II

(Preparatory Acts)

COMMISSION

Amended proposal for a European Parliament and Council Regulation on orphan medicinal products (1)

(2000/C 177 E/01)

COM(1999) 298 final — 98/0240(COD)

(Submitted by the Commission pursuant to Article 250(2) of the EC-Treaty 16 June 1999)


INITIAL PROPOSAL

The European Parliament and the Council of the European Union,

Having regard to the Treaty establishing the European Community, and in particular Article 100A thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the Economic and Social Committee,

Acting in accordance with the procedure laid down in Article 189 B of the EC Treaty,

(1) Whereas some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; whereas the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; whereas these medicinal products are therefore called ‘orphan’;

(2) Whereas patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; whereas it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; whereas incentives for the development of orphan medicinal products have been available in the United States since 1983 and in Japan since 1993;

(3) Whereas, in the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; whereas such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources; whereas action at Community level is preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Community trade;

AMENDED PROPOSAL

Unchanged

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Unchanged

Acting in accordance with the procedure laid down in Article 251 of the EC Treaty,

Unchanged
(4) Whereas orphan medicinal products eligible for incentives should be easily and unequivocally identified; whereas it seems most appropriate to achieve this result through the establishment of an open and transparent Community procedure for the designation of potential medicinal products as orphan medicinal products;

(5) Whereas objective criteria for designation should be established: whereas these criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; whereas a prevalence of no more than five affected persons per ten thousand is generally regarded as the appropriate threshold; whereas medicinal products intended for a life-threatening, seriously debilitating or seriously debilitating communicable condition should be eligible even when the prevalence is higher than five per ten thousand;

(6) Whereas a Committee composed of experts appointed by the Member States should be established to examine applications for designation; whereas this Committee should in addition include three representatives of patients’ associations, to be designated by the Commission, and three other persons, also designated by the Commission, on a recommendation from the Agency; whereas the Agency should be responsible for the adequate coordination between the Committee on orphan medicinal products and the Committee on proprietary medicinal products;

(7) Whereas patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; whereas orphan medicinal products should therefore be submitted to the normal evaluation process; whereas sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; whereas, in order to facilitate the granting of a Community authorisation, fee to be paid to the Agency should be waived at least in part; whereas the Community budget should compensate the Agency for the loss in revenue thus occurred;

(8) Whereas experience in the United States and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is the prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; whereas data protection under Article 4(8)(a)(iii) of Council Directive 65/65 is not sufficient incentive for that purpose; whereas market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained; whereas, in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal which is safer, more effective or otherwise clinically superior;
whereas market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights; whereas, in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal which could be of significant benefit to those affected by the condition;

(9) Whereas sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of any incentives granted by the Community or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases;

(10) Whereas the specific programme Biomed 2, of the Fourth Framework Programme for research and technological development (1994-1998), supported research on the treatment of rare diseases, including methodologies for rapid schemes for the development of orphan medicinal products and inventories of available orphan medicinal in Europe; whereas these grants were to promote the establishment of cross national cooperation in order to implement basic and clinical research on rare diseases; whereas research on rare diseases continues to be a priority for the Community, as it has been included in the Commission's Fifth Framework Programme (1998-2002) for research and technological development; whereas this Regulation establishes a legal framework which will allow the swift and effective implementation of the outcome of this research;

(11) Whereas rare diseases have been identified as a priority area for Community action within the framework for action in the field of public health (COM(93) 559 final); whereas the Commission, in its communication concerning a programme of Community action on rare diseases within the framework for action in the field of public health (COM(97) 225 final) has decided to give rare diseases priority within the public health framework; whereas the Commission has proposed a European Parliament and Council Decision adopting a programme of Community action 1999-2003 on rare diseases in the context of the framework for action in the field of public, including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations; whereas this Regulation carries out one of the priorities laid down in this programme of action.
Article 1

Purpose

The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and bringing to the market of designated orphan medicinal products.

