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Executive Director

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COMP REPORT TO THE COMMISSION IN RELATION TO ARTICLE 10 OF REGULATION 141/2000 ON ORPHAN MEDICINAL PRODUCTS

Executive Summary

EU orphan legislation entered into force in April 2000. The Committee for Orphan Medicinal Products (COMP) has been established within EMEA since March 2000 and has played an important role in stimulating the development of orphan medicinal products and in implementing the legislation.

This report reflects upon the more than 5 years of experience gained as a result of the application of this legislation and provides an account of the public health benefits which have been obtained through orphan legislation. It is published as a contribution to support the European Commission in finalising its general report before 22 January 2006.

Implementation of EU Orphan Drug Legislation

Orphan medicinal product legislation was timely to address the unmet medical needs of patients suffering from rare diseases within the Community, as they deserve access to the same quality of treatments as other patients. This legislation is part of a broader Community policy to identify rare diseases as a priority area for action in the field of public health as well as in the Framework Programmes for research and technology development.

The EMEA and its Committee on Orphan Medicinal Products (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.

5 years of Orphan Designation

Between April 2000 and April 2005, 458 applications for orphan designation were submitted to the EMEA. By April 2005, more than 260 products were designated, relating to over 200 different rare conditions. Twenty-two products have gone on to receive a marketing authorisation (20 of those through the centralised procedure).

Ninety percent (90%) of rare conditions, for which a medicinal product has received an orphan designation, have a low prevalence of less than 3 in 10 000. Of these, 43 % occur in less than 1 in 10 000. Only 10 % have a prevalence of 3-5 in 10 000. Sixty-nine percent (69 %) of positive COMP Opinions recommending designation have been based on the criterion of significant benefit. A substantial proportion (54 %) is intended for paediatric use: 11 % solely for paediatric use and 43 % for adult & paediatric use.

More than half (53%) of the products, which have been the subject of a designation application between 2000-2004, are novel/innovative products, including 92 (21%) biotech products and emerging therapies such as anti-sense, gene therapy and cell therapy.

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Protocol Assistance

Orphan medicinal products are eligible for protocol assistance and this has proved to be a major incentive created by EU orphan legislation, bridging between the orphan designation and marketing authorisation. Through protocol assistance sponsors request advice from the Agency on the tests and trials necessary to demonstrate the quality, safety and efficacy to optimise development. After 5 years of experience, protocol assistance has proved to be a very useful tool to assist sponsors bringing orphan medicinal products to the market, particularly with clinical investigations.

The COMP has recommended protocol assistance for 51 % of medicinal products that have been the subject of a positive opinion recommending designation. Eighty procedures for protocol assistance have been completed so far, with a 40 % increase from 2003 to 2004.

Orphan Marketing Authorisations

Twenty-two designated orphan medicinal products have received a marketing authorisation so far, 20 of these through the centralised procedure at the EMEA and 2 through national procedures. By adopting EU orphan legislation, the European Parliament and Council have created the opportunity for more than one million patients suffering from rare conditions to benefit from these new medicines. Orphan medicinal products now represent a significant proportion of EU centralised marketing authorisations. In 2004 the EMEA's Committee for Medicinal Products for Human Use (CHMP) recommended the grant of marketing authorisations for 34 medicinal products, 6 (18 %) of these were designated orphan medicinal products.

The EMEA expects the number of authorised orphan medicinal products to increase dramatically in the years to come. According to a recent EMEA survey among sponsors, 33 % of the designated orphan products appear to be in the final stage of clinical testing and up to 50 % of them plan to file an application for marketing authorisation in the next three years.

Other public health benefits

Overall, orphan designation has stimulated research into rare diseases across the European Union and has increased the level of scientific and public awareness of rare diseases. Scientific expertise is underpinned now by a network of approximately 350 rare disease experts in a broad variety of therapeutic fields.

The COMP was the first decision-making committee in the EU to include patient representatives as full members. This has not only stimulated dialogue with patient groups but has also had positive impact on structuring patient groups' work at EU level. The levels of transparency at the EMEA have been enhanced over the past five years, and the Agency has entered into a pro-active dialogue with all interested parties.

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.

COMP conclusions and recommendations on Regulation 141/2000

Regulation (EC) No 141/2000 is a practicable piece of legislation. The Committee has fully applied the new concepts it introduced and progressively clarified them based on practice. Based on five years of experience, the COMP does not see a need to revise the Regulation, but rather recommends a number of minor amendments to assure the smooth running of the system. In the future the introduction of a provision for alternate members of the COMP should be considered, as is the case for the EMEA's other scientific committees, the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee on Herbal Medicinal Products (HMPC).

The implementation of the EU orphan legislation has shown, however, that there are limitations in addressing public health needs as regards medicines for children and development of medicines for neglected diseases in less developed regions of the world. The Committee welcomes, therefore, the EU Draft Regulation on Medicinal Products for Paediatric Use that is currently under discussion by the European Parliament and Council. This will help to stimulate research and development of medicinal products for paediatric indications.

To support for the development of medicinal products for neglected diseases in less developed regions of the world, the COMP would like to be in a position to designate medicinal products for the so-called neglected diseases in the future. This could be achieved by waiving the significant benefit criterion in such cases and would be consistent with Commission policy in the Framework Programmes for research and technology development.

COMP conclusions and recommendations on EU Policy on Orphan Medicinal Products

While the COMP considers that the current legislative framework for orphan medicinal products is suitable overall to achieve public health benefits for patients suffering from rare diseases, it has identified a number of policy areas that require strengthening.

The COMP makes the following recommendations to stimulate and foster EU policy on orphan medicinal products, through:

- Supporting the European Medicine Agency proposal for a new policy on fee reductions and increased EU Special Contribution.
- Recognising that this Regulation is resource intensive for EMEA and for COMP members. Thus, the long-term sustainability of the Orphan legislation should be supported through appropriate financial resources taking into account the contributions of EMEA, the National Competent Authorities and Patient groups.
- Providing further guidance on the criterion of insufficient return on investment and on the definition of « sufficiently profitable » to review market exclusivity at 6 years. This may imply amending the current Commission Regulation (EC) N° 847/2000 of 27 April 2000 (medical plausibility, criterion of insufficient return on investment) and the Commission Communication of July 2003 (market exclusivity, sufficient profitability).
- Ensuring that designated orphan medicinal products that are already authorised nationally or through mutual recognition are considered in the same way as non-orphan products and can continue with further national authorisations (Annex of Regulation (EC) N° 726/2004).
- Reinforcing orphan medicinal product research through the 7th Framework Programme, by highlighting rare diseases as a research priority and further recognising as a priority the need to fund the non-clinical and early clinical (phases I and II) research of designated orphan medicinal products through research grants.
- Consolidating regular information exchange and policy coordination between COMP/EMEA, DG Enterprise, DG Research and DG Sanco.

The COMP advise the Commission to take appropriate actions:

- To increase the visibility of those medicinal products authorised for rare diseases prior to the implementation of the EU orphan legislation. The Committee support the EuroPharm initiative as a tool towards that aim.
- To encourage Member States to actively adopt national incentives (fee waivers, research grants, tax deductions, pricing and reimbursement supportive policy, national orphan drug steering committee) to support the development of and access to orphan drugs.
- To further explore co-ordination of transparency measures between Member States to speed up and ensure orphan drug availability to patients.

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I. BACKGROUND

Patients suffering from rare diseases within the Community deserve access to the same quality of medicinal products as other patients. EU Orphan legislation, which through incentives stimulates sponsors to develop medicinal products for rare diseases, was adopted by Parliament and Council in December 1999 and came into force in April 2000. To date, more than 5 years of experience has been gained.

In January 2006, the European Commission is required to publish a general report on the experience acquired as a result of the application of Orphan legislation, together with an account of the public health benefits that have been obtained. This report is published as a contribution to support the European Commission in finalising its general report before 22 January 2006.

Following the adoption of EU Orphan legislation, the EMEA with its new committee, the Committee for Orphan Medicinal Products (COMP), has taken on an important new role in stimulating the development of orphan medicinal products and implementing the regulations. A Community procedure for designation has been established which clearly identifies orphan medicinal products eligible for incentives.

Incentives for sponsors developing orphan medicinal products available in the European Union include, amongst others, a 10-year period of market exclusivity, protocol assistance from the EMEA, and the possibility to request reduction of fees for all types of activities linked to the centralised marketing authorisation procedure.

Based on US experience, where orphan legislation was passed in 1983 (17 years before the EU), a high number of applications were anticipated in the EU. The response 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 (April 2005) and 22 have gone on to receive a marketing authorisation.

Increased resources have been mobilised within EMEA to support the orphan activities. The Committee for Orphan Medicinal Products meets 11 times per year to evaluate applications for designation.

In light of the upcoming Commission review of the orphan initiative, this report presents the views of the EMEA and its Committee for Orphan Medicinal Products on the practical implementation of Orphan legislation. The success of the incentives, including protocol assistance, Community funding to support fee reductions and the market exclusivity, are reviewed. Areas where further action may be warranted in the future are highlighted. 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. The benefits seen to date, however, are discussed together with future expectations.

