

Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products

(2003/C 178/02)

Regulation (EC) No 141/2000⁽¹⁾ of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products entered into force on 28 April 2000. It lays down a Community procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development and placing on the market of designated orphan medicinal products.

In accordance with article 3(2) of the Regulation, the Commission adopted Commission Regulation (EC) No 847/2000⁽²⁾, of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

Following the first three successful years of application of the Regulation and in response to a number of requests for interpretation and clarification, the Commission wishes to set out its position on certain matters relating to the implementation of the designation and market exclusivity provisions. These interpretations are intended to provide guidance to the European Medicines Evaluation Agency, the Member States, the pharmaceutical industry and other interested parties. Also, several clarifications are provided in order to avoid a departure from the spirit of the Regulation.

This Communication, therefore, considers points in relation to Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), and 7 (Community marketing authorisation) of the Regulation.

In addition, the Commission is obliged to draw up detailed guidelines on the application of Article 8 of Regulation (EC) No 141/2000. This obligation is met in part by section D on market exclusivity (Article 8) in this Communication.

This Communication should be read in the context of the current interpretative texts and guidance documents for the Regulation listed in Annex 1.

A. CRITERIA FOR DESIGNATION — ARTICLE 3.1

1. Products intended for the diagnosis or prevention of a condition

Article 3(1) of the Regulation states that '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 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.'

With regard to the criteria envisaged for designation of an orphan medicinal product the terms of the Regulation do not distinguish between the concepts of a medicinal product intended for the treatment of a condition and a medicinal product intended for the diagnosis or prevention of a condition (e.g. vaccines). One of the criteria to be met relates to either the number of people affected by the condition or to the fact that the return on the marketing of a medicinal product would not be expected to justify the investment in its development.

In the case of a medicinal product intended for the diagnosis or prevention of a condition, the population 'affected by' the condition may be interpreted in several ways.

If a product for the diagnosis or prevention of a condition is effective, this may result in a decrease in the population actually suffering from the disease or condition to less than five in 10 thousand persons in the European Community. The objective of the Regulation is to provide incentives for the development of orphan medicinal products where such incentives are needed. Therefore, in the case of medicinal products intended for diagnosis or prevention, the Commission considers that the prevalence calculation of those persons affected by the condition shall be based on the population to which such a product is expected to be administered on an annual basis.

For example, following successful vaccination campaigns, although the vaccinated population is very large, the prevalence of the condition in question may be very low. The prevalence calculation in these cases shall be based on the population vaccinated on an annual basis.

⁽¹⁾ OJ L 18, 22.1.2000, p. 1.

⁽²⁾ OJ L 103, 28.4.2000, p. 5.

2. Prevalence of a condition outside the Community

Article 3(1)(a) of the Regulation concerns the prevalence of a condition. It requires conditions which may be considered as orphan to affect 'not more than five in 10 thousand persons in the Community'. Since prevalence as described in the Regulation refers only to the number of persons affected within the Community, the prevalence of the disease or condition outside the Community has no influence on the interpretation of these criteria. A medicinal product intended to treat a condition which affects a large number of people in certain countries but which has a low prevalence in the European Community, is therefore eligible for designation as an orphan medicinal product with respect to the prevalence criterion, and if all other criteria are met, eligible for the benefits set out in the Regulation.

3. Satisfactory method authorised in the Community

The first alternative in Article 3(1)(b) states that the sponsor has to establish 'that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community'. In order to ensure consistency of application and to aid applicants in providing appropriate justification, it is considered important to clarify the notion of 'satisfactory' method. In this context, Commission Regulation (EC) 847/2000 asks the applicant to provide details of the 'existing methods, which may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community.'

A treatment for a particular disease or condition may be associated with certain risks. These risks are balanced against the expected benefits when considering whether to grant or refuse a marketing authorisation in accordance with the criteria of safety, quality and efficacy as laid down in Directive 2001/83/EC⁽¹⁾. A marketing authorisation is granted if the risk/benefit assessment is positive. Therefore, at the time of the grant of a marketing authorisation in accordance with EU legislation, the authorised medicinal product is considered to be a satisfactory method as referred to in Article 3(1)(b). This being the case, applicants for orphan designation should seek to show an assumption of significant benefit over any existing authorised medicinal product in accordance with the second part of paragraph Article 3(1)(b), rather than seeking to show that an existing authorised medicinal product is not a satisfactory method.

In this context, a medicinal product authorised in one Member State of the Community is generally deemed to fulfil the criteria of 'authorised in the Community'. It is not necessary for the product to have either a Community authorisation or for it to be authorised in all Member States for it to be considered as 'authorised in the Community'.

