COMMISSION OF THE EUROPEAN COMMUNITIES

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Proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products

(presented by the Commission)

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EXPLANATORY MEMORANDUM

In recent decades, medicine and medical research have made remarkable progress in saving lives, extending life expectancy and ridding the world of a number of diseases. The most spectacular successes of all have been in the use of vaccines to prevent childhood illnesses, in the use of antibiotics to combat infectious diseases and in the development of anti-viral medicinal products for the diagnosis, prevention or treatment of AIDS. Great strides have also been made in the diagnosis, prevention or treatment of cancer and cardiovascular diseases.

Nevertheless, there are still a great many diseases which cannot be treated satisfactorily and for which no medication or other diagnosis, prevention or treatment is available. In addition to the widespread and well-known diseases of this kind, there is also a whole series of diseases which affect relatively few people; approximately 5 000 such diseases have been identified. The pharmaceutical industry is reluctant to develop medicinal products to treat these diseases: pharmaceutical research and development are so expensive nowadays that there is practically no chance of any company making the effort to develop a medicinal product, to obtain authorisation for its use and to place it on the market if it is to be supplied at normal prices to the few patients who require it. That is why such medicinal products are known as "orphan medicinal products".

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. All designated orphan products are eligible for a federal tax credit equal to 50 % of the clinical research expenditure; orphan products are exempted from the application fee for FDA approval, and the first product authorised for a specific indication gets a seven-year marketing exclusivity period. Congress also appropriates around $ 20 million for FDA for grants for orphan products. Over the last 13 years 837 medicinal products have been awarded the status of orphan drug, of which 323 have been aided by the grants program. 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 seek to emulate it. A similar regime was introduced in Japan in 1995, in Singapore in 1997 and in Australia in 1998.

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 and to improve their detection, diagnosis, prevention or treatment. In some cases, the relevant legislation or administrative provisions include a reference to the concept of "orphan drug" or

"uneconomic drug". These initiatives, however, are few and far between and have certainly not led to any significant progress in research on rare diseases.

At Community level, the fourth Framework Programme for research and technological development (1994-98), and in particular the "Biomedicine and Health" programme (Biomed 2), covers research on the development of orphan medicinal and supports fundamental, clinical and epidemiological research on rare diseases.

Rare diseases have further been identified as a priority area for Community action within the framework for action in the field of public health (COM(93) 559 final and COM(97) 225 final). The Commission has recently 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.

Experience in the United States and Japan clearly shows that the key element in an effective policy of support for orphan medicinal products research and development is the creation of an official system for recognising orphan medicinal products and granting exclusive marketing rights for a sufficient period of time from the date when the medicinal product is actually placed on the market.

JUSTIFICATION

Objective

The aim of this proposal is to establish a Community procedure for designating orphan medicinal products and to introduce incentives for orphan medicinal products research, development and marketing, in particular by granting exclusive marketing rights for a ten year period.

This proposal falls within a context of the completion of the internal market and is featured in the Commission's work programme for 1997.

Legal basis and procedure

The proposal establishes harmonised criteria and a Community procedure for designating orphan medicinal products; it provides access to the Community market, via the centralised authorisation procedure, for the medicinal products thus designated and confers upon them exclusive marketing rights throughout the Community for a ten year period.

Article 100a of the EC Treaty constitutes the appropriate legal basis for such a scheme. The importance of the 'market exclusivity' provision as an incentive to the success of this measure has been reinforced by the experience in the United States and Japan, and confirmed in consultations with Member States and industry. Clearly, Member States acting independently cannot introduce this measure without a Community dimension as such provision would be contradictory to Directive 65/65/EEC. Equally, 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 run contrary to a single market..

Since this proposal concerns health, a high level of health protection must be provided for, in accordance with Article 100a(3). This means, in particular, that the market exclusivity granted to an orphan medicinal product when it is authorised by the Community can be withdrawn if the criteria for designation are no longer met or if the price charged for the medicinal product concerned is such that it allows the earning of an unreasonable profit . Moreover, a second authorisation may be granted if the holder of the authorisation is unable to supply a sufficient quantity of the medicinal product or if another medicinal product proves safer, more effective or clinically superior to the one enjoying exclusive marketing rights.