II. EXPERIENCE WITH THE REGULATION

1. Article 3 - Designation Criteria

For a medicinal product to be designated as orphan according to the legislated criteria, it must be intended to diagnose/prevent/or treat a life-threatening or chronically debilitating condition, and the sponsor must establish that either the condition affects not more than five in 10 thousand persons in the Community at the time the application is made 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.

In addition, the sponsor must establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

1.1 Data Requirements

The *Guideline on the Format and Content of Applications for Designation as Orphan Medicinal Products and on the Transfer of Designations from one sponsor to another (ENTR/6283/00¹)*, which was prepared by the European Commission in close collaboration with the COMP and the EMEA, details the data requirements for a designation application and transfer of sponsorship. Initially drafted in April 2000, and subsequently revised in December 2000 and February 2004, the guideline serves as an essential point of reference for sponsors seeking EU orphan designation.

Based on the COMP's experience, it became clear that further guidance was warranted specifically on the prevalence criterion and an ad-hoc group of experts was convened, which led to the release of the COMP *Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (COMP/436/01¹)*, finalised in March 2002. The COMP ad-hoc group of experts on prevalence was reconvened in February 2004 to review the guideline. The group recommended that the need to support epidemiological research into rare diseases is highlighted to the European Commission.

In September 2004, the pre-submission guidance for sponsors was further supplemented with the release for consultation of the Draft *Guideline on the Elements required to support the Medical Plausibility and the Assumption of Significant Benefit for an Orphan Designation (COMP/66972/2004¹)*.

Based on experience with the 458 applications submitted to date (April 2005), the data requirements for designation applications appear to be adequate and understandable. From a practical viewpoint the information and the skills required to put together an application should not prevent any potential sponsor from applying.

As noted above, an EU application for designation may be based on the prevalence criterion or the insufficient return on investment criterion. It is noteworthy that to date only two applications have been submitted on the grounds of insufficient return on investment, one was under evaluation at the time of writing this report and the other resulted in withdrawal by the sponsor. Further Guidance on this criterion is warranted.

1.2 Medical Plausibility

When evaluating applications for orphan medicinal product designation, the COMP has routinely examined the above-mentioned designation criteria together with the "medical plausibility".

As background, in 1999, prior to the adoption of orphan legislation in the EU, the FDA underlined the importance of considering medical plausibility in the context of applications for orphan designation, based on their experience with the US designation system. This was taken into account in the Commission's Guideline (ENTR/6283/00), which outlines two aspects to "medical plausibility":

- (1) the rationale for use of the medicinal product in the proposed orphan indication; and
- (2) where the orphan indication refers to a subset of a particular condition, a justification of the medical plausibility for restricting the medicinal product in the sub-set.

While recognising that 'medical plausibility' is not an explicit designation criterion, the COMP's view is that the text of the Orphan Regulation implies a scientific need to consider 'medical plausibility' in the context of an application for designation. Firstly, a product which is the subject of such application must be a medicinal product as defined in Article 1, Directive 2001/83/EC and consideration of the

¹ Guidelines available on the EMEA web-site: <http://www.emea.eu.int>.

‘medical plausibility’ at this (early) stage of product development forms the basis for verifying this. Secondly, Article 3.1 of Regulation (EC) No 141/2000, which lays down the criteria for designation states that the medicinal product should be “intended” for the diagnosis, prevention or treatment of the condition applied for.

Furthermore, to define a suitable condition for designation, where the orphan indication refers to a particular subset of a broad condition, the COMP must consider the rationale for restricting the use of the medicinal product in the sub-set only. This is imperative as it provides a means to prevent sponsors from abusing the designation system by slicing common conditions into invalid sub-sets to meet the designation criteria, thereby accessing orphan incentives.

Based on more than 5 years of experience to date, the Committee considers that the notion of ‘medical plausibility’ forms an important aspect of the first arm of designation criteria and thus, while not an explicit criterion in its own right, the COMP may justifiably consider the notion of ‘medical plausibility’ when assessing an application for designation. In this regard the COMP included it in the Guideline on the Elements Required to Support an Orphan Designation (COMP/66972/04) that was released for consultation in September 2004. Having underlined the importance of medical or biological plausibility in the COMP review of applications for orphan designation, the European Commission should consider formalising this aspect in the appropriate regulatory document.

1.3 No Satisfactory Method/Significant Benefit

‘Significant benefit’ is defined in Regulation 847/2000 as a “clinically relevant advantage or a major contribution to patient care”.

At the time of designation, the Committee has adopted a pragmatic approach and bases its conclusions for significant benefit on assumptions as many sponsors are at an early stage of development when seeking orphan designation. This follows the spirit of the Regulation that encourages early designation so that optimum use can be made of protocol assistance. The significant benefit is then reviewed prior to the grant of a marketing authorisation, in accordance with Article 5.12 of the Regulation, once the sponsor has completed its development.

A variety of different arguments for significant benefit, some deemed acceptable some not, have been put forward by sponsors over the years. In the interests of transparency the Commission Communication of July 2003 and the Guideline on the Elements required to support an Orphan Designation (COMP/66972/2004) provided further information in this regard together with examples. It is clear, however, from the applications that have failed on this criterion that the term "significant benefit" requires further clarification, with additional examples in the appropriate guidance documents, as further experience is gained.

In 2002, when reviewing the first application for orphan medicinal product designation for a tropical disease, a legal constraint became apparent in the significant benefit criterion. Although the medicinal product in question was expected to be of significant benefit in developing countries affected by the proposed orphan condition, the Committee was not in a position to recommend a positive Opinion as the Regulation required the significant benefit criterion to be established in the EU population affected by the condition. As a consequence, although it appeared to the Committee to be contrary to EU policy and the spirit of the Orphan legislation, the Regulation as it was and is currently interpreted, did not permit the Committee to recommend designation of the application and a negative Opinion was adopted.

The Committee would, therefore, like the Commission to consider introducing a waiver of the ‘significant benefit’ criterion for those applications which concern diseases in developing countries. In the future the COMP would like to be in a position to support the designation of other similar applications that concern the so-called ‘neglected diseases’ through appropriate EU policy.

It is noteworthy that, although, the introduction of the no satisfactory method/significant benefit criterion in the EU introduced an additional hurdle to designation in comparison with other regions such as the US, Japan and Australia it does not appear to have had a negative impact on the number of orphan medicinal products being designated in the EU. In April 2005, the COMP invited an expert from the US FDA to update on the activities of the Office of Orphan Product Development and was

encouraged to note that, despite the significant benefit criterion in the EU, the success rate of designation applications reported in the US (62%) and EU (68%) are similar.

1.4 Overview of Experience (figures in Annexe 1)

Of the 458 applications for orphan designation submitted to the EMEA as of April 2005, with the exception of two, all have been based on the prevalence criterion. Two applications have been based on the insufficient return on investment criterion, one was under evaluation at the time of writing this report and the other resulted in withdrawal by the sponsor prior to COMP Opinion.

Of those orphan medicinal products recommended for designation by COMP, in 43% of cases the prevalence has been below 1 in 10,000, in 47% between 1-3 in 10,000, and in only 10% between 3-5 in 10,000 (Figure 1).

As of April 2005, 69% of positive opinions were issued with the assumption of significant benefit as one 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% opinions, respectively. In 10.4% of the opinions the three criteria were accepted in different combinations.

2. Article 4 - Tasks of the Committee

Article 4 establishes the Committee for Orphan Medicinal Products (COMP) at the EMEA and its main tasks:

- a) to examine applications for orphan designation
- b) to advise the Commission on the establishment and development of an EU policy on orphan medicinal products
- c) to assist the Commission in liaising internationally on matters related to orphan medicinal products and in liaising with patient support groups
- d) to assist the Commission in drawing up detailed guidelines.

2.1 Composition of the Committee

The legislated composition of the COMP does not include alternates at present. In line with the approach now adopted for other EMEA scientific committees and in light of the higher than expected workload of the COMP, the EMEA recommends that the introduction of a provision for alternate members of the COMP is considered by the Commission. This has already been implemented for CHMP and CVMP in accordance with Article 61 of Regulation (EC) No 726/2004.

2.2 Communication/Transparency

In accordance with Article 4.2 (c) of the Regulation the COMP, together with the EMEA, started a process of communication and transparency with both the Commission and with interested parties.

2.2.1 External parties

In advising the Commission on the development of a European policy on orphan medicinal products and liaising internationally on matters related to orphan medicinal products, the COMP has established a regular dialogue with the European Commission. DG Research and DG Sanco have been approached on specific issues related to rare diseases together with other external stakeholders committed to the field of rare diseases.

The EMEA and some COMP members actively participate in the DG Sanco Task Force on Rare Diseases (RD). The main objectives of this Task Force are to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention, diagnosis and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-ordination, and to provide a forum for discussion and exchange of views and experience on all issues related to rare diseases.

