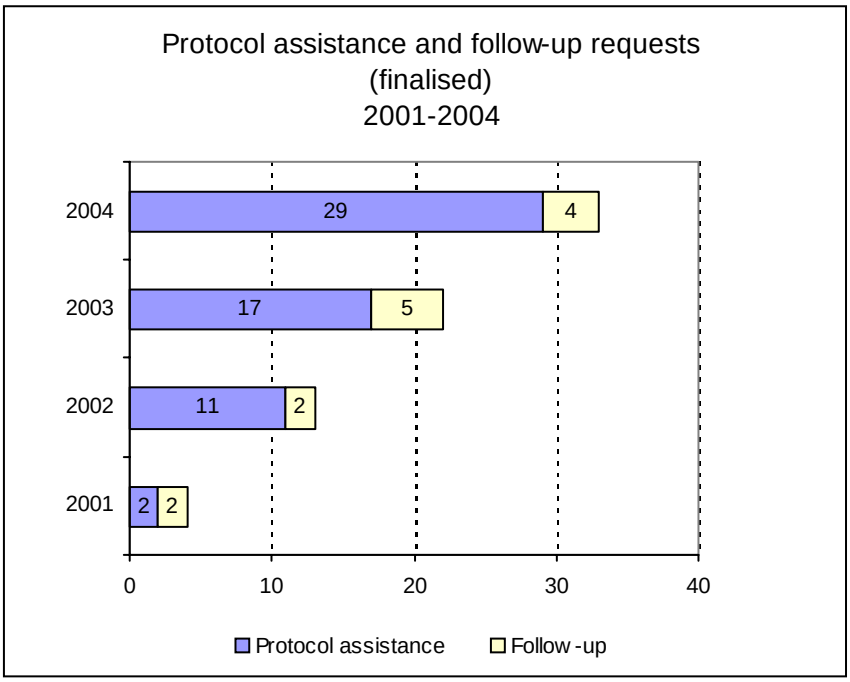


Figure 10: **Planned Requests for Protocol Assistance (April 2005)**

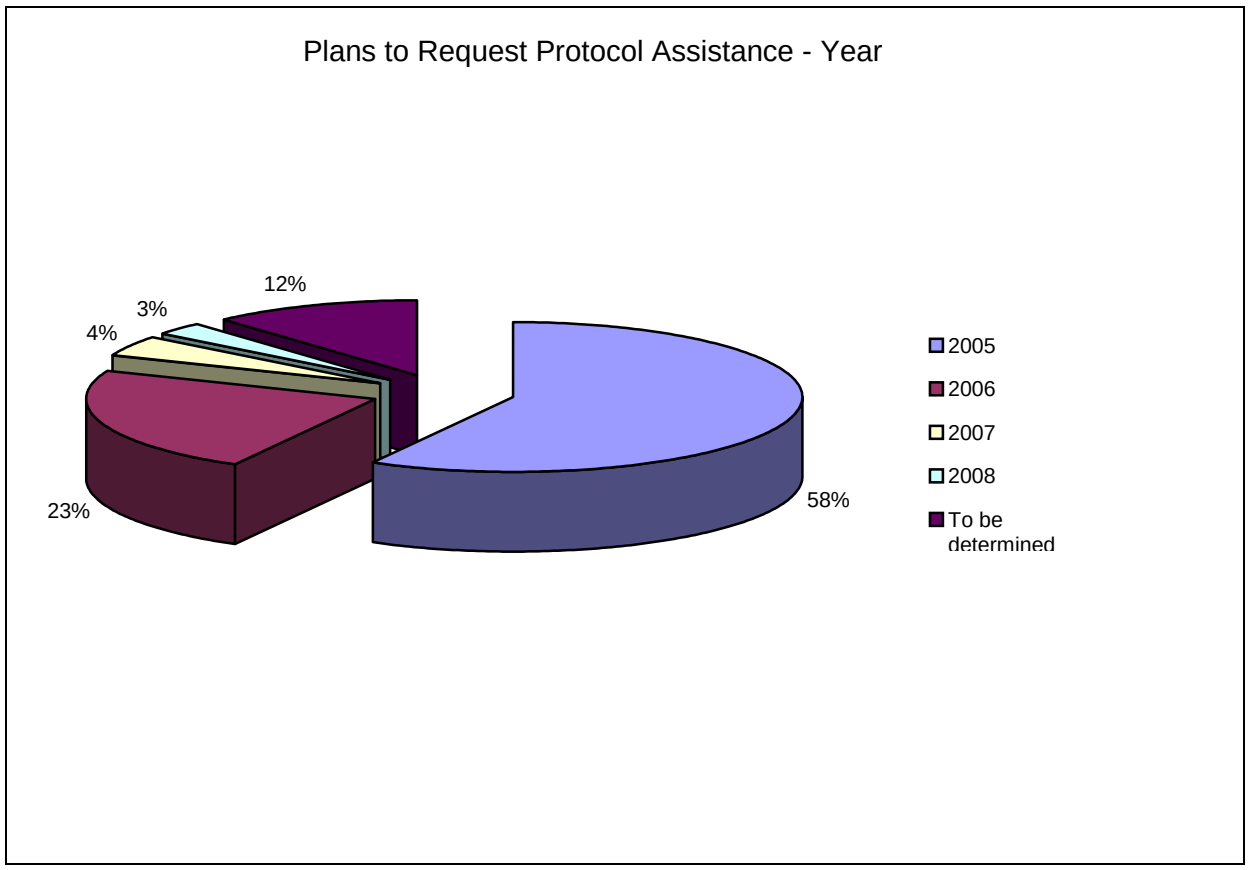


Figure 11: **Impact of Scientific Advice/Protocol