Subsidiarity and proportionality

As pointed out in the Council Resolution of 20 December 1995 on orphan medicinal products (OJ C 350, 30.12.1995, p. 3), "a common European approach to rare diseases and orphan medicinal products holds out advantages in epidemiological, public health and economic terms".

As stated above, the problem of orphan medicinal products has to do with the small number of patients concerned and the low commercial interest of the medication developed to treat them. A common and concerted Community approach is clearly more likely to help solve this problem than isolated national initiatives.

Furthermore, Community action allows the best possible use of the instruments set up in the pharmaceutical sector to complete the internal market, and in particular the European Agency for the Evaluation of Medicinal Products and the Community procedure for authorising the marketing of medicinal products, as established by Regulation (EEC) No 2309/93.

Member States should not, however, be prevented from playing their part in promoting research and development work on orphan medicinal products. Accordingly, this proposal provides for medicinal products designated as orphan medicinal products to be covered by the Community procedure for the authorisation to place medicinal products on the market, but it does not rule out the use of national procedures, particularly with regard to mutual recognition, where these are considered more appropriate by the operators concerned. Furthermore, the proposal invites the Member States to introduce incentives for research and development work on orphan medicinal products and for placing such products on the market, within the framework of their own powers and responsibilities.

Legislative and administrative simplification

The type of legislation proposed is a Regulation. This instrument does not have to be transposed into the Member States' national legislation and is well suited to introducing a Community procedure for designating orphan medicinal products and for creating exclusive marketing rights.

A simple and swift procedure is laid down for designating orphan medicinal products, making use of the existing structures: the European Agency for the Evaluation of Medicinal Products and the Standing Committee on Medicinal Products for Human Use

(whose opinion is, however, required only where the Commission's proposal differs from the Agency's opinion).

This proposal for a Regulation establishes the general legal framework. Where more detailed administrative provisions are required, it is proposed that they be adopted by the Commission as guidelines, in consultation with the Member States, the Agency and the parties concerned. This is the normal way of proceeding in the pharmaceutical sector.

Consistency with other Community policies

The accompanying proposal was announced in the Commission's Communication of 26 May 1997 concerning a *Programme of Community action on rare diseases within the framework for action in the field of public health* (COM(97)225 final). The main criterion for designating an orphan medicinal product within the meaning of the accompanying proposal is similar to the definition given as a guide in the proposed Programme for the concept of "rare diseases", i.e. diseases with a prevalence in the Community population of less than 5 per 10 000.

The proposal also extends the work being carried out under the *Fourth Framework Programme for Research and Technological Development (1994-1998)*: the Biomedicine and Health Programme (Biomed 2) includes an area entitled "Research on rare diseases" which covers research and development work on orphan medicinal products and supports fundamental and clinical research on rare diseases.

Finally, this proposal follows up the *Communication from the Commission on the outlines of an industrial policy for the pharmaceutical sector* (COM(93)718 final). The introduction of incentives for R&D work on orphan medicinal products contributes towards the objective of support for innovation and towards the creation of a stable and foreseeable legislative environment for pharmaceutical research in the European Union.

Outside consultation

Interested parties have been widely consulted on this proposal. In February 1995, a group of experts consisting of civil servants, academics and representatives of the pharmaceuticals industry and patients' associations met in Brussels to consider the results of a study which had been carried out for the Commission and to draw from it the necessary conclusions.

In December 1995, the Council adopted a Resolution calling on the Commission to study the situation with regard to orphan medicinal products in Europe and to make any appropriate proposals for improving access to medicinal products intended, in particular, for persons suffering from rare diseases.

In August 1996, Commission staff distributed to the interested parties a preliminary draft proposal for a Regulation on orphan medicinal products. This was discussed at two meetings of a working group of the Pharmaceutical Committee. It was also expounded and discussed at a number of public meetings, notably within the context of the European Parliament's Intergroup on Pharmaceutical Products.

Following these consultations, an amended preliminary draft was prepared in December 1996. This new preliminary draft received widespread support, in particular from associations of persons suffering from rare diseases. Moreover, in March 1997,

these associations set up a European umbrella organisation (EURORDIS), one of whose main objectives is to promote the swift adoption of European legislation on orphan medicinal products.

Evaluation

A number of evaluation mechanisms are included in this proposal.