The Committee has had a very fruitful collaboration with DG Research over the years and has appreciated the participation of members of DG Research in a number of COMP meetings to update on and discuss proposals for the Framework Programmes. There is a general agreement that the Regulation has stimulated communication and collaboration between stakeholders within the European Institutions. In the 6th Framework Programme, rare diseases were included in the work programmes of the calls for proposals, whereas the current proposal for the 7th Framework Programme is to include rare diseases as a specific topic under the area of translational research in major diseases, along with cancer, cardiovascular diseases, diabetes/obesity and other chronic diseases. It is noteworthy that the EMEA/COMP was invited to actively participate in the Workshop on Rare Diseases held on 12-13 April where proposals for research on rare diseases for the 7th Framework programme were discussed together with investigators.

2.2.2 Interested Parties

The Committee has set up a 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 policy recommendations on orphan medicinal products.

The EMEA organised a series of individual workshops with pharmaceutical industry, patient support groups and with health professionals and academia at the end of 2000-beginning of 2001. This culminated in a joint meeting with all interested parties, representatives of the European Parliament and the European Commission in December 2002. This series of workshops and the joint meeting, in particular, highlighted a number of issues related to the research and development of orphan medicines, and important information on the availability of these products. The results and conclusions of the joint meeting were reflected in the Key Recommendations of the COMP Report on its first 3-year mandate.

In March 2005, on the occasion of the 5th anniversary of Orphan legislation, a follow-up workshop with representatives of patients' organisations and learned societies was held to discuss the experience acquired to date with orphan legislation. It was agreed that there was a need to consider: improving communication, and the provision of more targeted and expanded access to information on orphan medicinal products; the implementation of additional measures to facilitate clinical trials in rare diseases such as expert networking, guidance, etc.; and increasing the visibility of those medicinal products authorised for rare diseases prior to the implementation of Orphan legislation in the EU in April 2000.

Representatives from the European Commission, from non-governmental organisations and from national science organisations are regularly invited to COMP meetings to present their views on regulatory, scientific, or general areas of interest in the field of orphan medicines, rare diseases and neglected diseases.

2.2.3 Transparency

A cumulative list of all designated orphan medicinal products, the *Community Register of Orphan Medicinal Products*, is available on the web-site of DG Enterprise: <http://pharmacos.eudra.org/F2/>.

A press release is 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. 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* commenced in January 2002.

In accordance with the Commission Communication on Orphan Medicinal Products², a further initiative to increase transparency of orphan medicinal products was introduced in September 2004, when details of designated orphan medicinal products which have been subject of centralised applications for marketing authorisation were published for the first time in the COMP Press Release.

² 'Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products' OJ C 178, 29.07.2003, p.2, available on the Commission's web-site: <http://pharmacos.eudra.org/F2/>
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3. Article 5 - Procedure for Designation

Article 5 provides the legislative framework for the procedure for designation and removal from the register and includes the following elements:

- the particulars to be included in an application for designation
- the procedure for designation, including the validation phase, 90-day COMP review period, 30-day decision-making phase, and appeal procedure
- establishment of a register
- basis for removal from the register of orphan medicinal products
- the requirement for annual reports
- procedure for transfer of designation

3.1 Application for Designation

Guidance on how to apply for orphan designation is published on the EMEA's web-site. Sponsors are encouraged to request a pre-submission meeting with the Agency prior to filing the designation application. The Agency currently holds on average 65 pre-submission meetings with potential sponsors of orphan applications each year. The Committee will now propose to increase COMP co-ordinator involvement in pre-submission phase.

Where a disease or condition has been considered within the Framework of other Community activities on rare diseases, this information is requested in the application for designation (section B.3 of an application). Although sponsors are routinely requested to complete this section during the validation phase by the EMEA, these data are currently not compiled for the COMP or the Commission. The Commission should reconsider whether this information is necessary or consider deleting this section of the designation application.

In the application for designation sponsors are required to review currently available diagnosis, prevention or treatment methods in the Community, and provide an overview of all authorised medicinal products where applicable (section D1 of an application). To date, in the absence of a European database on authorised medicinal products, COMP/EMEA co-ordinators have faced difficulties in validating this information. The COMP welcomes the creation of the Europharm database, which once implemented may facilitate the review of this section.

3.2 Procedure for Designation

Regarding the procedure for designation, currently the timetable is structured so that each application is discussed at two plenary Committee meetings. Where major objections/questions are raised by the Committee on an application, the sponsor is routinely given the opportunity to attend an oral hearing at the time of the second COMP discussion.

The written procedure has been used by the Committee on 10 occasions since April 2000. There is scope in the future to make more use of the written procedure to ease the workload of plenary meetings. The written procedure could be used to 'fast-track' applications for conditions that have been designated on a number of occasions previously where the nature of the medicinal product is such that discussion at a plenary meeting may not be necessary. A COMP procedure would need to be elaborated in this regard.

The Regulation requires the COMP Opinion to be adopted by two-thirds of the members of the Committee. The quorum of the Committee (i.e the minimum number of members that are required to be present for the Committee to adopt an Opinion on designation) is, therefore, currently set at 21. In practice, where members have been absent on occasion, the possibility to have an alternate member in attendance would facilitate the work of the Committee. The need for formal nomination of alternate COMP members should be taken into account in the review.

The appeal procedure has been used 14 times since April 2000, and has resulted in the Committee revising its view and reaching a final positive Opinion on 2 occasions and in the negative Opinions

being maintained on 12 occasions (in 5 cases the sponsors failed to provide the grounds for appeal in due time, in 5 cases the applications were withdrawn prior to the final negative Opinion). The Regulation provides sponsors with a 90 day period following receipt of the Opinion to submit detailed grounds for appeal, but does not require sponsors to notify their intent to appeal. This has resulted in the Agency delaying the transmission of negative Opinions to the Commission until the 90-day legislated appeal timeframe has elapsed, even where a sponsor has indicated that they do not intend to appeal. It would be of interest to introduce an additional requirement for sponsors to formally notify their intent to appeal within a short time-frame after receipt of the negative Opinion.

To assist in the review of biotechnology and biological issues, the COMP established the COMP Biotechnology Working Group (COMP-BWG) in 2001 to facilitate the efficient use of European expertise in this area.

The COMP regularly appoints external experts to assist it in the review of specific applications. Over the years the Committee has built up a network of more than 350 experts. The importance of identifying experts early on in the process is underlined, particularly when sub-sets are involved or where a non-conventional disease or product is presented.

The Commission Communication on Orphan Medicinal Products states that during the development of a product, a sponsor may apply to the COMP to amend the designated condition provided that the criteria for designation continue to be met. As any change in the condition may have an impact on the prevalence and other methods available, submission of a new application which could be reviewed according to a rapid time-table is the preferred option for handling such requests.

3.3 Maintenance of the Register

Article 5.12 of the Regulation states that an orphan medicinal product may be removed from the register: (a) at the request of the sponsor; (b) if it is established before the marketing authorisation is granted that the designation criteria are no longer met; (c) or at the end of the period of market exclusivity. To date, 15 medicinal products have been removed from the Register at the request of the sponsor. The most common reason for withdrawal is that the development of the medicinal product has been stopped. Prior to the grant of a marketing authorisation, the Committee has reviewed the significant benefit of 13 medicinal products, to date, this has however not resulted in removal from the Register.

3.4 Annual Reports

In accordance with the Regulation, sponsors are required to submit annual reports to the Agency to update on the status of development of the medicinal product. A *Note for Guidance on the Format and Content of the Annual Report on the State of Development of an Orphan Medicinal Product (COMP/189/01³)* was finalised by the Agency in April 2002. The annual report has proved an extremely useful means of tracking the development of the growing list of designated orphan medicinal products and motivates removal from the register where development has been stopped.

3.5 Overview of Experience (figures in Annexe 1)

In April 2005, the COMP adopted its 287th positive opinion recommending orphan designation and more than 260 medicinal products have been officially designated as orphan by the European Commission (Figure 2). The COMP reaches its Opinion on designation in 67 days on average, well below the 90-day legislated time limit (Figure 3).

The majority of the products designated to date are chemical products. Approximately 20% of the products are biotechnology products. This distribution is expected to change over time as an increasing number of innovative products are presented for orphan designation, including products for gene therapy and human cell therapy.

³ Guidelines available on the EMEA web-site: <http://www.emea.eu.int>

4. Article 6 - Protocol Assistance

Article 6 established an important incentive for sponsors, namely ‘protocol assistance’, introducing the possibility for the sponsor of an orphan medicinal product to request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, prior to the submission of an application for marketing authorisation.

In accordance with Article 6.2, the Agency finalised the procedure for protocol assistance and published guidance in April 2001. This was subsequently revised in June 2003.

With the experience gained to date, the protocol assistance procedure overall has turned out to be very successful. Uptake by sponsors has been extensive and is increasing markedly over time.