Article 2

Scope and definitions

For the purpose of this Regulation:

— medicinal product means a medicinal product for human use, as defined in Article 2 of Directive 65/65/EEC,

— orphan medicinal product means a medicinal product designated under the terms and conditions of this Regulation,

— sponsor means any legal or natural person, established in the Community, seeking to obtain the designation of a medicinal product as orphan medicinal product,

— Agency means the European Agency for the Evaluation of Medicinal Products.

Article 3

Criteria for designation

1. A medicinal product shall be designated as orphan medicinal product if its 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 persons in the Community at the time that the application is made and that there exists no satisfactory method of diagnosis, prevention or treatment of the considered condition that has been authorised 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.

2. Notwithstanding paragraph 1, a medicinal product may also be designated as orphan medicinal product if its sponsor can establish that the medicinal product is intended for a life-threatening, or seriously debilitating communicable condition in the Community and that it is unlikely that, without incentives, the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.

1. A medicinal product shall be designated as orphan medicinal product if its 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 persons in the Community at the time that the application is made and that there exists no satisfactory method of diagnosis, prevention or treatment of the considered condition 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 the condition.

2. Notwithstanding paragraph 1, a medicinal product may also be designated as orphan medicinal product if its sponsor can establish that the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or a serious and chronic condition in the Community and that it is unlikely that, without incentives, the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.
### Article 4

**Committee for Orphan Medicinal Products**

1. A Committee for Orphan Medicinal Products, hereinafter referred to as ‘the Committee’, is hereby set up within the European Agency for the Evaluation of Medicinal Products.

2. The task of the Committee shall be:

   (a) to examine any application for designation of a medicinal product as orphan medicinal product which is submitted to it in accordance with this Regulation,

   (b) upon request, to advise the Commission on the establishment and development of an orphan medicinal product policy for the European Union,

   (c) to assist the Commission in international liaison on matters relating to orphan medicinal products, particularly the United States and Japan, and in liaisons with patients support groups.

3. The Committee shall consist of one member nominated by each Member State, three members nominated by the Commission to represent patient organisations and three members nominated by the Commission on the basis of a recommendation from the Agency. The members of the Committee shall be appointed for a term of three years which shall be renewable. Where necessary they may seek the assistance of an expert.

4. The Committee shall elect its Chairman for a term of three years, renewable once.

5. The representatives of the Commission and the Executive Director of the Agency or his representative may attend all meetings of the Committee.

6. The Agency shall provide the Secretariat of the Committee.

7. Members of the Committee shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

### Article 5

**Procedure for designation**

1. In order to obtain the designation of a medicinal product as orphan medicinal product, the sponsor shall submit, an application to the Agency.
2. The application shall be accompanied by the following particulars and documents:

(a) name or corporate name and permanent address of the sponsor,

(b) proposed therapeutic indication,

(d) the justification that Article 3 paragraph 1 or 2 is applicable.

3. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidance on the format and content in which applications for designation are to be presented.

4. The Agency shall verify the validity of the application and prepare a summary report to the Committee. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application.

5. The Agency shall ensure that an opinion is given by the Committee within 60 days of the receipt of a valid application.

6. When preparing its opinion, the Committee shall use its best endeavours to reach a consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members. The opinion may be obtained by written procedure.

7. Where the opinion of the Committee is that the application does not satisfy the criteria set out in Article 3 paragraph 1, the Agency shall forthwith inform the sponsor. Within 30 days of receipt of the opinion, the sponsor may submit detailed grounds for appeal, which the Agency shall refer to the Committee. The Committee shall consider whether its opinion should be revised at the following meeting.

8. The Agency shall forthwith forward the final opinion of the Committee to the Commission, which shall adopt a decision within 30 days of receipt of the opinion. Where, exceptionally, the draft decision is not in accordance with the opinion of the Committee, the decision shall be adopted in accordance with the procedure laid down in Article 72 of Regulation (EEC) No 2309/93. The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.

9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.
10. Each year the sponsor shall provide the Agency with a report on the state of development of the designated medicinal product.

