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Editorial

1. Introduction

Society cannot accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. It is therefore up to the public authorities to provide the necessary incentives and to adapt their administrative procedures so as to make it as easy as possible to provide these patients with medicinal products which are just as safe and effective as any other medicinal product and meet the same quality standards.

In the United States, an incentive system for the development of orphan medicinal products (the "Orphan Drug Act") was introduced in 1983. [1] At the end of 1997, 152 orphan products had gone on to obtain marketing approval and are now being used by over 7 million patients.

The success of the U.S. orphan drug program has stimulated many foreign countries to seed to emulate it. The Singapore Government decided on an Orphan drug Act 1991, the Japanese in 1993, the Australian Government in 1997 and in July 1998, The European Commission approved the proposal for a European Parliament and Council Regulation on Orphan Medicinal products. [2]

In the European Union, in the course of the last decade, a number of Member States have adopted specific measures to increase our knowledge of rare diseases.

The Commission has proposed a Decision of the European Parliament and Council adopting a programme of Community action 1999–2003 on rare diseases, including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations.

2. The Commission's proposal

On July 27 1998, the European Commission presented its proposal for a European Parliament and Council Regulation on orphan medicinal products. [2] The ratio is lower that that used in the United States (7.5 per 10,000) and slightly greater that that used in Japan (4 per 10,000).

Market exclusivity is unanimously regarded as crucial to any system of incentives for research and development work on orphan medicinal products. *This exclusivity is for the entire Community. This new right is probably a new intellectual property right per se. It is something in between a patent and the data exclusivity.*

[1] Marlene E. Haffner. Director Office of Orphan Products Development, FDA. European Conference on Orphan Drugs/Rare Diseases. Advanced Biotechnology Center. Genoa. Italy. October 1 and 2, 1998.
[2] COM (1998) 450 final.

3. The role of the European Parliament

The Committee on the Environment, Public Health and Consumer Protection appointed Mr. Cabrol (UDF) rapporteur on 22 September 1998. The report was tabled on 24 February 1999. At on 9th March 1999, the European Parliament adopted a series of amendments at its first reading, notably in the following areas: [3]

- Providing for additional incentive measures to combat the main infectious diseases prevailing in developing countries.
- Underlining the need for the protection of intellectual property rights to be ensured.
- Specifying that the Committee for Orphan Medicinal Products will be set up within the European Agency for the Evaluation of Medicinal Products.
- Requiring committee members, even after their duties have ceased, to observe professional secrecy obligations.
- Allowing application for the status of orphan medicinal product to be made at any stage of the product's development before submission of a registration application.
- Requiring the sponsor to report to the Agency every year on the state of development of the designated medicinal product.
- Making extra provisions with regard to transferring designation of an orphan medicinal product from one sponsor to another.
- Providing for assistance in the development of a protocol for pre-clinical and clinical trials during the development phase.
- Allowing the Agency, in exceptional cases and under specific conditions, to authorise the medicinal product being made available before marketing authorisation had been granted.
- Specifying that the scale of the Community's special annual contribution to the Agency be of a sufficient scale to cover all the applications submitted in order to produce the maximum incentive.
- Calling for the Commission to propose establishment of an Orphan Medicinal Product Innovation Promotion Fund.
- Requiring the Commission to adopt definitions of similar medicinal product and clinical superiority in the form of an implementing regulation in accordance with the procedure laid down in article 72 of regulation 2309/93/EEC and to draw up detailed guidance for the application of this article 72 and the implementing regulation.
- Making provision for designated orphan medicinal products to be eligible for particular aid for research and SMUs under the Fifth Framework Programme for R&D.

[3] Report on the proposal for a European Parliament and Council Regulation on orphan medicinal products. A4-0078/99. Christian Cabrol.

– Requiring the Commission to publish a series of operational proposals to ensure uniform application without unjustified delay of Community and Member State incentives to support research, development and availability of orphan medicinal products.
– Making any application for designation as an orphan medicinal product after 01/04/99 subject of the requirements of the proposed regulation.

As the shadow rapporteur for the EPP Group, I tabled a series of amendments but only some of them were included in Mr. Cabrol's report.

One of my amendments intended to establish a fund to provide grants for orphan medicinal products.

> Article 8.3: *On a proposal from the Commission and in co-operation with the European Agency for the Evaluation of Medicinal Products and the interested parties, an Orphan Medicinal Product Innovation Promotion Fund shall be set up, to be administered by the EMEA. The fund shall be set up by means of the proceeds from the sale of orphan medicinal products following the expiry of the ten-year period of market exclusivity referred to in Article 8 (1). The running of the fund shall be supervised by the Commission. The revenue obtained shall be used in a similar way to the budget headings relating to EU investment programmes.* [4]

The reason to insist in the establishment of such a fund is that the Orphan Drug phenomenon is caused by a lack of commercial interest in developing products to treat rare diseases. Private operators would not normally expect sufficient return on their research and development investments. Therefore any Orphan Drug policy implies significant public funding in the general interest of public health. The costs of rare diseases are enormous both in monetary and human terms. The medical expenses for treating some rare disorders may reach the hundreds-of-thousand-dollar range per year. The human costs of rare diseases may be even greater: patients with rare diseases often are severely handicapped people, and suffer a loss of educational and employment opportunities. [5]

Another accepted modification was my amendment to article 4(1) *a Committee for Orphan Medicinal Products, is hereby set up within the European Agency.*

Another accepted amendment was related to the information provided by the sponsor. It was also admitted that the transfer of the designation of an orphan medicinal product should be submitted to specific requirements. It was also necessary to introduce a reference to clinical-trials: *assistance in the development of a protocol for pre-clinical trials during the development phase and for the follow up of clinical investigations.* [6]

[4] Profesor Valverde's amendmend, was included in Mr. Cabrol report but lately dropped by the Commission.