Protocol assistance offers a great incentive to sponsors of orphan medicinal products since many of them represent small and medium sized enterprises, which generally have limited experience in product development. In addition, development of orphan medicinal products may raise complex methodological issues as they are often based on clinical trials in very small populations. Thus, creative approaches must be employed to maximise the outcome in terms of useful study results with minimum procedural burdens and complications. Since Orphan designation can be granted at any stage of drug development, access to qualified scientific advice enables the sponsor to accomplish a registration file of high quality, thereby increasing the possibilities of achieving a marketing authorisation. The COMP, therefore, regularly recommends to sponsors at the time of designation to take advantage of the protocol assistance procedure. Since April 2000, the Committee has recommended protocol assistance to sponsors in just over half (51%) of all COMP Opinions.

Although it is titled differently, ‘protocol assistance’ adheres to the same procedural rules as ‘scientific advice’. However, thanks to the availability of EU funding in the form of the special contribution for orphan medicinal product, the Agency is currently in a position to waive the fee payable by the sponsor for protocol assistance (average of € 55,283 per request). Protocol Assistance offers a proactive approach to support the companies.

Upon receipt of a valid request for protocol assistance, two coordinators are nominated by the EMEA’s Scientific Advice Working Party (SAWP) to perform independent assessments of the application on behalf of the SAWP. External experts may be nominated to assist co-ordinators with their assessment. In addition, where a specific need is identified, patient representatives may also be nominated to participate in the advice process. At day 30 of the procedure, the SAWP discusses the application and the co-ordinator’s reports. In the majority of cases the sponsor is invited for a discussion meeting. Two weeks after the discussion meeting (on average), the advice letter is adopted and co-signed by the CHMP/COMP.

In addition, one COMP coordinator is nominated to assess questions on ‘significant benefit’. If claimed at the time of Orphan Drug Designation, this criterion is reviewed by the COMP at the time of application for marketing authorisation. Two COMP representatives to the SAWP were initially nominated in December 2001 to formulate advice on significant benefit issues. In September 2004, the number of COMP representatives in the SAWP rose from two to three to meet the increasing demand for Protocol Assistance.

4.1 Overview of Experience (figures in Annexe 1)

Overall 80 protocol assistance procedures have been completed since Orphan legislation entered into force. The number of requests for protocol assistance received increased from 5 in 2001 to 15 (2002), 25 (2003) up to 35 in 2004, i.e. a 40% increase compared to 2003 (Figure 4). At the end of 2004, the overall mean duration of protocol assistance and follow-up procedures was 112 days and 90 days respectively (Figures 5a & 5b). The number of protocol assistance/follow-up finalised on an annual basis has increased markedly from 4 in 2001 to 33 in 2004 (Figure 6).

The main therapeutic areas in which protocol assistance has been sought by and large reflect the distribution of designations by therapeutic area, with the largest proportion being oncology and immunomodulatory (32 %) followed by alimentary tract and metabolic disorders (21 %), blood (18 %) and respiratory disorders (12%) (Figures 7a & 7b). The scope of the requests have been clinical

development in 50%, and preclinical in 34% (Figure 8) and the most prevalent phases of clinical trials discussed have been phases III (49%) and II (26%) (Figure 9). Twenty-four percent of the products which have been the subject of protocol assistance have been biologicals (Figure 10). The proportion of emerging therapies in the protocol assistance procedure were 16%, a.a. gene therapy, antisense products and human cell therapy (Figure 11). Out of the 34 applications for marketing authorisation receiving a positive opinion from the EMEA in 2004, 6 (18 %) were designated orphan medicinal products.

5. Article 7 - Community Marketing Authorisation

5.1 Access to the Centralised Procedure

Article 7.1 introduced the option for sponsors of designated orphan medicinal products to use the centralised procedure, even if the medicinal product would not have qualified under Part B of the Annex to Regulation EC No 2309/93. This incentive has been taken a step further in Regulation (EC) No 726/2004, and from 20 November 2005, it will be obligatory for all applications for marketing authorisation for designated orphan medicinal products to be filed via the centralised procedure. From the patients' viewpoint, this move was welcomed by COMP, as the medicinal products authorised to date through national/mutual recognition procedure have achieved a marketing authorisations in just a fraction of Member States.

Although the principle of having orphan medicinal products authorised through the centralised procedure is seen as an improvement in terms of patient availability, it is noteworthy that designated orphan medicinal products applying for marketing authorisation will fall under the mandatory scope of the centralised procedure regardless of whether they have a prior national marketing authorisation in some Member States or not. There is no 'cut-off date' for orphan medicinal products in the Annex of Regulation (EC) No 726/2004.

For designated orphan products that are already authorised nationally or through the mutual recognition procedure, a strict interpretation of Article 3 of Regulation (EC) No 726/2004 would mean that no further national marketing authorisation(s) could be granted after November 2005. The same strict interpretation of Article 3 could also lead to the conclusion that these products cannot even be on the market from 20 November 2005 onwards, as they are not the subject of a Community authorisation.

Two designated orphan products are currently authorised nationally only, but neither of them has obtained a marketing authorisation in all 25 Member States (i.e. neither has market exclusivity). If the strict interpretation is applied, market exclusivity could never be obtained for these products via repeat-use mutual recognition procedures. Moreover, in view of the upcoming enlargement (Bulgaria/Romania/Croatia), even if 25 national marketing authorisations were to be obtained before November 2005, they would still be blocked from applying for mutual recognition in the new accession countries.

As this may have serious implications for patients affected by rare diseases, and thus conflict with the spirit of the Orphan Regulation (EC) No 141/2000, the Commission is asked to ensure that these medicinal products are considered in the same way as the non-orphan products already authorised through the mutual recognition procedure and are allowed to continue with further authorisations.

5.2 Use of the EU Special Contribution

An important incentive offered by the legislation, Article 7.2, is the possibility for 'Orphan' sponsors to request reductions in the regulatory fees payable to the Agency. The EU Budgetary Authority allocates a special contribution annually to the EMEA for this purpose.

To date (April 2005), more than € 12 million of Community funding has been used to support fee reductions for designated orphan medicinal products. The breakdown by year is provided in Figure 12.

Since 2002 the Agency has implemented the same fee reduction policy, granting a 100% fee waiver for requests for protocol assistance and a 50% fee reduction for all other fees. Based on the recommendation from the COMP, the Agency continues to consider protocol assistance as a priority in its policy on fee reductions and thus agreed a full fee waiver for fees on protocol assistance. Protocol assistance is imperative in guiding sponsors of orphan medicinal products towards a successful application for marketing authorisation and ultimately providing patients with more rapid access to the medicinal products

For 2005, € 3 700 000 has been granted. As of April 2005, 48% of the fund had already been utilised. It is estimated that up to € 6 million will be needed in 2005 to cover the higher than expected number of protocol assistance and post-authorisation activities.

Looking to the future, the number of orphan medicinal products obtaining a marketing authorisation and requesting fee reductions in the post-authorisation phase will continue to increase each year. Introduction of a revised policy is, therefore, necessary to re-focus this important incentive in the pre-authorisation phase and to stabilise spending in the post-authorisation phase once products are on the market. It has been recognised that any change in fee reduction policy must not undermine the orphan initiative by weakening this important incentive, particularly for micro, small and medium-sized enterprises (SMEs).

In accordance with Regulation (EC) No 726/2004 of 31 March 2004, at the end of 2005, based on further recommendations from the European Commission, the Agency is expected to implement the Commission Regulation establishing the circumstances in which SMEs in the field of pharmaceuticals may pay reduced fees, defer payment of the fee or receive administrative assistance. The introduction of a new policy for SMEs in 2005, has set the scene for parallel revision of the orphan policy, which will limit spending on post-authorisation activities but make an exception for SMEs.

For designated orphan medicinal products, the Agency's proposal for 2006 is to maintain the 100 % fee reduction for protocol assistance and 50% reduction for the application for marketing authorisation, and increase the fee reduction for inspections from 50% (2004/2005 level) up to 100%. The aim is to maximise the number of products that are brought to the market and ultimately to the hundreds of thousands of patients who are suffering from rare diseases.

Following the grant of the marketing authorisation, the level of benefit in the form of fee reductions will remain the same (50%), but will be limited to the first year, as this corresponds to the average time necessary to place a medicinal product on the market. In line with Regulation (EC) No 726/2004 of 31 March 2004 and the Commission Regulation on SMEs, an exception to this policy will be made for SME's where long term and sustained support in the post-authorisation phase is deemed necessary to maintain medicinal products on the market.

With the expected implementation of this new policy in 2006, a special contribution of € 5.1 million has been requested from the Community to fund fee reductions for orphan medicinal products. With the new policy, on the assumption that the level of applications for protocol assistance and for marketing authorisation should remain relatively stable over years by limiting the post-authorisation support to the most needed companies, the level of the Community special fund for compensating fee reductions for orphan drugs, whilst increasing initially, should remain relatively stable over the years to come.

5.3 Activities Funded through Basic Subsidy from the European Commission

The additional meeting and staffing costs required for orphan activities are not funded through the special contribution. These costs must be covered by the EU basic subsidy to the Agency.

In 2005, six of the Agency's staff members are employed full time solely to support orphan activities. In addition, scientific staff from other sectors of the Agency support orphan activities on a part-time basis, particularly in the role of EMEA co-ordinator for particular applications for designation. The designation process is distinct from the evaluation process for authorisation of medicinal products and therefore creates additional staff costs. In 2004, a total of € 1 353 784 was spent on staff costs for orphan designation.