Assistance on the Proportion of Approvals Over Time (2004)**

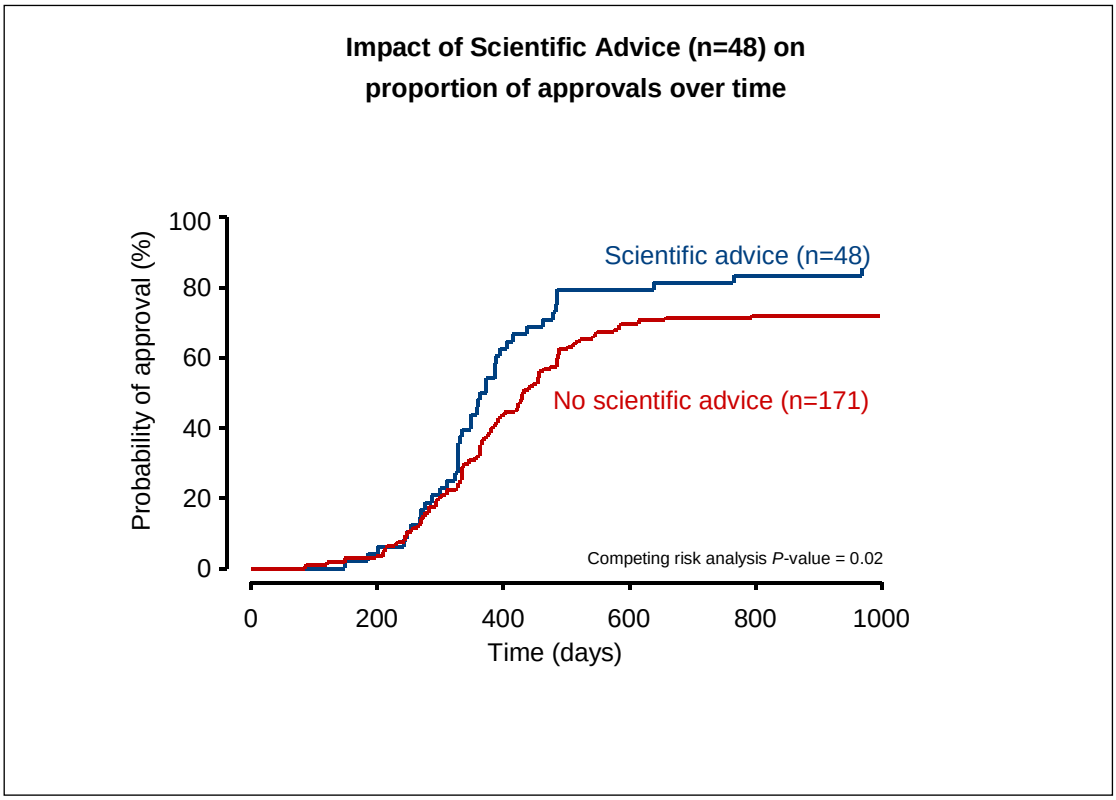


Figure 12: **Type of Medicinal Products Subject of an Application for Orphan Designation (2000-2004)**

