

**3 YEARS OF SUCCESSFUL
EXPERIENCE ON ORPHAN DRUGS**



European Medicines Agency

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Three years of success followed the adoption of the European Regulation on orphan medicinal products by the European Parliament and Council in 1999. European Medicines Agency (EMA) and its Committee for Orphan Medicinal Products (COMP) have been the major players of implementation. They have achieved success beyond expectations and forecasts.

At the end of its first 3-year mandate, the Committee for Orphan Medicinal Products of the EMA prepared a report on their activities. The report provides recommendations to further stimulate research and development of medicines intended for rare diseases, and to increase patients' access to treatment.

Setting up a European policy on medicines intended for rare diseases

Because return on investment into research and development of medicines intended for rare diseases was not profitable, patients affected by rare diseases were left without therapeutic options. In Europe, a political decision with strong support from the European Parliament to change this situation was made resulting in a European legislative framework implemented in April 2000. The legislation set up a range of incentives to stimulate development for medicines for rare diseases.

Establishment and experience of a new Scientific Committee at the EMA

The Orphan Regulation created the COMP. The Committee is composed of one representative per member state, 3 EMA representatives and, for the first time in a Community scientific committee, 3 patients' representatives. A patient representative was twice elected vice-chair of the Committee. The 3 years mandate of the Committee was renewed for the first time in April 2003.

The Committee meets once a month at the EMA to discuss applications for orphan designation and protocol assistance. It also monitors marketing authorisation applications for orphan medicinal products.

A major support given to COMP by EMEA

In line with the Orphan Regulation, the EMEA is committed to provide major support to the activities of the COMP through its secretariat: the EMEA validates the applications, prepares, monitors and supports all activities and meetings of the COMP; in addition, the EMEA writes summary reports of orphan applications, providing high-level scientific reports used as a basis for the work of the Committee.

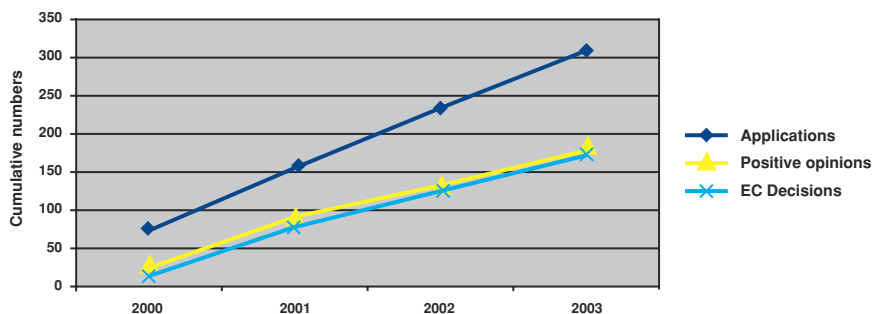
A successful experience with orphan designation

At the end of December 2003¹, more than 320 applications for designation had been received at the EMEA. More than 70% of sponsors came for a pre-submission meeting at the EMEA to seek help in drafting their application. Of all applications 67% received a positive opinion from the COMP, subsequently transformed into designation by the European Commission. The remaining applications resulted in negative opinions (2%) or withdrawals (31%) from the sponsors. This is mainly due to sponsors failing to meet a criterion required by the Orphan Regulation, for example the 5/10,000 prevalence threshold when the disease their product intends to treat is not so rare.

The products designated are innovative in the majority of cases; some are intended for conditions so rare that less than 100 patients exist in the whole Community. The orphan conditions designated the most often are rare cancers, rare metabolic diseases or rare neurologic disorders. Small and medium-size companies represent two thirds of the sponsors. The COMP encourages sponsors to apply for designation at an early stage of development, even when the studies in man have not started. Sponsors are also encouraged to seek protocol assistance from the Agency's scientific committees as early as possible to maximise the chances of success at the time of evaluation of the application for marketing authorisation.

¹ At the time of drafting the COMP report, only February figures were available.

Orphan Medicinal Products Designation April 2000 - November 2003



Marketing authorisations of orphan products

The number of products effectively reaching the market and the patients can measure the success of orphan legislation. Experience in the US shows that it takes a mean 5 years from the designation to the marketing authorisation of orphan products. Only 3 years after adoption of the European Orphan Regulation, 12 products² had been authorised via the Community procedure. This is a very encouraging result and more products are being evaluated for authorisation. Applicants for marketing authorisations have direct access to the centralised procedure and currently benefit from 50% fee reductions.