In April 2000 meetings of the COMP commenced. In 2004, € 566 065 were spent on annual meeting costs. These costs were covered by the general subsidy from the Community.

Recognising that the Orphan Regulation is resource intensive for EMEA and for COMP members, the long-term sustainability of the Orphan legislation should be supported through appropriate financial resources taking into account the contributions of EMEA, the National Competent Authorities and Patient groups. It must be stressed that adequate policy recommendations from the European Commission and funding from the EU budgetary authority are absolutely imperative to the continued success of the orphan initiative in the long term.

6. Article 8 - Market Exclusivity

Article 8 underpins the main incentive of the Orphan Regulation, introducing the ten-year period of market exclusivity. Market exclusivity commences from the date that a marketing authorisation is granted in all EU Member States, protecting the originator's medicinal product in the authorised 'orphan' therapeutic indication. Similar medicinal products will not be granted a marketing authorisation for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantity of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is clinically superior to the originator.

The wording of Article 8 of the Regulation implies that any marketing authorisation granted for an orphan product, at least under the centralised procedure, is capable of conferring full market exclusivity. The Commission Communication on orphan medicinal products clearly states that the second authorised orphan medicinal product will share the market exclusivity with the originator product for the remainder of the originator's period of market exclusivity, but it is not clear if the second authorised orphan medicinal product will benefit from its own 10-year period of market exclusivity. The period of market exclusivity awarded to orphan medicinal products that enter the market by breaking the market exclusivity of an originator product requires further clarification by the Commission.

The definitions of 'similar' medicinal product and 'clinically superior', in the context of market exclusivity, are laid down in Article 3 of Commission Regulation (EC) No 847/2000. In December 2004, a draft guideline⁴ on aspects of the application of Article 8 of Regulation (EC) No. 141/2000 was released for consultation. This guideline details the procedural aspects related to the assessment of similarity and clinical superiority of orphan medicinal products when assessing marketing authorisation applications and variations. Furthermore, it provides additional guidance on the definition of similarity illustrated with the use of examples.

The appropriateness and practicality of the legislated definitions will only become apparent as more experience is gained by the CHMP in assessing 'similarity' and 'clinical superiority'.

Paragraph 8.2 of Regulation (EC) No. 141/2000 introduces a provision for limiting the period of market exclusivity to six years where it is established that the product is 'sufficiently profitable' not to justify the maintenance of market exclusivity. There is a certain degree of ambiguity around the interpretation of this paragraph and further clarification is warranted. The COMP consider that this review should only take place where a particular concern is raised by a Member State, the Commission Communication, however, recommends a systematic check. The Communication further notes that the criterion on non-profitability should be assessed whenever there is a review of the criteria for orphan designation, which may occur at any time.

The Agency, through the COMP, will be responsible for providing the Commission with an Opinion on this indent when required. It is noteworthy that in August 2005 the first authorised orphan medicinal products will be entering their fifth year of market exclusivity. In this regard, the Committee

⁴ European Commission Guideline on Aspects of the Application of Article 8 of Regulation (EC) No. 141/2000: Assessment of Similarity and/or Clinical Superiority of Orphan Medicinal Products when Assessing Marketing Authorisation Applications and Variations, available on the Commission's web site:

<http://pharmacos.eudra.org/F2/>

EMEA/35218/2005

notes that guidance on the interpretation of this indent and in particular a definition of “sufficiently profitable” are urgently required.

6.1 Overview of Experience

Of the 268 designated orphan medicinal products (April 2005), 49 (19 %) have already applied for a marketing authorisation. Of these, 44 have filed through the centralised route and 5 nationally or through mutual recognition.

Of the 44 orphan medicinal products that have been the subject of a centralised application for marketing authorisation, 20 (45 %) have received positive outcomes and 2 (5 %) negative outcomes. Fifteen are under evaluation and 7 have been withdrawn.

Of the 5 applications that have been the subject of national application(s) for marketing authorisation, 2 (40 %) have received positive outcomes. Two are under evaluation and 1 has been withdrawn.

Thirty-five per cent (35 %) of the centrally authorised orphan medicinal products have been approved on the basis of phase III double-blind, randomised, placebo controlled or phase III, single blind, randomised, active controlled multicentre clinical trials, whereas 40 % were based on phase II studies (two of them double-blind, randomised, placebo controlled). Compassionate use data and bibliographic data was the basis for successful applications in four cases. Sixty five percent of the marketing authorisations were granted under ‘exceptional circumstances’, which means that at the time of the evaluation it was deemed that the applicant could not reasonably be expected to provide comprehensive evidence on the safety and efficacy of the medicinal product.

7. Article 9 Other Incentives

Article 9 of the Regulation deals with the incentives that are offered to designated orphan medicinal products in addition to the EU incentives of protocol assistance (Article 6) and market exclusivity (Article 8).

7.1 Commission Inventory of Incentives for Designated Orphan Medicinal Products

On the 1st June 2001, in accordance with the 2nd and 3rd paragraphs of Article 9, the European Commission published the first inventory of measures enacted by Member States to support research into, and the development and availability of orphan medicinal products or medicinal products that may be designated as such. On 27th August 2002 the Commission released an update of the inventory and is currently working on a new version.

The inventory is an important tool because it allows both a clear follow up of the implementation of the Orphan Regulation by each Member State, and provides useful information for sponsors, patients, scientists, physicians and regulators from all Member States. This improves access to all available incentives and ultimately facilitates the development of orphan drugs across the EU. Furthermore, because the inventory allows comparison to be drawn between Member States, the inventory may indirectly stimulate the introduction of incentives in some Member States based on the experience in others.

The Regulation requires that the inventory is updated regularly and an annual update would appear to be a reasonable frequency to aim for in the future.

To date, the Committee has witnessed a lack of collaboration from Member States in providing the required information on local incentives for orphan medicinal products, rendering the Commission’s task of releasing regular updates of the inventory impracticable. The absence of national co-ordination structures for orphan product development makes the collection of information on incentives difficult inside the Member States. There is, thus, a clear need for a more structured system for the collection of all relevant information from Member States in order to facilitate the regular update and publication of orphan incentives across the EU.

7.2 Incentives from Member States

Notwithstanding the difficulties encountered with collection of the information on national incentives, it is unfortunately noteworthy that further to the implementation of EU orphan legislation, the majority of Member States have yet to enact any specific measures to support the research into, and the development and availability of orphan medicinal products. That having been said, some Member States have adopted different measures to support rare diseases and orphan drugs and the efforts made by these Member States are acknowledged and should hopefully serve as examples to those Member States who are yet to act.

7.3 Incentives from the Community

Apart from those incentives described in Articles 6 and 8, which act on the development and availability of orphan medicinal products, namely protocol assistance and market exclusivity, the EU Community supports the research into rare diseases through the Framework Programmes. The 6th Framework Programme (2003-2006), had a particular focus also on financial support for small and medium-sized enterprises (SMEs) by fixing the objective of allocating 15% of 6th Framework Programme calls budget to SME partners.

In the frame of the first three calls of the 6th Framework Programme, DG Research has granted 26 projects dealing with rare diseases and/or orphan medicinal products for a total budget of € 93 million.

Furthermore, DG Research has requested COMP advice for the preparation of the 7th Framework Programme in particular on research areas of interest for rare diseases/orphan medicinal products. The COMP has had fruitful interactions with DG Research and in the recent proposal from the EU Commission to the EU Parliament and Council, concerning the 7th Framework Programme for research, technological development and demonstration activities (2007-2013), rare diseases are clearly indicated amongst the list of activities.

III PUBLIC HEALTH BENEFITS

1. Introduction

The ultimate benefit of the Orphan Regulation would be an increase in the survival, the life expectancy and / or the quality of life of patients affected by a rare disorder and treated with an orphan medicine developed and authorised as a consequence of that very Regulation.

It is, however, still too early to assess in full the benefits of the Regulation. EU legislation on orphan medicinal products, entered into force only quite recently (April 2000). Since then a total of 268 medicinal products have been granted orphan designation (April 2005) and 22 of those have gone on to receive a marketing authorisation. The period of time that has elapsed since the introduction of legislated EU incentives for the development of orphan medicinal products and the availability of the first designated orphan medicines to patients is too short for the full public health impact of these new medicines on the key parameters, such as survival, life-expectancy and quality of life, to be assessed.

Taking these limitations into account, the COMP has nevertheless looked into those 22 authorised orphan medicines. The views of representatives of patients' organisations on these new medicines and their general views on the orphan initiative have been sought and the comments received are highlighted in text boxes throughout this chapter.