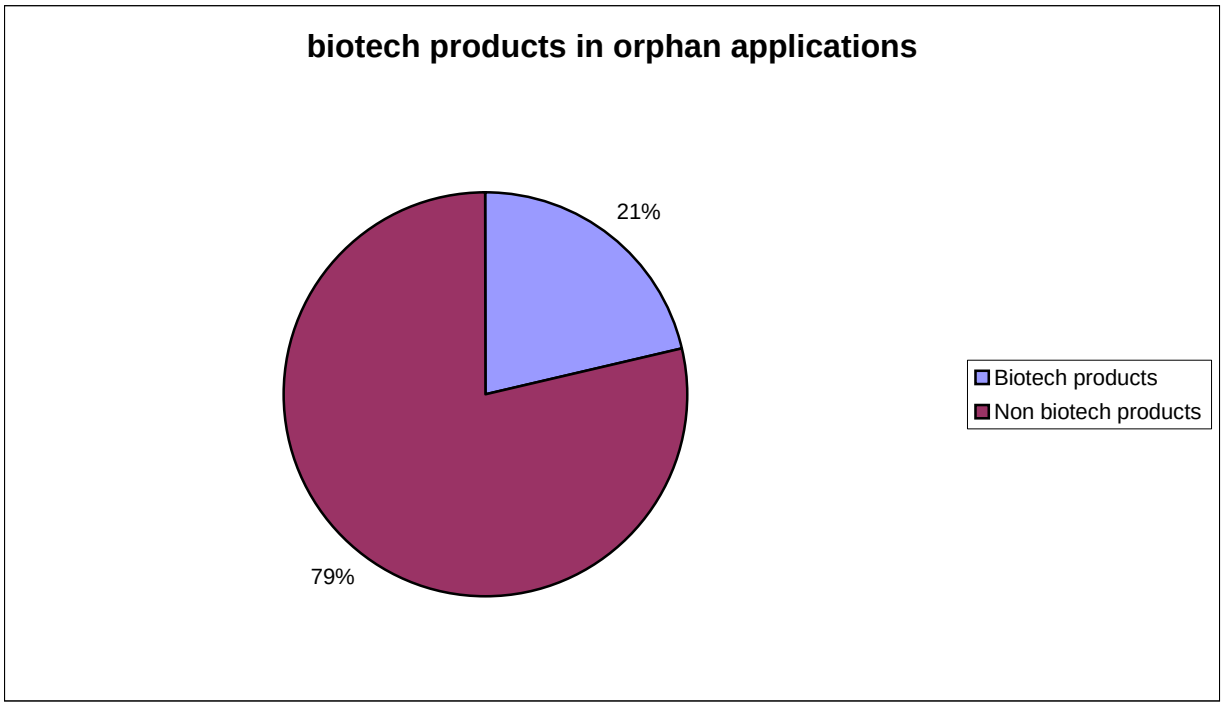


Figure 13: **Percentage of Designation Applications for Biotech Products (2000-2004)**