Interactions with other Committees and Working Groups of the EMEA

In keeping with one of the objectives of the Regulation, the COMP liaised with the Committee for Proprietary Medicinal Products (CPMP) on regular occasions. This exchange takes place during informal meetings held each semester, and through the nomination of 2 CPMP members in the COMP as proposed by the Agency to the European Commission. In addition, COMP members are members of the CPMP Scientific Advice Working Group in charge of protocol assistance. The COMP also liaises with the Mutual Recognition Facilitation Group as orphan products may currently be authorised via the mutual recognition procedure.

² As of December 2003

Protocol Assistance is a major tool for the success of marketing authorisation applications

The Regulation aimed at early and proactive support to sponsors through protocol assistance. Twenty-five applications have been submitted, with follow-up procedures, facilitating the dialogue between regulators and sponsors.

The EMEA and COMP together with the Commission prepared guidance for sponsors, both on regulatory aspects and scientific aspects of designation and protocol assistance.

In parallel, the specificity of efficacy and safety trials in very limited numbers of patients such as in rare diseases prompted the EMEA to organise an international scientific workshop on this issue inviting participants from COMP and CPMP, patients' representatives, academia and representatives from the FDA.

Other aspects of Research and Development for rare diseases

The COMP initiated a dialogue with European Commission DG Research in particular on the place of rare diseases in the EU 6th Framework Programme.

Encouraging proper clinical trials in rare diseases, whenever feasible, is one of the key messages of the COMP to sponsors. It is hoped that the European Clinical Trials Directive will help in this respect. Full transparency on clinical development would serve patients and society at large, making quality information available, avoiding unnecessary replication of data, waste of resources, and facilitating recruitment in a safer environment for the patients willing to participate in clinical trials.

Experts network

The COMP has helped build a network of experts in rare diseases, used for the purpose of designation and consulted by the CPMP where appropriate. This also contributed to increase awareness of the European orphan policy among health professionals.

Transparency and Communication

Rare diseases have always been an area of poor communication, due to the dispersion of patients and experts across the Community. Within the transparency policy of the EMEA, several initiatives were set up for orphan diseases. A specific COMP working group of interested parties including members of industry, patients' representatives, and learned societies was created to address issues of communication and transparency.

A special area of the Agency's website was set up including monthly press releases of the COMP meetings, and summaries of COMP opinions for products newly designated. The summaries explain to patients, in lay language, the main characteristics of the disease and designated products.

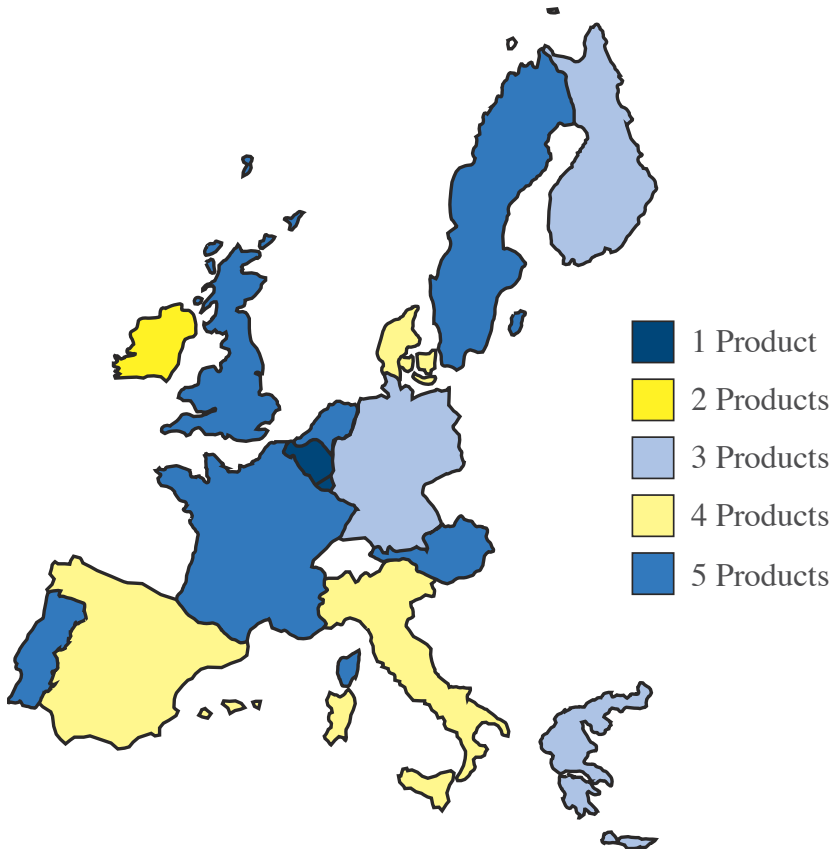
Separate workshops with patients' organisations, industry representatives, learned societies and health professionals were organised. A Joint meeting of all interested parties in December 2002 crowned the end of this first mandate. The meeting was the opportunity for a critical review of the achievements and proposals for the way forward, and its conclusions have been taken on board in the COMP report. Concerns on pricing and reimbursement of orphan products were expressed, however these responsibilities are outside the remit of EMEA.