[5] Arrigo Schieppatti. Perpective from Science. A Clinical Research Center for Rare Diseases. European Conference on Orphan Drugs/Rare Diseases. Advanced Biotechnology Center. Genoa. Italy. October 1 and 2, 1998.

[6] Article 6(2) a of the Commission's new proposal.

Another accepted amendment referred to the status of Committee members. The amendment intended to avoid the release of confidential data. Finally, it was necessary to stress the importance of some technical terms: The Commission should adopt definitions of similar medicinal product and of clinical superiority.

4. The new Commission's proposal

The Commission did not accept the EP amendments that sought to give the EP the right to select the members of the COMP, as well as that which sought to strengthen the financial contribution of the European Agency for the Evaluation of Medicinal Products in view of its new tasks. The Commission rejected the idea of the creation of a fund to promote innovation in orphan medicines, which would be managed by the Agency and established using the income from the sale of orphan medicines.

5. State of the procedure and final remarks

The Commission's new proposal was adopted by the European Parliament in second reading, at its plenary session, last December in Strasbourg, by the co-decision procedure laid down in Article 251 of the Treaty establishing the European Community. Madam Grossetête (EEP) substituted Mr. Cabrol as responsible of the European Parliament's report.

After the adoption of the Regulation it is be very important that the individual Member States commit themselves to promoting national action programmes, in connection with European initiatives, in order to foster the true availability of these medicinal products.

A promotional tool already used in the US entails tax credits covering a percentage of certified clinical research expenses supported for a particular rare disease. At a European level, it could be foreseen to establish tax credits at a national level equal to 50% of the costs sustained for clinical trials performed on an orphan medicinal product.

Attention to patients and their representatives should be the key element of the whole European policy on Orphan Drugs and Rare Diseases.

Another key issue is the support of research efforts in order to clarify the mechanisms of single rare diseases for the implementation of clinical studies that are abbreviated but predictive of the efficacy of the treatment.

It is still necessary to constitute a special fund for the research on rare diseases addressed to the study of pathogenic mechanisms and to the definition of more rapid and more predictive models for clinical trials. This fund already exists in the United States and, taking account of the success of the American Orphan Drugs Act, I do not see why should Europe do without this valuable tool.

But this is not enough. International legislation at a European level will be useless if national action plans are not implemented in accordance with the objectives of the European Action Programme for rare diseases.

Problematic seems the criterion, which says: . . . *the price charged for the medicinal product concerned is such that if allows the earning of an unreasonable profit.* [7] In the light of the already existing price and profit control systems established in most of the Member States, we do not see any need for this provision. It just makes the regulation more difficult to handle and it will create problems: what is an unreasonable profit? Who defines it? How is it controlled and by whom?

Finally, the draft regulation remains silent on two ways to accelerate the bringing to the market of orphan drugs: a fast track procedure and simplified requirements.

It should be underlined that the one and only aim for this regulation is to encourage companies to invest resources into R & D of orphan drugs through the provision of incentives. The additional amount of R & D investment and the number of novel orphan drugs introduced will measure quality of the regulation. The attractivity of the incentives decides on the success of the regulation.

I sincerely thank the authors participating in this new issue of Pharmaceuticals, Policy and Law. I specially thank Ms. Françoise Grossetête, European's Parliament rapporteur for this regulation, to explain the role of the European Parliament in this important new legislation. I also thank Ms. Emer Cooke, in charge of the Orphan Medicinal Products department at the European Commission's Pharmaceuticals and Cosmetics Unit, for having co-ordinated this issue and invited some of the world's leading experts on the matter such as FDA's Director of the Office of Orphan Products Development, Ms. Marlene Haffner, Japan's MHW Mr. Mamoru Narukawa, and EMEA's Mr. Patrick Le Courtois. I would finally like to express my recognition and gratitude to Mr. Erik Tambuyzer and Mr. Patrick Capri for analysing the issue from an industrial perspective; to Mr. Andrea Rapaggliosi for covering the implications of this legislation for the patients; to Mr. Giampiero De Luca for studying how the "market exclusivity" provision resulting from this new legislation and the "patent exclusivity" resulting from the traditional patent system affect each other; and last but not least, Dr. Torrent, Chairman, COMP/EMEA, to foresee the future developments of the Committee on Orphan Drugs.

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Editor-in-Chief

[7] Article 8 (2) of the Commission's Proposal.