Essentially, these mechanisms relate to the ten-year period of exclusive marketing rights, which provides the main incentive for R&D work on orphan medicinal. The exclusive marketing rights constitute a particularly sensitive instrument which should be surrounded with appropriate safeguards. That is why the proposal lays down that the exclusive rights may be withdrawn at the end of the sixth year 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 orphan medicinal product no longer apply or that the price charged for the medicinal product concerned is such that it allows the earning of an unreasonable profit. Moreover, a derogation may be granted at any time either because the holder of the exclusive authorisation cannot supply a sufficient quantity of the medicinal product or because another medicinal product has been shown to be safer, more effective or clinically superior to the product which has been enjoying exclusive rights.

The proposal also provides that the Commission should assess the application of the system six years after it had been introduced and should, within this period, publish a report on the experience acquired.

Impact on firms

This proposal will benefit all firms engaged in pharmaceutical research and development, regardless of their size, location or sphere of activity.

It should, however, be noted that in the United States - where a similar system to that being proposed has been operating for more than 12 years - most applications for the designation of orphan medicinal products are filed by small firms specialising in biotechnology and genetic engineering (since the vast majority of rare diseases are developmental disorders of a genetic or other kind).

No changes in the industrial sector will result from the adoption of this proposal, since it provides for an incentive system which firms are clearly at liberty to ignore.

The proposal should stimulate pharmaceutical research and development within the Community, and this can only have a positive effect in terms of job creation (in particular highly-qualified jobs), investment and the creation of new firms.

There is no particular provision relating to small and medium-sized enterprises.

PRESENTATION

Scope

The proposed system covers medicinal products for human use within the meaning of Directive 65/65/EEC. This includes any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or for treating or preventing a disease. It should be noted, in particular, that vaccines are thus covered.

This definition excludes medical devices and nutrition supplements. This does not mean that these products can play no role in the diagnosis, prevention or treatment of rare diseases. However, the incentive arrangement introduced by this proposal can be applied, by means of its own mechanism, only to medicinal products which are covered by the marketing authorisation system.

Medicines for veterinary use are also excluded, as will readily be understood from the aim of the proposal. Although a similar problem arises in the field of animal health, particularly with regard to "minor species", it cannot be dealt with in the context of this proposal.

Designation criteria

It is generally accepted that two types of criteria can be used for the designation of orphan medicinal products: epidemiological criteria (the prevalence or incidence of the disease concerned within a given population) and economic criteria (the presumption that the medicinal product to be used for treating the disease concerned is not commercially viable). These two types of criteria are not necessarily mutually exclusive and may therefore be combined where appropriate.

Epidemiological criteria present clear advantages as they are much better suited than economic criteria to an objective evaluation at the time of designation. Assessing whether it will be possible to obtain a reasonable return on the investment needed to develop a medicinal product many years before it is actually placed on the market obviously involves a good deal of speculation.

In the United States, an economic criterion was used initially (Orphan Drug Act 1983): it had to be established that the costs of developing the medicinal product and supplying it to the general public could not reasonably be expected to be covered by sales of the medicinal product in the United States. This system, however, proved unsuccessful and Congress amended it in 1984 by adding a concurrent epidemiological criterion: designation may now be obtained by showing either that the condition in question affects fewer than 200 000 persons or that the development costs cannot reasonably be expected to be covered. All designations obtained between 1984 and 1992 in the United States were awarded on the basis of the epidemiological criterion alone.

The only objection sometimes raised to the use of epidemiological criteria is based on the observation that some of the medicinal products designated as orphan drugs in the United

States have subsequently proved to be (extremely) profitable. Such cases, however, are very rare (approximately 1% of all designations!), which suggests that the epidemiological criterion used in the United States does indeed enable appropriate candidates to be selected for designation.

It is therefore proposed that an epidemiological criterion, based on prevalence, be used initially. In the above-mentioned Communication concerning a programme of Community action on rare diseases, the Commission has proposed to define rare diseases as life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them so as to prevent significant prenatal and early morbidity and mortality or a considerable reduction in an individual's quality of life or socio-economic potential; it is further indicated that, as a guide, low prevalence can be understood as meaning a prevalence in the total Community population of less than 5 per 10 000. For the sake of consistency, the same prevalence is proposed in the accompanying proposal. It should be noted that this ratio is lower than that used in the United States (7.5 per 10 000) and slightly greater than that used in Japan (4 per 10 000). Prevalence is established within the Community so that medicinal products intended for preventing or treating diseases which are very widespread in the Third World (tropical diseases, for example) but uncommon in Europe will benefit from the new system.