Any reference to an already authorised medicinal product can only refer to the terms of the marketing authorisation. Therefore the off-label use of an authorised medicinal product (i.e. use not in accordance with the approved Summary of Product Characteristics of the product cannot be considered as a satisfactory method for the purposes of Article 3(1)(b).

Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (e.g. surgery, medical devices) may be considered satisfactory methods if there is scientific evidence as to the value of such method(s). The assessment as to whether a particular method may be considered satisfactory shall take into account the experience with the method in question, documented results, and other factors including whether or not the method is invasive and/or requires hospitalisation.

4. Significant benefit

Article 3(1)(b) further states that in the case where a satisfactory method of diagnosis, prevention or treatment of the condition exists, the sponsor has to establish 'that the medicinal product will be of significant benefit to those affected by that condition'.

Significant benefit is defined in Commission Regulation (EC) 847/2000 as 'a clinically relevant advantage or a major contribution to patient care.' The applicant is required to establish significant benefit compared with an existing authorised medicinal product or method at the time of designation. As there may be little or no clinical experience with the orphan medicinal product in question, the justification for significant benefit is likely to be made on assumptions of benefit by the applicant. In all cases the Committee on Orphan Medicinal Products (COMP) is required to assess whether or not these assumptions are supported by available data/evidence supplied by the applicant.

In all cases the assumption of significant benefit must be justified by the applicant through the provision of evidence/data, which must be considered in the light of the particular characteristics of the condition and the existing methods. Thus different considerations such as ease of self-administration may be considered a benefit if the patient is ambulant, but may not be considered a benefit if the patient is likely to be hospitalised during treatment.

If the argument for significant benefit is based on an increase in supply/availability of the method, the sponsor must provide details of the supply/availability problem and explain why this results in the unmet needs of patients. All claims should be substantiated by qualitative and quantitative references. If the supply of existing methods is sufficient to meet patients' needs in the orphan indication an increase in supply will not be viewed as a significant benefit.

⁽¹⁾ OJ L 311, 28.11.2001, p. 67.

With respect to potential availability of the product to the Community population, a medicinal product that is authorised and available in all Member States may constitute a significant benefit compared with a similar product that is authorised in a limited number of Member States only.

Supply problems, which arise from manufacturing process limitations should be differentiated from those which arise 'artificially', e.g. due to cost limitations or health care policy. Where supply/availability problems with existing methods are of a transient nature, e.g. due to manufacturing problems, it will not be possible generally for sponsors to argue significant benefit based on supply problems unless it can be shown to be a recurring problem or a long term interruption in supply.

It should be noted that the enhancement of the pharmaceutical quality of a product in compliance with the relevant Committee on Proprietary Medicinal Products guidelines is a part of the obligation of every marketing authorisation holder and does not constitute a basis for the assumption of significant benefit in the context of orphan medicinal product designation.

In order to provide further examples for guidance, assumptions of significant benefit may be based on:

- expected benefits to a particular population sub-set, including benefits in patients resistant to the existing method,
 - a new source of an existing medicinal product which has hitherto been sourced from human blood or plasma at risk of viral or TSE transmission. The risks must be more than theoretical, e.g. if there have been documented cases of viral transmission with a plasma derived product. In any case, the inherent risks of such a new source material (e.g. recombinant, transgenic) would also have to be put in perspective for the assumption of significant benefit,
 - expectations of a clinically relevant improved safety profile. The reasons for these expectations must be justified, either by clinical experience or exceptionally by reference to the pharmacological properties of the product,
 - justification as to why more favourable and clinically relevant pharmacokinetic properties compared with the existing authorised medicinal product can be assumed,
 - where there are serious and documented difficulties with the formulation or route of administration of an authorised medicinal product, a more convenient formulation or route may be considered as a significant benefit,
 - limitation in availability of authorised product due to extreme storage conditions,
 - insufficient quantity of authorised product on the market
- due to limited source of starting materials (e.g. plasma-derived medicinal products),
 - limitation in scale of manufacturing process (e.g. fermentation),
 - long term interruption in supply of authorised product (e.g. due to manufacturing difficulties).

Finally, in view of the Community nature of the orphan designation process and the fact that by virtue of Article 8(1) the market exclusivity benefits are linked to a marketing authorisation in the entire Community, the Commission is concerned that the process should not be undermined. For example, a company obtains the designation of a medicinal product as an orphan medicinal product. It is the right of any sponsor to decide whether or not to apply for orphan designation and to decide on the route for marketing authorisation, in cases where application via the centralised procedure is not obligatory. However, different mechanisms could be used by another, second company in order to attempt to block unduly the market exclusivity from which the first company's product might benefit. For example, the second company could apply for a marketing authorisation for the same medicinal product in one Member State without prior application for designation as an orphan medicinal product. This second company could then attempt to block the authorisation of the designated orphan medicinal product on the grounds either of the presence of a satisfactory method or of failure to establish significant benefit over this same medicinal product now authorised in a single Member State.