In evaluating the public health benefit seen thus far, the Committee has taken into account the key parameters referred to above and has come up with a number of alternative parameters, which are indirect measures of any potential effect and are deemed to be very relevant in the present context. For the purposes of this report, these have been broadly categorised as being of direct benefit to patients, being linked to clinical trials/compassionate use or as having an impact on research into rare diseases, as listed below:

- Benefit to patients suffering from rare diseases, by evaluating:
 - the number of patients that may potentially benefit from these new orphan medicines
 - the interaction with patient organisations

- the influence that orphan legislation has had on the EU's paediatric initiative.
- Impact on clinical trials and compassionate use programmes, by analysing:
 - the status of development of designated orphan medicinal products
 - the impact of protocol assistance with regard to quality of performed clinical trials
- Stimulus for rare disease research, by considering:
 - the level of innovation of orphan medicinal products
 - the level of awareness of rare diseases i.e. any improvement in the knowledge base of relevant persons on rare disorders and orphan medicines. The number of published articles and other publicity, both in professional and scientific journals and meetings, as well as in the non-scientific press, may serve as evidence of that.
 - the results of COMP/EMA's endeavour to establish a network of clinical and preclinical experts in the field.

In the following sections of this report the results of the COMP review are presented together with the feedback received from patient representatives highlighting the public health benefits that have been witnessed to date.

2. Benefit to Patients suffering from Rare Diseases

As the European organisation representing people with epidermolysis bullosa (EB), the knowledge that the Committee on Orphan Medicinal Products is there to ease the path once an effective treatment has been found gives us the heart to continue our growing research programme for our very rare condition.

*John Dart
Director, DEBRA Europe (20 May 05)*

2.1 Number of Patients that may Potentially Benefit from New Orphan Medicines

Since orphan legislation was implemented in the EU in April 2000, a total of 22 designated orphan medicinal products have been granted marketing authorisations. Twenty have received Community-wide marketing authorisations through the centralised procedure and 2 have received national marketing authorisations through national/mutual recognition procedures. The first orphan medicinal products reached the market in 2001.

An overview of these new medicines, and the 20 diseases they have been approved to treat and the potential number of patients affected by each condition in the Community is provided in Tables 1 and 2 (Annexe 2). Additional information is provided in Annexe 3 in the form of the abstracts of the European Public Assessment Reports (EPARs).

It is noteworthy that prior to the authorisation of these new orphan medicines for 8 out of 20 (40 %) of these life-threatening or chronically debilitating diseases there were no satisfactory treatment options and they thus represent new hope for patients where there were previously no alternatives.

For the remaining 12 rare diseases these new authorised orphan medicinal products are expected to bring a significant benefit to patients. Twenty-nine percent (29 %) were designated on the basis of potential for improved efficacy over authorised treatments, 14 % on the basis of improved safety, 7 % due to a major contribution to patient care, and the remaining 50 % on a combination of two of these factors.

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 Orphan legislation came into force.

“There are 7 drugs now on the market treating six metabolic diseases-Fabry, Gaucher,hyperammonaemia, MPS1, Wilsons and Hereditary Tyrosinaemia Type 1. Without exception their availability has led to improved health and quality of life and reduction in hospital admissions. Treatments for Fabry, Gaucher and MPS 1 are enabling individuals to take up educational and work opportunities which ill health made difficult or impossible before these treatments. Outlook for babies with Tyrosinaemia I is very positive where before chances of survival beyond a few years were unlikely”.

*Lesley Greene, Regional and Development Manager,
Climb National Information and Advice Centre for Metabolic Diseases (9 May 05)*

“... our members have seen, at first hand, how orphan drugs can help them. Zavesca, which is the first oral drug to be developed for Gauchers disease, has benefited from orphan drug status.

Orphan drug legislation has helped facilitate faster development of drugs for rare diseases which has given hope, not only to those patients and families who can directly benefit, but to those who are still seeking a cure or treatment”.

*Susan Lewis,
Executive Director the Gauchers Association (19 May 05)*

“Regarding the thalassemic patients which my organisation represent and support, in the list of 20 medicinal products approved for MA...only the drug: Tracleer (Bosentan) for treatment of pulmonary arterial hypertension (PAH secondary) will be of interest to treat the disease which in thalassemic patients represent a new complication.....I met recently some patients which are affected only by pulmonary arterial hypertension (PAH primary), in this case the new oral orphan drug (Bosentan) changed drammmatically their life, they said: we are discovering a new life.

The orphan drug designation represents a written promise and in particular a great hope to have a treatment that will change the real life of the people which at the moment don't have any successful treatment. The 20 orphan medicinal products approved for the market are 20 promises performed to the patients and their families”.

Michele Lipucci, Venetian Thalassemia Association (12 May 05)

2.2 Illustration of 3 Orphan Diseases

Of the 20 centrally authorised orphan medicinal products, the COMP has selected three rare conditions that have been the subject of at least one authorisation. This has been done with a view to providing a more in-depth illustration of the type of products that have been authorised to date, their availability and potential added value to the patient. To provide an overview of the different grounds that can form the basis for designation, products that have been designated on the basis of a lack of satisfactory treatment option for patients, an expectation of significant benefit or a major contribution to patient care, have been taken as examples.

The COMP has selected:

- Fabry disease on the basis that orphan designations for Fabrazyme/Replagal were based on the then lack of satisfactory treatment methods;
- Chronic myeloid leukaemia on the basis that the orphan designation for Glivec was based on potential significant benefit at the time;
- Busilvex as a conditioning treatment prior to hematopoietic progenitor cell transplantation as its orphan status was based on an expectation of a major contribution to patient care.

Further detailed information on all of the 20 centrally authorised orphan medicinal products can be found in Annexe 3 where the abstracts of the EPARs are provided. The full version of the EPAR for each of the products is available on the EMEA web-site: <http://www.emea.eu.int>.

2.2.1 Fabry Disease

Fabry disease results from abnormal deposits of a particular fatty substance (called globotriaosylceramide) in blood vessel walls throughout the body. The primary defect which allows this to occur is the inherited deficiency of the enzyme, alpha galactosidase A, which is normally responsible for the breakdown of globotriaosylceramide.

The disease typically begins in childhood and is slowly progressive. Fabry disease is chronically debilitating and life-threatening. Kidney, heart and/or neurologic involvement usually occur between the ages of 30 to 45.

Fabry disease is rare, affecting not more than five in ten thousand persons in the Community. At the time of designation, the COMP concluded that there were less than 1,000 patients in the European Union⁵ (then 15 Member States).

Fabrazyme (agalsidase beta) and Replagal (agalsidase alfa) were designated for treatment of Fabry disease on 8 August 2000 and were authorised on 3 August 2001.

Prior to the authorisation of Fabrazyme and Replagal only symptomatic treatment options were available for Fabry disease. These products represent a novel enzyme replacement therapy aimed at treating the underlying cause of the disease.

Since August 2001, when enzyme replacement therapy was authorised, it is estimated that a total of 1,000 patients in the Community (25 Member States) have received either Fabrazyme or Replagal⁶.

The drugs which have received marketing authorisation ... and are of direct interest to our members are Fabrazyme and Replagal for Fabry disease and Aldurazyme (Laronidase). Words are inadequate to describe the difference between hopelessness and a slow death and hope and a future. Before these three drugs became available, adults and children with Fabry disease and MPS faced a progressive deterioration and certain early death.

Unless you are the sufferer of these dreadful diseases it is impossible to fully appreciate how it is living with no hope for a future. The EU orphan regulation provides that hope. Never have we seen before the pharmaceutical industry so interested in these diseases. There is still a long way to go before the science is overcome in developing treatment for some of these diseases, ...but when the scientific breakthroughs come, it is fantastic to know the EU orphan regulations are there opening doors.

*Christine Lavery,
Chief Executive of the Society for Mucopolysaccharide Diseases (16 May 05)*

"My organisation represents children and adults with over 160 different metabolic diseases (aka inborn errors of metabolism). 35% of the first 20 approved orphan drugs are meant for the treatment of a metabolic disease. ... Especially the enzyme replacement products (3) have a tremendous influence on the quality of life of app. 45 individuals which are treated for Fabry's disease and MPS I. The only problem left in the successful treatment of these diseases are problems with reimbursement of this relatively expensive therapy which has to be followed through lifelong. Patients are very keen on their weekly or biweekly infusions because they feel their health is improving. Even the numerous small children which are treated with aldurazyme are undergoing this invasive therapy willingly, because they notice the difference in health and quality of life."...

Hanka Meutgeert, Executive Director of Dutch Association for Patients with Metabolic Illness (9 May 05)

2.2.2 Chronic myeloid leukaemia

Chronic myeloid leukaemia is a cancer in which one specific type of abnormal blood cells multiplies abnormally in the bone marrow. The bone marrow is the spongy tissue inside the large bones in the body. Normally, the bone marrow makes cells called "blasts" that mature into several different types of blood cells that have specific functions in the body. These include red cells, white cells and platelets. Red blood cells carry oxygen and other materials to all tissues of the body. White blood cells fight infection. Platelets make the blood clot. When leukaemia develops, the bone marrow produces

⁵ Based on a population of 375 million (Eurostat 1999)

⁶ Estimated number of patients treated as provided by the sponsors of Fabrazyme (Genzyme) and Replagal (TKT-Europe AS), in June 2005 upon request of EMEA.

large numbers of abnormal blood cells. There are several types of leukaemias. In myeloid leukaemia blasts that are developing into white blood cells called granulocytes, are affected. The blasts do not mature and multiply without any control. These blast cells are then found in the blood and also accumulate in the bone marrow. When this disease develops very slowly, it is called “chronic” myeloid leukaemia. Chronic myeloid leukaemia is life-threatening.