It also appears desirable to encourage research and development work on medicinal products for the diagnosis, prevention or treatment of certain conditions which, while not exactly fitting into the category of rare diseases, have hitherto not benefited sufficiently from medical progress, namely life-threatening or chronically debilitating communicable diseases. These medicinal products should be awarded the status of orphan medicinal products even where prevalence of the condition exceeds 5 per 10 000, always provided it can be shown that, without the incentives provided by this status, development of these medicinal products would not be undertaken.

Finally, where it can be established that the marketing of an orphan medicinal product is proving more profitable than had been foreseen, any Member State may request that the exclusive marketing rights be withdrawn at the end of the sixth year following issue of the authorisation to place the product on the market (see below "Market exclusivity").

Committee for Orphan Medicinal Products

With regard to the evaluation of applications for designation, it seems reasonable in the first instance to use the existing structures, namely the European Agency for the Evaluation of Medicinal Products, set up under Regulation (EEC) No 2309/93, which has the necessary infrastructure and resources for carrying out this task.

The evaluation itself could, no doubt, be carried out by the Committee for Proprietary Medicinal Products - which, within the Agency, is responsible for all scientific matters relating to the evaluation of medicinal products for human use. This, however, would present a number of disadvantages. For one thing, it would confer upon one single Committee the power both to express a view on applications for designation as orphan medicinal product and, subsequently, to give opinions on applications for the authorisation to place those products on the market. Furthermore, the Committee for Proprietary Medicinal Products already has a considerable workload.

It therefore appears preferable to establish a new committee, operating within the Agency - which would provide it with a Secretariat - and consisting of persons appointed by the Member States and selected on account of their role and experience in the field of rare diseases. The committee would also have three representatives of patients' associations, to be designated by the Commission, and three persons, also appointed by the Commission, on a recommendation from the Agency, specifically to liaise with the Committee for Proprietary Medicinal Products. The setting up of such a Committee, including representatives of patients' associations, has been supported both by the Member States' representatives and in the context of the European Parliament's Intergroup on Pharmaceutical Products.

Designation procedure

The designation procedure should be flexible and rapid. Applications would be processed by the Agency Secretariat, enabling the Committee for Orphan Medicinal Products to deliver its opinion within 60 days of the Secretariat's validation of the application.

The designation of an orphan medicinal product entails important legal consequences not only for the sponsor but also for the third parties concerned and must therefore be the subject of a decision by a Community institution, in this case the Commission. The Commission would have 30 days to take this decision. Where, in exceptional circumstances, the Commission considers taking a decision which differs from the opinion of the Committee for Orphan Medicinal Products, the procedure of the Standing Committee on Medicinal Products for Human Use would be applicable (type IIIa committee procedure).

Protocol assistance

The development of an orphan medicinal product presents specific problems which must be taken into account. To take but one example, it may be difficult to find enough patients willing to take part in clinical trials for a medicinal product which might be of benefit only to a very few people.

The proposal therefore allows the sponsor the possibility of requesting the Agency's assistance in developing a protocol, in carrying out or following up clinical trials and in connection with any other matter relating to the application for an authorisation.

Community marketing authorisation

The Community marketing authorisation (issued by the Community under what is known as the "centralised procedure") is the simplest and quickest way of placing medicinal product on the market throughout the Community. Orphan medicinal products must therefore be given (easier) access to this procedure. Two measures are provided for this purpose.

First, the applicant for an authorisation relating to an orphan medicinal product should be exempted from the requirement to show that the medicinal product meets the conditions set out in the Annex to Regulation (EEC) No 2309/93. In most cases, an orphan medicinal product will indeed meet the criteria set out in that Annex, either because it has been produced by biotechnology (most rare diseases are developmental disorders of a

genetic or other kind and the diagnosis, prevention or treatment of such diseases normally calls for genetic engineering), or because the medicinal product is regarded as being of significant therapeutic importance. The simplest solution, however, is to lay down that an orphan medicinal product has full right of access to the centralised procedure.

