ORPHAN MEDICINAL PRODUCTS REGULATIONS IN EUROPE

European Member States have decided that they cannot accept that certain individuals be denied the benefits of medical progress because these individuals suffer from a disease that affects only a small fraction of the population. It is therefore their role to provide incentives to sponsors, and to adapt their administrative procedures, so as to facilitate access to medicinal products for these patients, provided that these products are as safe and effective as any other medicinal product, and meet the same quality standards. In addition, the success of the US Orphan Drug Act implemented in 1983 has stimulated other countries to follow the U.S. example.

1. PURPOSE AND CONTENTS OF THE REGULATION

The purpose of Orphan/EN-07 is to establish a European Community procedure for designating Orphan Medicinal Products (OMPs), and to introduce incentives for conducting research, developing and marketing OMPs for rare diseases.

The European Parliament and the Council Regulation on OMPs have prepared a proposal for establishing the application of a product as an OMPs (OMP designation), and to introduce incentives for their development. The proposed legislation is a Regulation, it is therefore binding after enforcement. This proposal, named Orphan/EN-07, will provide exclusive marketing rights for a period of 10 years, and faster access to the European Community market via the centralized authorization procedure. It includes 11 articles, as follows:

- Article 1: Purpose
- Article 2: Scope and Definitions
- Article 3: Criteria for Designation
- Article 4: Committee for Orphan Medicinal Products
- Article 5: Procedure for Designation
- Article 6: Protocole Assistance
- Article 7: Community Marketing Authorization
- Article 8: Market Exclusivity
- Article 9: Other Incentives
- Article 10: General Report
- Article 11: Entry into Force

2. CRITERIA FOR DESIGNATION AS OMP

A medicinal product shall be designated as OMP if the sponsor can establish that the medicinal product is intended for the diagnosis, prevention or treatment of a condition affecting less than five per ten thousand (5/10,000) patients in the European Community at the time the application is made. Also, the sponsor must establish that there is no satisfactory method of diagnosis, prevention or treatment of the considered condition authorized in the community or, if such method exists, that it can reasonably be expected that the medicinal product will be safer, more effective or otherwise clinically superior.
Designation will be granted if the sponsor can demonstrate that the medicinal product is intended for a life-threatening or seriously/chronically debilitating communicable diseases in the European Community, with the required low prevalence.

Finally, designation will be granted if the sponsor can demonstrate that the development of the product would generate insufficient return on investment to justify the necessary.

3. **LEGAL AUTHORITIES IN CHARGE OF OMPS**

The EMEA and the Standing Committee on Medicinal Products for Human Use will be in charge of designating OMPs, through a simple swift procedure, making use of EURORDIS. EURORDIS is an umbrella organisation created in March 1997 for promoting the swift adoption of European legislation on OMPs. Following submission of the sponsor’s request to apply for OMP status, the European Commission will have to make a decision about the designation within 30 days.

4. **RIGHTS GRANTED TO OMP SPONSORS**

4.1 **Market Exclusivity**

The primary incentive for a sponsor to develop an OMP is market exclusivity within the European Community for a period of 10 years. The protection granted prevents the European Community or a Member State from subsequently issuing a marketing authorisation for the same product (i.e. the same active substance) and for the same indication. Market exclusivity is unanimously regarded as crucial to any system of incentives for R&D activities on OMPs.

The European Commission has not yet provided a detailed list of other incentives available, and will be issuing this list on the basis of information provided by the Member States. However, the regulation states that sponsors will be provided with financial and technical assistance.

4.2 **Financial Incentives**

At this time, the proposal anticipates to grant financial support for the research undertaken by the sponsor. This is considered as an effective incentive for sponsors to conduct research on OMPs.

At the national level, within each Member State, tax incentives will be implemented.

At the European level, the European Community plans to allocate a specific budget to research on OMPs. Following designation, fee exemptions for Marketing Authorisation Application are planned. which will facilitate access to centralised procedure in particular to small and medium size entreprises.

The European Commission’s contribution is shown in Table 1.
Table 1

<table>
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<th>Year</th>
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<td>1 508 000</td>
<td>1 922 000</td>
<td>1 936 000</td>
</tr>
</tbody>
</table>

4.3 Technical Incentives

The proposed regulation will give sponsors access to EMEA resources and help them develop their products faster, as described below:

- Scientific human resources from Member States, made available to the EMEA for evaluation purposes, will be shared with the sponsors. Sponsors will have access to the network of 2 000 experts covering the full range of expertise used by the Agency to ensure the highest possible quality of its scientific opinions. Scientific and regulatory advice, as well as protocol design assistance will provide sponsors with the EMEA’s expertise, in particular to set-up and follow-up clinical trials, and to prepare the Dossier. A close involvement of the CPMP and its Working Parties in the development process will also establish a relationship aimed at facilitating the evaluation of the Dossier.

- Sponsors will have direct access to the Centralised Procedure which allows for a fast and high quality review, leading to the granting of a single Marketing Authorisation valid throughout the Community. This will ensure fast availability of OMPs to patients whilst allowing sponsors a fast return on investment.

4.4 Limitations to the Duration of the Grant

The proposal states that exclusive rights will be granted for a period of 10 years, however it may be revised after 6 years. The rights may be withdrawn at the end of the six-year period at the request of a Member State where the latter can establish that the conditions which originally led to the designation of a product as an OMP no longer apply, or that the price charged for the medicinal product concerned is such that it allows the earning of an “unreasonable” profit.

The grant may be revised at any time either in case the holder of the exclusive authorisation cannot supply a sufficient quantity of the medicinal product or in case another medicinal product has been shown to be safer, more effective or clinically superior to the product which has been enjoying exclusive rights.

5. ENTRY INTO FORCE OF THE REGULATION
The implementation date is currently unknown, however, it may be anticipated that the regulation will enter into force by 2000.

6. MARKETING AUTHORISATIONS GRANTED TO OMPS IN EUROPE

The following products are examples of OMPs developed in Europe between 1996 and 1998: Cystagon, for use in nephropathix cystinosis, Benefix, a Factor IX replacement therapy in patients with hemophilia B, and Cerezyme, an enzyme replacement therapy for patients with type I Gaucher disease.

7. ORPHANET

Of major importance in the application of the new regulation is the recent implementation of Orphanet, an organization aimed at providing to the European Community information on rare diseases. The Orphanet database contains information about 550 rare diseases, over 1500 clinical laboratory tests, 700 research projects, 100 patient organizations, 400 specialized clinics. It also provides addresses of related websites. (http://www.infobiogen.fr/services/orphanet).

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