Glivec (imatinib mesilate) was designated for treatment of chronic myeloid leukaemia (CML) in February 2001 and authorised in November 2001.

CML was estimated to be affecting approximately 34,000 persons in the Community⁷ (then 15 Member States) at the time the designation. Although satisfactory methods of treatment of the condition had been authorised in the Community at the time of designation, significant benefit was justified based on the novel mechanism of action of imatinib and its potential to improve the long-term outcome of patients.

Since November 2001, it is estimated that between 35,000-37,000 patients in the Community (25 Member States) have received treatment with Glivec⁸.

“ I am 64 years old ...in 1998 a diagnosis was made of chronic myeloid leukaemia. Although I had, apart from the changes in my blood, no real symptoms, my treating doctors proposed nevertheless intensive chemotherapy. But I, taking all things into consideration, preferred the usual and less intensive treatment. This treatment was begun in March 1998 and although my blood improved, I had all sorts of problems such as fatigue, problems with my feet, a change of my skin and loss of hair. Within a fortnight of the diagnosis of leukaemia I also developed diabetes....In April 2001, however I was offered treatment with this drug named Glivec. My recovery is remarkable: a return of energy, my hair recovers and becomes dark again and even the treatment my diabetes is easier, I changed from insulin to tablets.... In October 2001 my bone marrow was normal and a later repeat examination showed the same result. The future of my treatment is not yet certain and both I and my treating doctor must wait for long-term results of treatment...”

F.G., Patient with Chronic Myeloid Leukaemia (20 June 05)

2.2.3 Conditioning treatment prior to hematopoietic progenitor cell transplantation

The term of “progenitor cell” is used to indicate those cells which are still immature and do not express all the characteristics of the future mature cells which will derive from them. Haematopoietic progenitor cells are able to produce the cells of the immune system and bone marrow. For diseases where the bone marrow or the immune system are absent, or working abnormally, or invaded by cancer cells, it is sometimes appropriate to use a treatment called haematopoietic progenitor cell transplantation. This consists of replacing the abnormal cells of the immune system and bone marrow, and introducing new progenitor cells, generally from another person (‘donor’). Before the transplantation can take place, the abnormal cells and the immune cells that might react against the new donor cells have to be eliminated. This is called “preparation” treatment or “conditioning” treatment. Diseases requiring such transplantation are life-threatening.

Busilvex (intravenous busulfan) was designated for the conditioning treatment prior to hematopoietic progenitor cell transplantation in December 2000 and authorised in July 2003. At the time of designation it was estimated that not more than 26,000 persons in the European Union⁹ (then 15 Member States) fell within the scope of the orphan indication. Although a satisfactory treatment containing the active substance, in the form of oral busulfan, was authorised at the time of designation the significant benefit of the intravenous formulation was justified on the expectation of a major contribution to patient care, i.e. provision of an easy and convenient form of administration of the drug (a 70 kg adult has to swallow 560 tablets of oral busulfan during the overall treatment period), decreasing the variability in absorption, eliminating the first pass effect, and enhancing physician’s ability to maintain blood levels within an optimal therapeutic window. These advantages are expected to minimise the risk of toxicity (especially the risk of very serious hepatic veno-occlusive disease) and increase the probability of achieving a complete effect.

⁷ Based on a population of 377 million (Eurostat 2001)

⁸ Estimated number of patients treated as provided by the sponsor, Novartis, in July 2005 upon request of EMEA.

⁹ Based on a population of 377 million (Eurostat 2001)

In the period between November 2003, when Busilvex was launched in the EU, and March 2005, it is estimated that 737 patients have been treated with this new orphan medicine¹⁰.

2.3 Partnership with Patient Organisations in the Field of Rare Disorders

The development of the legislation that resulted in the adoption of the Orphan Medical Product Regulations, and the frequent inclusion in the membership of the COMP of the patient group representatives as full members marked a substantial step forward for European Institutions – giving reality to a commitment to stakeholder engagement that hitherto was marked more by rhetorical flourishes than real involvement.

This membership acted as a stimulator to patient groups to “raise their game”, and to demand proper involvement in other Commission programmes and activities, such as Rare Diseases Task Force of DG Sanco for example. It also supported patients’ demands for greater transparency in decision making and supported the development of a number of other initiatives by EMEA such as the “Working Group with Interested Parties”, and opened up dialogue beyond the COMP with patient groups and other stakeholders.

The emphasis on transparency has led to an expectation on the part of patient groups as well as regulators that the basis for future work will be partnership. This has increased expectations across the board, especially for small organisations that have been able to build the criticalness and take part in ways that they would not hitherto have thought possible.

“...It seems that after being ignored and put aside for so many years, these "orphan" diseases now emerge, are better recognised and known, which is quite extraordinary. Experts and patients are consulted about them and can bring to the community, to other scientists and regulatory agencies their knowledge and expertise.

This legislation acts like a key : the simple fact of a disease being labelled as an "orphan disease" is doing wonders : it means in one word that this disease is rare, difficult to treat or without any treatment, often affecting children, severely disabling and lethal, and thanks to that only word, "orphan", they benefit of a totally new way of thinking, they are considered differently in terms of methodologies and statistics, (accepting small numbers in clinical trials), in terms of benefit/risk and rapid access to drugs when proved safe and efficient... and for us parents, it is such a relief and an excitement to know that things are speeded up in the benefit of our children ! not in terms of less quality but in the apprehension of our day to day reality and the urgency we are in”....

Françoise Salama,

Board Member of Eurordis representing the French Muscular Dystrophy Association (10 May 05)

2.4 Setting the Scene for the Paediatric Initiative

Following on from the Orphan initiative, the next piece of pharmaceutical legislation which is expected to have a major impact on public health is the paediatric initiative. The European Commission has acknowledged the importance of COMP and Eurordis input into the EU paediatric proposal.

Following several years of preparatory discussions and consultation with Member States and various stakeholders (patient organisations, medical experts and pharmaceutical industry), in October 2004 the European Commission published a proposal for a Regulation on medicines for children.¹¹ The proposal was clearly inspired by the existing need in Europe for better and safer medicines for children. In contrast to the situation in adults, more than 50% of the medicines used to treat the children in the EU have not been tested and are not authorised for use in children.

¹⁰ Estimated number of patients treated as provided by the sponsor, Pierre Fabre, in April 2005 upon request of EMEA

¹¹ Proposal for a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004
EMEA/35218/2005

In the preliminary discussions of the paediatric proposal it became clear that the Commission, had drawn on both the US experience with measures aimed to stimulate the development of medicines for children in the US, and also on the EU experience with the Regulation on orphan medicinal products.

To that end, the Orphan Regulation, has set the scene politically in the European Union for further legislation aimed to stimulate medicinal product development in particular areas or for particular populations, such as the paediatric initiative. More than half of the medicinal products (54%) recommended for designation by the Committee are suitable for use in children (Figure 13). For orphan medicinal products with a paediatric indication further incentives are proposed.

3. Impact on Clinical Trials / Compassionate Use Programmes

“Our European Organisations for Spinal Muscular Atrophy sufferers are excited by the prospect of a treatment for Spinal Muscular Atrophy. We have seen the first orphan designation for SMA which has caused a lot of excitement among our families. ...EUROSMA, like many patient organisations, are no longer prepared to wait for a chance cure to arrive. Our organisations across the EU have many experts in Science, Medicines, Government Affairs, Banking, Commerce, Teaching or just simply life. We have decided to use these skills/talents to drive forward projects that will allow us to push companies, clinical experts, scientists to help us find a treatment for our children and adult sufferers. For years the world of science was just confusing the Orphan Designation system has brought the process of the registration of medicines a little bit closer to the wider community. The European Medicines Agency website is now looked at by many organisations seeking information on illnesses not only for treatments but for guidelines on the assessment of new possible medicines. We are excited and hopeful that one day we will also see on this website an EU approval for a treatment for SMA”.

*Joseph Irwin, Honorary Director of Research
The Jennifer Trust for Spinal Muscular Atrophy (10 May 05)*

3.1 Status of Development of Designated Orphan Medicinal Products

The 260 orphan designations granted up to April 2005 already covered a wide variety of rare diseases. The majority of designations have been granted in the area of cancer (36%), followed by metabolism (11), immunology (11%), and cardiovascular and respiratory (10%) (Figure 14).

Introduction of EU orphan legislation has clearly stimulated orphan drug development and clinical research into rare diseases. With a view to quantifying the public health benefit in this context, the EMEA contacted the sponsors of all designated orphan medicinal products to request information on the development status as of April 2005. Although sponsors normally update the Agency on the status of development of each orphan medicinal product once a year in the annual report, sponsors were asked to respond to a short questionnaire to ensure the Agency presented the most up to date information on all products.