Secondly, it must be borne in mind that access to the centralised procedure is subject to the payment of a fee to the Agency, in accordance with Regulation (EEC) No 297/95. In the case of a medicinal product whose commercial viability is doubtful, the payment of this fee may constitute a serious obstacle. Moreover, people suffering from rare diseases have the right to expect the same guarantees of quality, safety and efficiency as for any other medicinal product, and there should be no question of lowering these standards. A mechanism must therefore be set up whereby the applicant for an authorisation for an orphan medicinal product could be exempt from paying all or part of the fee while the Agency (and thus the rapporteur and experts responsible for the evaluation) would be paid for the services provided. Accordingly, it is proposed to introduce an annual contribution, from the Community budget, to be allocated specifically to exemptions from fees in the case of orphan medicinal products (see the Financial Statement).

It should be noted that, while the centralised procedure can certainly be used for orphan medicinal products, such use is not obligatory. Any such obligation would be incompatible with the aim of this proposal and with the principle of proportionality. If, for whatever reason, the sponsor of an orphan medicinal product prefers to use the decentralised procedure (mutual recognition), he must be able to do so.

Market exclusivity

Market exclusivity is unanimously regarded as crucial to any system of incentives for research and development work on orphan medicinal products.

In the accompanying proposal, market exclusivity is granted only where the medicinal product has been designated as an orphan medicinal product by the Community and where the Community has issued a marketing authorisation in respect of the medicinal product concerned.

The protection thus granted prevents the 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. It does not prevent the marketing of another product for the same indication, which would constitute an unjustified restriction on therapeutic innovation, on the rights of third parties and on patient expectations. It is certainly not easy to establish the degree of similarity between medicinal products, particularly in the case of macro-molecules (proteins) which differ only very slightly in their sequence of amino acids. Experience acquired in the United States in this field will be particularly useful in helping the Commission to draw up the necessary guidelines, in consultation with the Member States and the Agency.

It is important to note that designation alone confers neither exclusive rights nor rights of precedence. It follows that a number of sponsors may, in principle, obtain the designation of the same product/indication combination, subject to the application of other intellectual property rights which, of course, are in no way affected. In this event, the first sponsor to obtain a Community marketing authorisation for this product/indication combination will

prevent the other sponsor(s) from subsequently obtaining a Community or national authorisation for the same product/indication combination.

It is proposed to limit the duration of the exclusive right within the Community to a period of ten years (seven years in the United States). This is the same period as is granted for the protection of data relating to the test results provided by the holder of the marketing authorisation in support of his application. This period may, however, be reduced to six years at the request of a Member State if the latter can show either that the criterion or criteria used at the time of designation no longer apply (prevalence of less than 5 per 10 000 or presumed commercial non-viability of a medicinal product to be used for treating a life-threatening or chronically debilitating communicable disease) or that the holder of the marketing authorisation demands a price for the product which cannot be justified.

Although market exclusivity is very important in encouraging industrial firms to spend money on research which is of low commercial interest, it must not be allowed to run counter to the interests of patients or the requirements of public health. Accordingly, this proposal provides for a possible derogation from the exclusive marketing rights if the holder of those rights is unable to provide the medicinal product in sufficient quantities or if another applicant can show that his own version of the medicinal product is safer or more effective. These matters will also be dealt with in the above-mentioned guidelines to be published by the Commission. It should be noted that where such a derogation is granted, the market exclusivity is not actually withdrawn, and still prevents further authorisations for the same medicinal product in the same indication.

Other incentives

Market exclusivity is undoubtedly the primary incentive for a firm to develop orphan medicinal products, but it is certainly not the only one. It would be up to the Community and the Member States, within their respective spheres of competence, to provide other incentives for developing medicinal products - notably, but not exclusively, those designated as orphan medicinal products by the Community. At Community level, the main incentives will no doubt take the form of support for research. At national level, tax incentives (in particular tax credits) will provide the most effective stimulus to research.

The Commission will draw up a detailed list of all the incentives available, on the basis of information provided by the Member States.

