**ORPHAN DRUG REGULATION IN EUROPE**

**Introduction**

Rare diseases are referred to as “orphan diseases”, and the products intended to treat them as “orphan medicinal products”. In addition to rare diseases, orphan diseases include those for which developing new therapeutic tools is not profitable.

Following the international examples of the United States, Australia and Japan, Europe adopted its “Orphan Regulation” on December 16, 1999 (European Commission Regulations EC No. 141/2000(1) and EC No. 847/2000(2)). This Orphan Regulation proposes official regulatory status for orphan medicinal products, with full or partial exemption from registration fees, an exclusive marketing period of 10 years, and “protocol assistance”, help with clinical trials and R&D. A Committee for Orphan Medicinal Products (COMP) was created at the European Medicines Evaluation Agency (EMEA).

Following the first article on the new European Orphan regulations in the previous issue of the Medical & Healthcare Marketplace Guide, the evolution of the orphan medicinal products regulations are discussed, as well as the general evolution of orphan medicinal products in Europe.

**Evolution of orphan medicinal products process and regulations**

**Application Procedure**

Sponsors should use the EMEA Draft Guideline ENTR/6283/00(3) to prepare their application. The latest version of ENTR/6283/00 guideline published in December 2000 was revised to add points to consider regarding the evaluation of the plausibility of an orphan “condition”
and guidance on the transfer of sponsorship. Sponsors should follow the General Principles outlined in document EMEA/14222/00\(^{(4)}\) to fill in the application. These General Principles were revised in January 2001. A deadline of three months for response to validation issues by sponsors and a number of other minor changes were incorporated.

In addition, recently published documents provide assistance in the orphan medicinal product designation application process, such as the “Frequently Asked Questions” document (EMEA/4795/00\(^{(5)}\)).

**Improvement of the COMP procedure**

In February 2001, the COMP agreed upon the procedure for a sponsor to appeal a negative COMP opinion on orphan medicinal product designation (EMEA/2677/01\(^{(6)}\)).

The COMP has created an extended network of experts on rare diseases. To increase transparency and communication in the field of rare diseases and orphan medicinal products, the COMP further discussed proposals for identifying and liaising with interested parties, in specific patient organisations, the scientific community (including health professionals and independent researcher) and the pharmaceutical sector.

An ad-hoc COMP Working Group (COMP-BWG) was established in March 2001 to provide the COMP with advice on general and product specific biotechnological matters, which are raised in applications for orphan designation.
The first EMEA Workshop for Patient Organisations on Orphan Medicinal Products was held in March 2001 (EMEA/COMP/108/01\(^7\)). Forty-four representatives of patient organisations met with COMP members and EMEA staff. The COMP’s achievements to date were discussed as well as several proposals for the near future, including provision of more rapid and expanded access to information on orphan medicinal products, external experts involvement in the designation process, and the possibility of increased involvement of patients representatives in COMP meetings and in *ad-hoc* meetings of the COMP.

The first EMEA Workshop with the Pharmaceutical Industry on Orphan Medicinal Products was held in April 2001 (EMEA/COMP/141/01\(^8\)). Members of the COMP, the European Commission and the EMEA met with fifty representatives of the pharmaceutical industry. The European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Association for Bioindustries (EuropaBio), the Emerging Biopharmaceutical Enterprises (EBE) and sponsors of products which have been subject of positive opinions were represented. The Committee’s achievement to date were discussed as well as proposals for improving transparency.

The COMP established a COMP Working Group with Interested Parties (COMP-WGIP), composed of EMEA/COMP members and representatives of patient organisations and the pharmaceutical industry. At its first meeting, the COMP-WGIP will work on proposals for improving transparency on orphan activities, optimising the orphan designation procedure and delineating policy recommendations on orphan medicinal products.
Annual Reporting Requirements

The requirement for sponsors to submit annual reports to the EMEA on the status of development of designated medicinal products, in accordance with Regulation EC 141/2000, was discussed by the COMP in June 2001, and a guidance document is to be released for consultation.

Deadlines for Submissions

In order to synchronise each evaluation with the meetings of the COMP, validation dates (Day 1, start of orphan medicinal product designation procedure) have been fixed and agreed by the COMP, as well as deadlines for submission of the applications. The deadlines for submission of applications are available in the 15th Meeting of the COMP Press Release, Annex II (EMEA/COMP/286/01(9)).

General Evolution of Orphan Medicinal Products in Europe

As of July 2001, the COMP adopted 60 positive opinions on applications for orphan medicinal product designation, and 49 designations have been granted by the European Commission (EC). Today, two orphan products (designation of 8 August 2000) have already obtained a marketing authorization in Europe: Fabrazyme™ and Replagal™ of Genzyme BV, and TKT Europe-5S AB respectively, both intended for long-term enzyme replacement therapy in patients with Fabry Disease). Interestingly, the two products were developed for the same indication, and, fortuitously, were not only designated the same day, but also received marketing authorization the same day. The EMEA decided to let them share the market exclusivity.
When analysing the first year of the COMP’s existence, the first remark is to acknowledge the achievement. The COMP has evaluated and designated much more products than originally expected, with limited resources, both financial and human. The small group composed of very few dedicated EMEA staff members has worked with professionalism, efficiency, timeliness, and has faced a heavy workload. Solid relationships were created with industry members, which generated an unprecedented synergy in achieving their common goal. In addition to these operational aspects, the COMP members have developed a network with the main organizations involved in rare diseases. The committee is now at the center of the key players in the area, as demonstrated, for example, by their strong involvement with patient associations and professional associations of industry representatives.

Despite a late start, when compared with the US and other systems in place, it appears today that the European system is functioning fast and efficiently. It is reaching a level of activity that will allow sponsors to develop a large number of products for rare diseases, often representing unmet medical needs. Its further growth is now pending on the appropriate budget provided by the EC.

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(2) - (EC) No 847/2000 Regulation of 27 April 2000 - Official Journal of the European Communities L103/5, 28.4.00.


(6) - EMEA/2677/01 - Procedure for a sponsor to appeal a negative COMP opinion on orphan medicinal product designation – Published in the 10th Meeting of the COMP Press Release, Annex II (EMEA/COMP/50/01) – Available at: [http://www.emea.eu.int/htms/human/press/comp.htm](http://www.emea.eu.int/htms/human/press/comp.htm)