Interactions with the European Commission and other bodies

A representative from DG Enterprise attends the meetings of the COMP. Other DGs have been invited, in particular DG Research on the Framework Programmes and DG Sanco on the Community actions for rare diseases.

Availability of orphan medicines to patients

The European orphan regulation will not reach its goal if, ultimately, patients do not have actual access to authorised orphan medicines. This may be currently the case because of major delays and inequality in the outcome of national pricing and reimbursement procedures. A first survey of the 5 first authorised orphan medicinal products made by EURORDIS, the umbrella organisation of patients' associations, showed marked differences in access throughout the Community.



Availability of orphan medicinal products in Member States (EURORDIS survey)

The survey suggests that in some Member States, patients have extremely limited access to orphan products as they are not reimbursed, and in other Member States, prices are three times higher than in the neighbouring state without clear justification. COMP made a strong recommendation to the European Commission to make proposals on this important issue in co-operation with Member States.

Special contribution of the Community for orphan drugs

On the one hand, all activities relating to regulatory assistance, designation of orphan medicinal products, and management of the COMP meetings, is funded by the part of the EMEA budget based on the Community subsidy. As opposed to the marketing authorisation procedure, the designation procedure attracts no fees from the sponsor and consequently provides no financial compensation to COMP members.

On the other hand, once designated, orphan medicinal products are entitled to reductions in the fees due for Community procedures, funded by a special contribution from the Community. The COMP made recommendations for priority to protocol assistance with a view to helping sponsors, in particular those with little drug development experience, to increase their chances of successful development. Currently, protocol assistance benefits from 100% fee waiving. Other activities related to centralised applications benefit only from 50% reduction of fees, i.e., marketing authorisation applications, inspections, variations and annual fees. The use of the special contribution amounted to € 297 500 in 2001, € 2 407 500 in 2002 and € 2 814 100 in 2003.

Taking into consideration the increasing number of orphan products coming to the stage of marketing authorisation, and the need for a sustained policy on incentives, continuing financial support from the Community is required. Full fee waivers, are granted by the US FDA and the success of the orphan drug policy in Europe should not be jeopardised by the lack of appropriate funding by the Community special contribution.

Following the conclusions made by the COMP, the EMEA makes the following recommendations to the European Parliament and to the European Commission:

- To individualise funding of research on orphan medicines designated by the Commission, in the Framework Programmes and other projects of research on rare diseases
- To develop the co-ordination of European research networks on rare diseases
- To develop the co-ordination at European level of the assessment of therapeutic value of orphan medicines to ensure speedy access to patients
- To ensure the sustainability of the special contribution from the Community for orphan medicines in order to obtain maximal incentives before marketing authorisation with full fee waiver for all related activities, while limiting post authorisation support up to the placing on the market unless marketing authorisation holders are small and medium size companies
- To develop within the Agency guidance, and education of sponsors and to promote protocol assistance supported by additional expertise; in particular for biotechnology products and emerging therapies and technologies
- To develop within the Agency guidance on alternative designs and methodology for clinical trials in rare diseases to help sponsors in particular from academia, and to facilitate clinical trials as a tool to improve access of patients to orphan medicines



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