TEXT OF THE PROPOSAL

Proposal for a European Parliament and Council Regulation (EC) 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 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 189b 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 diseases 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 ;

(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 person per ten thousand is generally regarded as the appropriate threshold ; whereas medicinal product intended for a life-threatening or seriously debilitating communicable disease 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 by reason of their experience in the research or treatment of such conditions 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 co-ordination 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, the 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 ;

(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), is supporting 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 are to promote the establishment of cross national co-operation in order to implement basic and clinical research on rare diseases; whereas research on rare diseases will continue to be a priority for the Commission, as it has been introduced in the Commission's proposal for the 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,

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 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 disease 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.

3. 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 4

Committee for Orphan Medicinal Products

1. A Committee for Orphan Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up.
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. They shall be chosen by reason of their role and experience in treatment of or research into rare diseases.
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 Agency or his representative may attend all meetings of the Committee.
6. The Agency shall provide the Secretariat of the Committee.

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) qualitative and quantitative particulars of the medicinal product,
   c) 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) N° 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.*

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) N° 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) N° 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) N° 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) N°

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) 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.*
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 products.
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.
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.

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.

FINANCIAL STATEMENT

1. TITLE OF OPERATION

Proposal for a European Parliament and Council Regulation on orphan medicinal products

2. BUDGET HEADING INVOLVED

B5-3120	Community Contribution to EMEA budget - EMEA staff and operational expenditure related to the functionning of the Committee for Orphan Medicinal Products and the provision of protocol assistance.
B5-3121	Special contribution for orphan medicinal products for the financing of fee exemptions (to be created)

3. LEGAL BASIS

Art 100a of the Treaty establishing the European Community

4. DESCRIPTION OF OPERATION

4.1 General objective

The present proposal aims at :

- establishing a Community procedure for the designation of orphan medicinal products
- setting out incentives for research, development and marketing of orphan medicinal products, in particular by the granting of a 10 year market exclusivity period.

4.2 Period covered and arrangements for renewal

The proposed Regulation has no fixed duration.

The Commission will publish, within one year from entry into force of the Regulation, a detailed inventory of all incentives made available by Community and Member States to support the research, development and availability of orphan medicinal products.

The Commission will publish within 6 years of entry into force of the Regulation a general report on experience acquired.

5. CLASSIFICATION OF EXPENDITURE OR REVENUE

NCE; NDA

6. TYPE OF EXPENDITURE OR REVENUE

Contributions from the Community will cover the following types of expenditure:

6.1 EMEA operational expenditure related to the designation of orphan medicinal products (Title 3 of EMEA budget), compensated by the basic Community contribution to the EMEA budget.

6.2 EMEA staff expenditure related to designation and protocol assistance for orphan medicinal products (Title 1 of EMEA budget), compensated by the basic Community contribution to the EMEA budget.

6.3 Fee exemptions for applications for protocol assistance and marketing authorisations (Title 3 of EMEA budget), compensated by the special Community contribution to the EMEA budget for medicinal products.

7. FINANCIAL IMPACT

The management of applications for designation, protocol assistance and marketing authorisations will result in the following expenditure on the EMEA budget.

Meetings costs at the EMEA and staff costs to be financed by the basic subsidy. Fee exemptions will be financed by a a special contribution from the Community budget.

Projections are based on the following estimated number of applications for designation and fee waivers for protocol assistance and marketing authorisations under the centralised procedure :

Projected number of applications for designation, protocol assistance and marketing authorisations for orphan medicinal products :

Year	2000	2001	2002	2003
Number	5	8	12	12

7.1 Meetings costs and staff costs to be financed by an increase of EMEA basic subsidy

A - Meeting costs

Quarterly two-days meetings of the Committee for Orphan Medicinal Products at the EMEA with interpretation.

Reimbursement of travel and accommodation expenses for 21 delegates in accordance with the rules set out by the Management Board of the Agency.

Cost per meeting (ECU) in 1998	24 000
Total annual meeting costs (4 meetings per year)	**96 000**

2000	**2001**	**2002**	**2003**
100 000	102 000	104 000	106 000

B - EMEA Staff costs

The management of designation and protocol assistance for orphan medicinal products will require the creation of a specific team within the EMEA Secretariat.