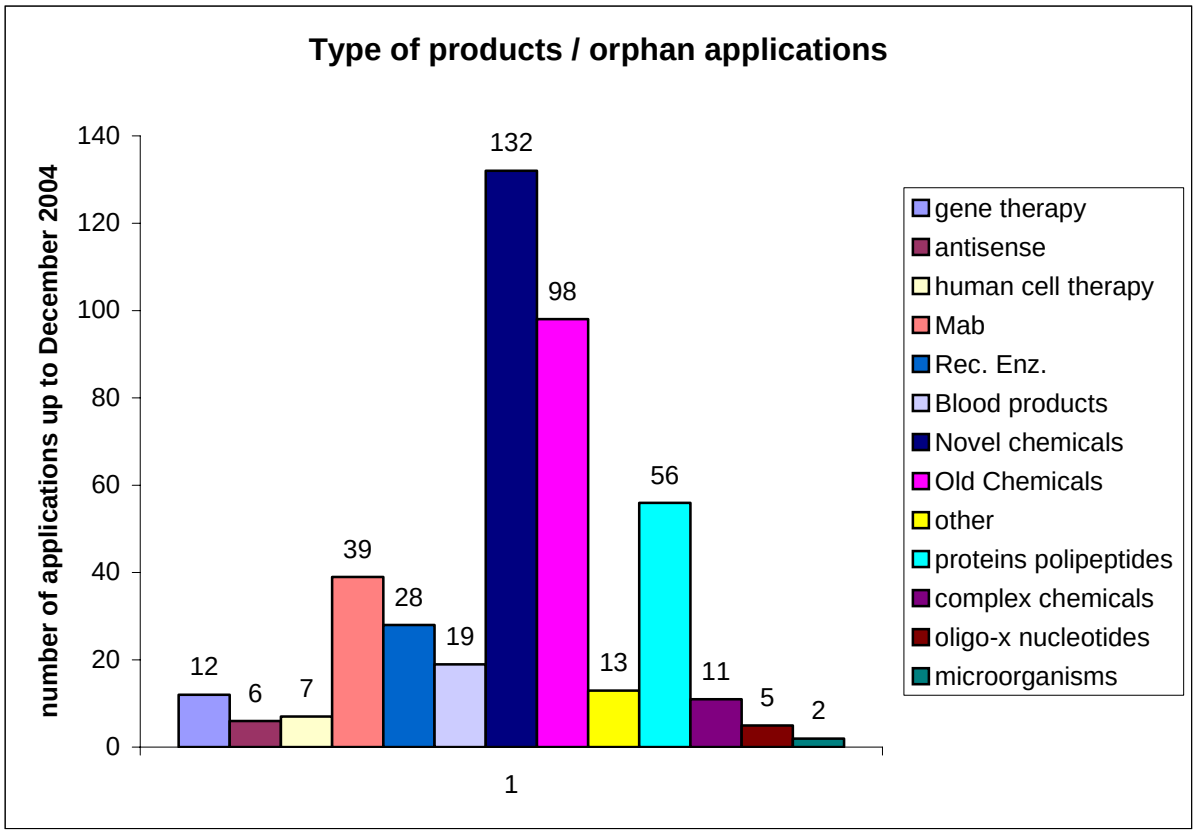
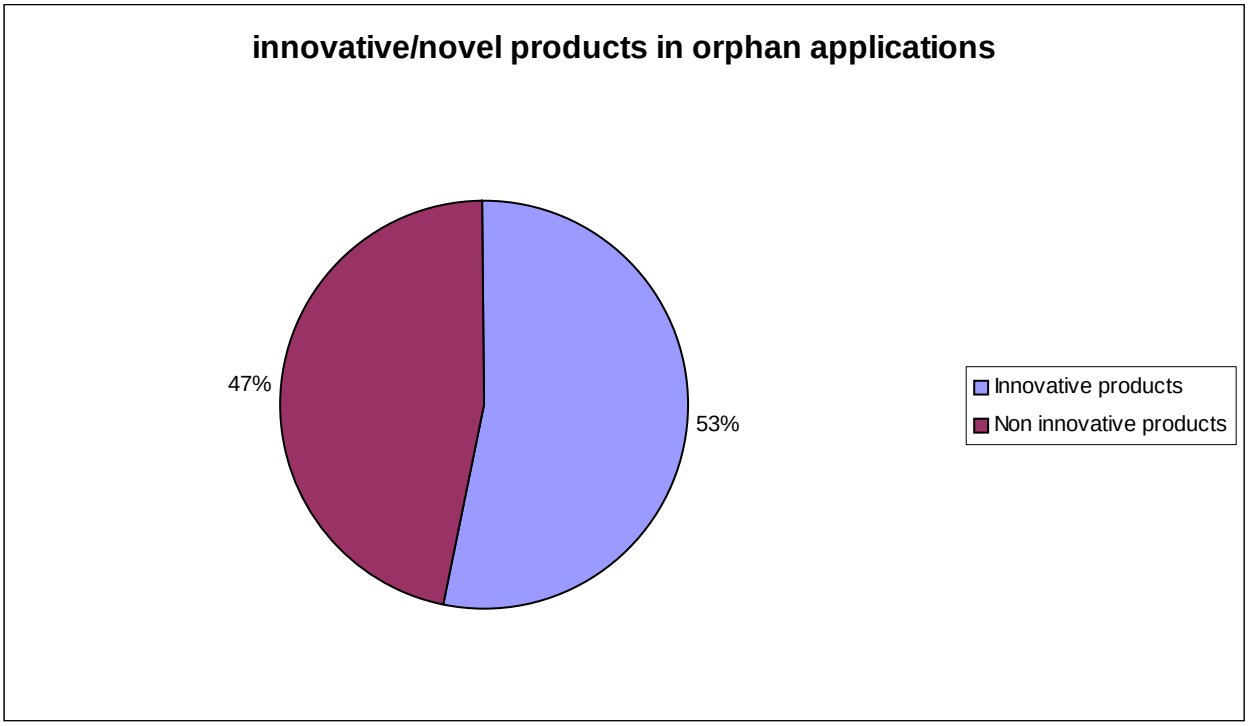