11. In order to secure the transfer to another sponsor of the designation of an orphan medicinal product, the holder of that designation shall submit a specific application to the Agency. In consultation with the Member States, the Agency and the interested parties, the Commission shall draw up detailed guidance concerning the form in which transfer applications must be submitted and also the contents of such applications.

**Article 6**

**Protocol assistance**

1. The sponsor of an orphan medicinal product may, prior to the submission of an application for marketing authorisation, 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.

2. The Agency shall draw up a procedure on the development of orphan medicinal products, which shall cover in particular:

(a) assistance in the development of a protocol and for the follow up of clinical investigations;

(b) regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of Council Regulation (EEC) No 2309/93.

**Article 7**

**Community marketing authorisation**

1. The person responsible for placing on the market an orphan medicinal product may request that authorisation to place the medicinal product on the market be granted by the Community in accordance with the provisions of Regulation (EEC) No 2309/93 without having to justify that the medicinal product qualifies under any part of the Annex to that Regulation.

2. A special contribution from the Community, distinct from that provided for in Article 57 of Regulation (EEC) No 2309/93, will be allocated every year to the Agency. This contribution will be used exclusively by the Agency to waive, in part or in total, the fees payable under Community rules adopted pursuant to Regulation (EEC) No 2309/93. A detailed report of the use made of this special contribution shall be presented by the Executive Director of the Agency at the end of each year. Any surplus occurring in a given year shall be carried forward and deducted from the special contribution for the following year.
3. The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. This is without prejudice to the possibility to apply for a separate marketing authorisation for other indications outside the scope of this Regulation.

Article 8

Market exclusivity

1. Where a marketing authorisation is granted pursuant to Regulation (EEC) No 2309/93 in respect of an orphan medicinal product the Community and the Member States shall not, for a period of ten years, accept another application for a marketing authorisation, nor grant a marketing authorisation or extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

2. This period may however be reduced to six years if, at the end of the fifth year, a Member State can establish that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned or that the price charged for the medicinal product concerned is such that it allows the earning of an unreasonable profit. To this end, the Member State shall initiate the procedure laid down in Article 5.

3. By derogation to paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

(a) the holder of the marketing authorisation of the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation of the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

4. At the end of the period of market exclusivity, the orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products.
5. For the purpose of this Article, a 'similar medicinal product' means one which consists of:

- the same chemical active substance or active moiety of the substance, including isomers and mixture of isomers, complexes, esters, other non-covalent derivatives, provided that the pharmacological and toxicological activities of the latter are qualitatively and quantitatively identical to those of the original product,

- a substance with the same biological activity (including those that differ from the original substance in molecular structure, source material and/or manufacturing process) provided that the pharmacological activity of said substance is qualitatively and quantitatively identical to that of the original product,

- a substance with the same radiopharmaceutical activity (including those with a different radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism) provided that its diagnostic or therapeutic indications are identical to those of the original product.

6. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidance for the application of this Article.

---

Article 9

Other incentives

1. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support the research, development and availability of orphan medicinal.

2. Within six months of the adoption of this Regulation, the Member States shall communicate to the Commission detailed information about the measures they have enacted to support the research, development and availability of orphan medicinal products. This information shall be updated on a regular basis.

3. Member States shall also consider waiving, in part or in total, the fees to be paid in respect of applications to place orphan medicinal products on the market.

Deleted
4. Within one year from the adoption of this Regulation, the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support the research, development and availability of orphan medicinal products. This inventory will be updated on a regular basis.

3. Within one year from the adoption of this Regulation, the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support the research, development and availability of orphan medicinal products. This inventory will be updated on a regular basis.

**Article 10**

**General report**

Within six years of the entry into force of this Regulation, the Commission shall publish a general report on the experience acquired as a result of the application of this Regulation.

**Article 11**

**Entry into force**

This Regulation shall enter into force on the thirtieth day following its publication in the *Official Journal of the European Communities*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.