Team human resources and corresponding staff costs (in ECU at current costs)			
Position and grade	**Annual salary per staff member**	**Total team direct staff costs**	**Total team staff costs (including overheads)**
1 principal administrators (A5)	94 000	94 000	124 080
3 scientific administrators (A7)	70 000	210 000	277 200
1 administrative assistants (B3)	56 000	56 000	73 920
2 clerical assistants (C3)	45 000	90 000	118 800
Total staff costs per budget year		450 000	**594 000**

C - Total of meeting and staff costs

	2000	**2001**	**2002**	**2003**
Meetings	100 000	102 000	104 000	106 000
Staff	400 000	606 000	618 000	630 000
TOTAL	**500 000**	**708 000**	**722 000**	**736 000**

7.2 Fee exemptions to be financed by a special Community contribution to EMEA

Under article 7(5) of Council Regulation (EC) 297/95 on fees payable to the EMEA, the Executive Director may grant fee waivers or reductions to applications submitted under the centralised procedure, in exceptional circumstances and for imperative reasons of public and animal health. Fee exemptions are granted after consultation of the competent scientific committee on the basis of criteria determined by the Management Board.

The same procedure would be used for fee exemptions or reductions for applications for marketing authorisations for orphan medicinal products under the new Regulation.

On the basis of the current proposal for a Council Regulation on fees payable to the EMEA, the basic fee for a full application for a marketing authorisation would amount to ECU 200 000. The contribution for fee exemptions is based on the expected number of applications and on the assumption that, on average, fees would be reduced by half.

7.3 Overall budgetary impact

The overall impact of the proposed measures on the EMEA budget can be estimated as follows and would determine the basis for Community contributions.

Contributions would be constituted by the following :

	2000	**2001**	**2002**	**2003**
Community contribution (meeting and staff costs)	500 000	708 000	722 000	736 000
Special Community contribution for fee exemptions	500 000	800 000	1 200 000	1 200 000
Total	**1 000 000**	**1 508 000**	**1 922 000**	**1 936 000**

8. FRAUD PREVENTION MEASURE

Council Regulation (EEC) No 2309/93 provides for specific adoption and budgetary control procedures. The Management Board, composed of representatives of Member States, Parliament and Commission, is responsible for adopting the annual draft budget (Article 55). Budgetary control mechanisms are described in Article 57, including the appointment of a financial controller by the Management Board.

9. ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantitative objectives

In its Resolution of 20 December 1995 on orphan drugs (OJ no C 350, 30.12.1995), Council called for "a common European approach to rare diseases and orphan drugs" with a view to hold "advantages in epidemiological, public health and economic terms" and called on the Commission to "make appropriate proposals with a view to improving access to medicinal products intended particularly for people suffering from rare diseases".

This proposal is designed to harmonise the legislative provisions relating to orphan medicinal products and creates incentives for the research and development at Community level, without prejudice to other incentives which could made available at national level.

The proposed Regulation will in particular allow for access to EMEA resources to sponsors, and in particular :

- Scientific resources made available by Member States to the EMEA for evaluation work, notably the network of 2 000 experts covering the full range of expertise needed to ensure the highest possible quality of the Agency's scientific opinions.
- Direct access to the centralised procedure which allows for a speedy and high quality review leading to the granting of a single authorisation to market valid throughout the Community, thereby ensuring quick availability of medicinal products to patients whilst allowing sponsors a speedy return on investments.

In addition, the Regulation provides for financial and technical assistance as follows

- Following designation, possibility of fee exemptions for applications for marketing authorisations and scientific and regulatory advice, which will facilitate access to centralised procedure in particular to small and medium size enterprises ;
- Scientific/regulatory advice and protocol assistance, which will provide sponsors with the scientific and regulatory expertise available at EMEA, in particular in the follow up of clinical trials and preparation of the dossier. The close involvement of CPMP and its working parties in the process will establish a link which would eventually facilitate evaluation of the dossier should the sponsor choose to submit the application under the centralised procedure.

9.2 Grounds for the operation

The Regulation provides for efficient mechanisms and substantial incentives for research and development likely to facilitate access to European patients of medicinal products intended for rare diseases, in line with Community policy in this respect.

9.3 Monitoring and evaluation of the operation

A detailed report of the use made of the Community's special contribution will be presented by the Agency's Executive Director at the end of each year.

In addition, time for designation of orphan medicinal products, time to marketing authorisation and availability of orphan medicinal products on the European market will be assessed, particularly in comparison with the USA and Japan, as part of the EMEA's performance goals and targets monitored by the EMEA Management Board.

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