Information on the status of development of the pharmaceutical, non-clinical and clinical programmes was collected together with details on any ongoing compassionate use programmes. Plans for protocol assistance and filing the application for marketing authorisation were also requested.

Of the 259 orphan medicinal products at the time of the survey, updated information was received for 170 (66%) (Figure 15). A total of 33 % of the medicinal products are in the final stage of clinical testing (Phase III) and a further 38 % are in phase II (Figure 16). Furthermore, twenty-one percent of sponsors noted that a compassionate use programme was in place (Figure 17).

As mentioned earlier it is important that medicinal products developed for rare diseases meet the same standards in terms of quality, safety and efficacy as all other medicinal products. The extent of ongoing clinical trials are promising and with the availability of protocol assistance should be conducted optimally to ensure those products that prove to be safe and effective receive regulatory approval in the shortest possible timeframe. Interestingly, of the sponsors surveyed, 88 % plan to seek protocol assistance (Figure 18). This is clearly an orphan incentive that is being utilised to the full in the interests of public health.

Although it is still too early to assess the full public health impact of orphan legislation, to date 20 new orphan medicines have been authorised and based on the achievements seen so far the future looks promising. The number of orphan medicinal products authorised has increased each year since the EU orphan initiative was implemented. This trend looks set to continue with the number of orphan products reaching the market expected to escalate. Of the sponsors surveyed by the Agency, 50% plan to file for marketing authorisation over the next two years (9% in 2005, 15% in 2006 and 26% in 2007) (Figure 19). Based on experience, it is estimated that the number of products reaching the market will escalate dramatically in the next 3 years.

3.2 Impact of Protocol Assistance with regard to the Quality of Performed Clinical Trials

“The vast majority of the orphan drugs being developed in Europe today are for extremely rare diseases affecting less than 120 000 patients in the EU (90%), of these 43% are for ultra orphan diseases affecting less than 40 000 patients in the EU; for these patients there usually exist no therapeutic alternatives or satisfactory methods of treatment. Obviously this high level of clinical research for diseases affecting the very small number of patients affected by each rare disease was not possible at the national level; it is only possible today because we have a common policy at the European level.

The EU Orphan Regulation has also had a tremendous impact in developing the rare disease knowledge-base, in stimulating both excellence in the scientific communities and greater awareness of these neglected diseases, and in shaping national policies for better information and care for people affected by rare diseases”.

Yann Le Cam, Chief Executive of Eurordis (6 May 05)

Although it is too early to analyse the impact of protocol assistance alone on the quality of clinical trials performed by sponsors, the EMEA recently assessed the impact of both scientific advice and protocol assistance on the outcome of the scientific evaluation at the marketing authorisation stage.

In 2004, 22% (8/37) of applications for marketing authorisation that had an outcome in the centralised procedure received prior scientific advice or protocol assistance. Six (75%) of those eight applications with prior scientific advice/protocol assistance received a positive CHMP opinion, indicating that, while scientific advice/protocol assistance is no guarantee of a positive outcome, it appears to have a favourable influence (Figure 20). This has been the overall experience of the Agency since 1998.

Although only a minority of the applications examined were orphan, conclusions on the impact of protocol assistance can be drawn by analogy. In fact, as discussed in section II.4 of this report, rare diseases often raise complex developmental issues so a larger impact may even be expected.

4. Stimulus for Rare Disease Research

“The fear is that the next drug that is needed will not be developed, or, if it is, that it is beyond reach of the patient who needs it because of regulatory or cost issues. The regulation has brought the significant health impact of rare diseases to the attention of a wider population, including physicians, and policy makers. It has restored hope that there is enough incentive and therefore interest in researching treatments where there were none before. Parents/patients who experience or witness the benefits of orphan drugs dare to begin to think beyond “day to day”, to a more “normal” future for patient and family alike. As one patient says “With this treatment I have a future-without it I don’t”.

*Lesley Greene, Regional and Development Manager,
Climb National Information and Advice Centre for Metabolic Diseases (9 May 05)*

4.1 Level of innovation of orphan medicinal products

To ascertain the “innovativeness” of the medicinal products seeking orphan designation, the EMEA reviewed the all products that have been the subject of a designation application over the 5-year period from 2000-2004. Medicinal products were classified under one of the following headings:

- Gene Therapy
- Human Cell Therapy

- Xenogeneic therapy
- Tissue Engineering
- Monoclonal Antibody
- Microorganisms
- Antisense
- Recombinant Enzymes
- Blood Products
- Novel chemicals
- ‘Old’ Chemicals

Products not falling in any of these groups were classified as “other” and encompassed, amongst other, protein polypeptides, complex chemicals, oligo nucleotides, and herbal extracts. The results are summarised in Figure 21.

As of December 2004, ninety-two (21 %) applications for orphan medicinal product designation have been submitted for biotech products and 336 (79 %) for non-biotech products (Figure 22). A slight increase in biotech products was noted in 2003 compared to other years. In 2004 an increase in novel chemicals was observed together with a decrease in the number of biotech products compared to previous years. Applications for the so-called ‘old’ chemicals have remained at a relatively constant level each year. No applications for tissue engineering products have been received to date.

From this review, it is noteworthy that novel/innovative products constitute more than half (53%) of all applications for orphan designation (Figure 23). The orphan initiative would, thus, appear to have already made a positive impact on research into rare diseases. This is encouraging news for the COMP and most importantly for those patients who currently have no therapeutic options.

“For patients and families affected by rare diseases in Europe, there is a "before" and an "after" the EU Orphan regulation. The EU Orphan Regulation has generated the designation of 260 orphan drugs: 260 concrete hopes based on drugs currently being developed to address unmet medical needs. At a stable rate of 100 per year, the number of applications is overwhelming, and we are struck by their high quality which is increasing as experience is gained. This success underlines Europe’s extraordinary potential for drug development based on solid research and innovative therapeutic approaches, as well as the dramatic unmet needs of the 30 million patients suffering from rare diseases in the EU”.

Yann Le Cam, Chief Executive of Eurordis (6 May 05)

4.2 Level of Scientific and Public Awareness of Rare Diseases

The availability of new orphan treatments has generated new interest in rare diseases both within the scientific community and the general public.

It was considered of interest to ascertain whether there has been any increase in awareness of the problems related to rare disorders (e.g. via publications in the medical literature and in the lay press) since the introduction of EU Orphan legislation. To provide a crude indication of this, searches of the medical/scientific literature and some of the national lay press were made and the number of articles/publications on orphan medicinal products and/or rare disorders, prior to the entry into force of EU legislation (1995-1999) and following its introduction (2000-2005) were compared in April 2005.

The results of the search of the medical/scientific literature, conducted on Medline, revealed that using search criteria¹² for orphan medicinal products or rare diseases, for the period from 1995-1999 there were 1875 publications and using the same criteria for the period 2000-2005 there were 3208 publications. The search was repeated with the same criteria plus ‘Europe’ and ‘European Union’ as additional search terms. Narrowing the search to Europe revealed 105 publications between 1995-1999 and 194 between 2000-2005.

¹² Search criteria: ‘orphan drug(s)’, ‘orphan medicinal product(s)’, ‘rare disorder(s)’, ‘rare disease(s)’, and ‘orphan disease(s)’

From the results of the Medline search it is clear that the number of scientific publications on orphan medicinal products/rare disorders has increased world-wide by 71% in the five-year period since the introduction of EU Orphan legislation. Interestingly, this trend becomes even more marked (85%) when the search is narrowed to those publications specifically referring to 'Europe' and the 'European Union'.

A similar, although limited, preliminary search was carried out in the national press publications of five Member States in their respective languages. The results were as follows:

• The Netherlands (59 newspapers)-	1995-1990: 194	2000-2005: 357
• UK (6 newspapers)-	1995-1999: 170	2000-2004: 298
• Germany (6 local and 4 national newspapers):	1995-1999: 12	2000-2004: 16
• France (3 national and one local newspaper):	1995-1999: 26	2000-2005: 130
• Spain (2 national newspapers):	1995-1999: 1	2000-2004: 17

Once again comparing the two five-year periods, the number of newspaper articles in each of the five Member States increased. The broadsheet newspapers and popular press have paid increasing attention to rare disorders and orphan drugs in their publications over recent years. This is important because it has created awareness of rare diseases among several non-specialist audiences.

4.3 Expert network

The COMP, when it met for the first time in April 2000, underlined the need to establish a network of experts to assist it in its review of designation applications and respond to its specific needs. To date more than 350 experts in a variety of fields have been nominated by the COMP and included in the EMEA's expert database. These experts include clinicians specialised in rare disorders, representatives of patients' organisations with first hand experience of the conditions, pharmacologists, research scientists, and epidemiologists. The use of experts in the designation process is essential and will continue.

The expert network built up by the Agency 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.

To facilitate the timely appointment of experts in all areas in the future the Committee will continue to endeavour to identify potential experts as early as possible in the designation process. Currently experts are not reimbursed for their professional services and the introduction of a fee to compensate experts for their time and contribution should be considered in the future.