Figure 14: **Percentage of Designation Applications for Innovative/Novel Medicinal Products (2000-2004)**



Annex II – Tables

Table 1: **Centralised Marketing Authorisations for Orphan Medicinal Products – Status in May 2005** (Source : COMP Report to the Commission in relation to article 10 of Regulation 141/2000)

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients[1]	Grounds for designation	Date of Designation/ Marketing Authorisation	Authorised Therapeutic Indication
Fabrazyme, recombinant human alfa galactosidase	Genzyme B.V.	Treatment of Fabry disease 1 200	No authorised treatments were available.	08.08.2000 03.08.2001	Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (a-galactosidase A deficiency)
Replagal, α-galactosidase A)	TKT Europe AS	Treatment of Fabry disease 1 200	No authorised treatments were available.	08.08.2000 03.08.2001	Replagal is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (a-galactosidase A deficiency)
Trisenox, Arsenic trioxide	Cell Therapeutics (UK) Ltd.	Treatment of acute promyelocytic leukaemia (APL) 91 900	Assumption of significant benefit.	18.10.2000 05.03.2002	TRISENOX is indicated for 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. The response rate of other acute myelogenous leukaemia subtypes to TRISENOX has not been examined

[1] Based on a population of 459,700,000 (Eurostat 2004)

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients	Expected Benefit at time of designation	Date of Designation / Marketing Authorisation	Authorised Therapeutic Indication
Tracleer, Bosentan	Actelion Registration Limited	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension 101 100	Assumption of significant benefit.	14.02.2001 15.05.2002	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in: Primary PAH PAH secondary to scleroderma without significant interstitial pulmonary disease
Glivec, Imatinib mesylate	Novartis Europharm Limited	Treatment of chronic myeloid leukaemia 41 300	Assumption of significant benefit.	14.02.2001 07.11.2001	Glivec is indicated for the treatment of adult patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
				14.02.2001 19.12.2002 Variation	Glivec is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
		Treatment of malignant gastrointestinal stromal tumours 27 500	No authorised treatments were available.	20.11.2001 24.05.2002 Variation	Glivec is indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients	Expected Benefit at time of designation	Date of Designation / Marketing Authorisation	Authorised Therapeutic Indication
Somavert, Pegvisomant	Pharmacia Enterprises S.A	Treatment of acromegaly 27 500	Assumption of significant benefit.	14.02.2001 13.11.2002	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated
Zavesca, Miglustat 1,5-(Butylimino)-1,5-dideoxy, D-glucitol	Oxford GlycoSciences (UK) Ltd.	Treatment of Gaucher disease 27 500	Assumption of significant benefit.	18.10.2000 20.11.2002	Zavesca is indicated for the oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable
Carbaglu, N-carbamyl-L-glutamic acid	Orphan Europe Sarl	Treatment of to N-acetylglutamate synthetase (NAGS) deficiency 46	No authorised treatments were available.	18.10.2000 24.01.2003	Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency
Aldurazyme, Laronidase	Genzyme Europe BV	Treatment of Mucopolysaccharidosis type I 1 100	No authorised treatments were available.	14.02.2001 10.06.2003	Aldurazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; a [alpha]-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease
Busilvex, Busulfan	Pierre Fabre Medicament	Conditioning treatment prior to haematopoietic progenitor cell transplantation 32 100	Assumption of significant benefit.	29.12.2000 09.07.2003	Conditioning treatment prior to haematopoietic progenitor cell transplantation in adult patients

