►B REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 1999

on orphan medicinal products

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REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 1999

on orphan medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission ([1]),

Having regard to the opinion of the Economic and Social Committee ([2]),

Acting in accordance with the procedure laid down in Article 251 of the Treaty ([3]),

Whereas:

(1) 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; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called ‘orphan’;

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

(3) 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; 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; 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;

(4) orphan medicinal products eligible for incentives should be easily and unequivocally identified; 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) objective criteria for designation should be established; those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or

([1]) OJ C 276, 4.9.1998, p. 7.
([2]) OJ C 101, 12.4.1999, p. 37.
([3]) Opinion of the European Parliament of 9 March 1999 (OJ C 175, 21.6.1999, p. 61), Council Common Position of 27 September 1999 (OJ C 317, 4.11.1999, p. 34) and Decision of the European Parliament of 15 December 1999 (not yet published in the Official Journal).

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serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand;

(6) a Committee composed of experts appointed by the Member States should be established to examine applications for designation; this Committee should also include three representatives of patients' associations, designated by the Commission, and three other persons, also designated by the Commission, on a recommendation from the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as 'the Agency'); the Agency should be responsible for the adequate coordination between the Committee on orphan medicinal products and the Committee on proprietary medicinal products;

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

(8) experience in the United States of America and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; data protection under Article 4(8)(a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products ([1]) is not a sufficient incentive for that purpose; Member States acting independently cannot introduce such a measure without a Community dimension as such a provision would be contradictory to Directive 65/65/EEC; if such measures were adopted in an uncoordinated manner by the Member States, this would create obstacles to intra-Community trade, leading to distortions of competition and running counter to the single market; 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; in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition;

(9) 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) the specific programme Biomed 2, of the fourth framework programme for research and technological development (1994 to 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 products in Europe; those grants were intended to promote the establishment of cross national cooperation in order to implement basic and clinical research on rare diseases; research on rare diseases continues to be a priority for the Community, as it has been included in the fifth framework

([1]) OJ 22, 9.2.1965, p. 369. Directive as last amended by Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).

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programme for research and technological development (1998 to 2002); this Regulation establishes a legal framework which will allow the swift and effective implementation of the outcome of this research;

(11) rare diseases have been identified as a priority area for Community action within the framework for action in the field of public health; 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 has decided to give rare diseases priority within the public health framework; the European Parliament and the Council have adopted Decision No 1295/1999/EC of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003) ([1]), including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations; this Regulation implements one of the priorities laid down in this programme of action,

HAVE ADOPTED THIS REGULATION:

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 placing on the market of designated orphan medicinal products.

Article 2

Definitions

For the purposes of this Regulation:

(a) 'medicinal product' means a medicinal product for human use, as defined in Article 2 of Directive 65/65/EEC;

(b) 'orphan medicinal product' means a medicinal product designated as such under the terms and conditions of this Regulation;

(c) 'sponsor' means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product;

(d) 'Agency' means the European Agency for the Evaluation of Medicinal Products.

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is

([1]) OJ L 155, 22.6.1999, p. 1.

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unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question 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 that condition.

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2. The Commission shall, in accordance with the regulatory procedure referred to in Article 10a(2), adopt the necessary provisions for implementing paragraph 1 of this Article in the form of an implementing Regulation.

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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 Agency.

2. The task of the Committee shall be:

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

(b) to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union;

(c) to assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;

(d) to assist the Commission in drawing up detailed guidelines.

3. The Committee shall consist of one member nominated by each Member State, three members nominated by the Commission to represent patients' 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. They may be accompanied by experts.

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 any information of the kind covered by the obligation of professional secrecy.

Article 5

Procedure for designation and removal from the register

1. In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation is made.

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2. The application shall be accompanied by the following particulars and documents:

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

(b) active ingredients of the medicinal product;

(c) proposed therapeutic indication;

(d) justification that the criteria laid down in Article 3(1) are met and a description of the stage of development, including the indications expected.

3. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidelines on the required format and content of applications for designation.

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 90 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 be adopted by a majority of two-thirds of the members of the Committee. 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(1), the Agency shall forthwith inform the sponsor. Within 90 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.

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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, in exceptional circumstances, the draft decision is not in accordance with the opinion of the Committee, the decision shall be adopted in accordance with the regulatory procedure referred to in Article 10a(2). The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.

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9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.

10. Each year the sponsor shall submit to the Agency a report on the state of development of the designated medicinal product.

11. To have the designation of an orphan medicinal product transferred to another sponsor, the holder of the designation shall make specific application to the Agency. In consultation with the Member States, the Agency and interested parties, the Commission shall draw up detailed guidelines on the form in which applications for transfer shall be made and the content of such applications and all the particulars of the new sponsor.

12. A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products:

(a) at the request of the sponsor;

(b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned;

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(c) at the end of the period of market exclusivity as laid down in Article 8.

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, in accordance with Article 51(j) of Regulation (EEC) No 2309/93.

2. The Agency shall draw up a procedure on the development of orphan medicinal products, covering regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of 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 Part B 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, shall be allocated every year to the Agency. The contribution shall be used exclusively by the Agency to waive, in part or in total, all 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 of applying for a separate marketing authorisation for other indications outside the scope of this Regulation.

Article 8

Market exclusivity

1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products ([1]), and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing

([1]) OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).

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authorisation or accept an application to 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, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.

3. By way of derogation from 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 for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for 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.

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4. The Commission shall adopt definitions of 'similar medicinal product' and 'clinical superiority' in the form of an implementing Regulation.

Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 10a(3).

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

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 research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.

2. Before 22 July 2000, the Member States shall communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. That information shall be updated regularly.

3. Before 22 January 2001, the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support research into, and the development and availability of, orphan medicinal products. That inventory shall be updated regularly.

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Article 10

General report

Before 22 January 2006, the Commission shall publish a general report on the experience acquired as a result of the application of this Regulation, together with an account of the public health benefits which have been obtained.

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Article 10a

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, referred to in Article 121(1) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use ([1]).

2. Where reference is made to this paragraph, Articles 5 and 7 of Council Decision 1999/468/EC ([2]) shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

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Article 11

Entry into force

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

It shall apply as from the date of adoption of the implementing Regulations provided for in Article 3(2) and Article 8(4).

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

([1]) OJ L 311, 28.11.2001, p. 67.
([2]) OJ L 184, 17.7.1999, p. 23.