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients	Expected Benefit at time of designation	Date of Designation / Marketing Authorisation	Authorised Therapeutic Indication
Ventavis, Iloprost	Schering AG	Treatment of primary and of the following forms of secondary pulmonary hypertension: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease, chronic thromboembolic pulmonary hypertension 101 100	Assumption of significant benefit.	29.12.2000 16.09.2003	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms
Onsenal, Celecoxib	Pharmacia-Pfizer EEIG	Treatment of Familial Adenomatous Polyposis (FAP) 46 000	No authorised treatments were available.	20.11.2001 17.10.2003	Reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance
Photobarr, Porfimer sodium (for use with photodynamic therapy)	Axcan Pharma International BV	Treatment of high-grade dysplasia in Barrett's Esophagus 165 500	No authorised treatments were available.	06.03.2002 25.03.2004	Photodynamic therapy (PDT) with porfimer sodium is indicated for: - Ablation of high-grade dysplasia (HGD) in patients with Barrett's Esophagus (BE)
Litak, Cladribine	Lipomed GmbH	Treatment of indolent non-Hodgkin's lymphoma 167 800	Assumption of significant benefit.	18.09.2001 14.04.2004	Treatment of hairy cell leukaemia

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients	Expected Benefit at time of designation	Date of Designation / Marketing Authorisation	Authorised Therapeutic Indication
Lysodren, Mitotane	Laboratoire HRA Pharma	Treatment of adrenal cortical carcinoma 4 600	Assumption of significant benefit.	12.06.2002 28.04.2004	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established
Pedea, Ibuprofen	Orphan Europe SARL	Treatment of Patent Ductus Arteriosus 97 900	Assumption of significant benefit.	05.03.2001 29.07.2004	Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age
Wilzin, Zinc acetate dihydrate	Orphan Europe	Treatment of Wilson's disease 27 500	Assumption of significant benefit.	31.07.2001 13.10.2004	Treatment of Wilson's disease.
Xagrid Anagrelide Hydrochloride	Shire Pharmaceuticals Contracts Ltd	Treatment of essential thrombocythaemia 138 000	Assumption of significant benefit.	29.12.2000 16.11.2004	Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk patient An at risk essential thrombocythaemia patient is defined by one or more of the following features: >60 years of age or A platelet count >1000 x 10E9/l or A history of thrombo-haemorrhagic events.
Orfadin, Nitisinone	Swedish Orphan International AB	Treatment of tyrosinaemia type 1 4 600	No authorised treatments were available.	29.12.2000 21.02.2005	Hereditary tyrosinemia type 1
Prialt, Ziconotide	Elan Pharma International Ltd.	Treatment of chronic pain requiring intraspinal analgesia 71 200	Assumption of significant benefit.	09.07.2003 21.02.2005	Ziconotide is indicated for the treatment of chronic pain requiring intrathecal (IT) analgesia in patients who fail to obtain adequate analgesia and/or suffer intolerable adverse events with systemic opioids

Table 2: National Marketing Authorisations for Orphan Medicinal Products – Status in May 2005 (Source : COMP Report to the Commission in relation to article 10 of Regulation 141/2000)

Medicinal Product	MAH/Sponsor	Designated Orphan Indication / Estimated Number of patients[2]	Expected Benefit at time of designation	Date of Designation / Marketing Authorisation	Authorised Therapeutic Indication
Dudopa Levodopa/Carbidopa (Gastroenteral use)	NeoPharma	Treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations and not responding to oral treatment. 110 328	No authorised treatments were available.	10.05.2001 21.01.2004 in Sweden 08.06.2004 in Austria, Denmark, Finland, France, Germany, The Netherlands, Norway, Portugal, Spain	Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.
Impavido Miltefosine	Zentaris AG	Treatment of visceral leishmaniasis. 4 600	Assumption of significant benefit.	12.06.2002 19.11.2004 Germany	Treatment of visceral leishmaniasis caused by Leishmania donovani after failure of standard therapy.

[2] Based on a population of 459,700,000 (Eurostat 2004)

Table 3 : FP5 Quality of Life projects supporting research into rare diseases and orphan medicinal products. (Source: European Commission, DG Research)

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)

Table 4: FP6 projects supporting research into rare diseases and orphan medicinal products (Source: European Commission, DG Research)

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