The Commission considers that the imminent expectation of a Community authorisation as compared with the existence of a national authorisation in one or a limited number of Member States may be sufficient to maintain an assumption of significant benefit. In this situation the designated orphan medicinal product will be maintained in the register, provided that the criteria are still met.

B. PROCEDURE FOR DESIGNATION AND REMOVAL FROM THE REGISTER — ARTICLE 5

Article 5 defines the procedure for designation and removal from the register.

1. Definition of condition in the context of designation of an orphan medicinal product by the Committee on Orphan Medicinal Products

The Commission guideline ENT 6283/00 (See Annex 1) defines a condition as 'any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)'.

When considering an application for orphan designation, the Committee on Orphan Medicinal Products may take into account the available data to modify the condition under application (for example, because the Committee considers that the designatable condition is broader than the one under application). In such cases, the Committee on Orphan Medicinal Products shall grant the designation for the condition it considers suitable, provided the criteria laid down in Article 3(1) are met.

During the development of a product, the sponsor may apply to the Committee on Orphan Medicinal Products to amend the designated condition provided that the criteria for designation continue to be met.

2. Reevaluation of designation and /or removal from the Register

Article 5(12)(b) of the Regulation provides the possibility of removing a designated orphan medicinal product from the Community Register of Orphan Medicinal Products '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'.

This implies that a removal on this basis must be preceded by a re-evaluation by the Committee on Orphan Medicinal Products of the criteria laid down in Article 3. Removal in these circumstances might occur if there is evidence that the basis on which the original designation was granted has changed, in particular when the designation was based on significant benefit which included an expectation of better clinical efficacy or better safety.

2.1. Justification of continued fulfilment of the criteria by the applicant

When a sponsor submits an application for marketing authorisation for a designated orphan medicinal product, he/she shall include the information that the product concerned has been designated as an orphan medicinal product. In addition the sponsor is requested to inform the European Medicines Evaluation Agency (EMA) and to submit a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria.

The information will be assessed in parallel to the marketing authorisation assessment. In case of reasonable doubt as to whether the criteria for designation continue to be met, the sponsor may be invited to provide additional justification either orally or in writing.

2.2. Removal from the register

The responsibility for assessing the criteria for orphan designation rests solely with the Committee on Orphan Medicinal Products. The Committee on Orphan Medicinal Products is

responsible for giving a scientific opinion on initial designation. As initial designation leads to the inclusion of a medicinal product in the Community Register of Orphan Medicinal Products, it follows that, unless it is at the request of the sponsor, removal from the register must follow the same procedure of scientific opinion followed by a legal decision by the Commission in accordance with Article 5(8).

The Community Register of Orphan Medicinal Products is kept by the Commission and published on the Commission's web-site. A medicinal product shall be removed from the register in accordance with Article 5(12)(b) in the case of a Commission decision following an opinion from the Committee on Orphan Medicinal Products that the criteria laid down in Article 3, and on which the original decision was based are no longer met.

The procedure set out in Article 5 should be followed whenever the criteria are reviewed. Similarly, unless it is at the request of the sponsor, the same procedure should be followed should the review result in removal from the register.

2.3. Re-evaluation of orphan designation criteria at time of Marketing authorisation — preauthorisation phase

According to article 5(12)(b) a designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products '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'.

The Commission interprets this as meaning that the criteria for orphan designation shall be reviewed before a marketing authorisation is granted. The Commission considers that the most appropriate time to reconsider designation is when the marketing authorisation of a designated orphan medicinal product is imminent, that is at around the time of an expected positive opinion from the Committee on Proprietary Medicinal Products (CPMP) or at around the time of granting the first national marketing authorisation. For national procedures, the competent authorities of the Member States shall ensure that appropriate information is forwarded to the EMA at the time of submission of a marketing authorisation application for a designated orphan medicinal product.

2.4. Effect of removal from the Community register on marketing authorisation procedure

According to Article 7(1) of the orphan regulation, a designated orphan medicinal product is entitled to be granted a Community authorisation in accordance with the provision of Council Regulation (EEC) No 2309/93⁽¹⁾ without having to justify that the medicinal product qualifies under Part B of the annex to that Regulation. This requires that the medicinal product is designated as an orphan medicinal product at the time of the initial application.

⁽¹⁾ OJ L 214, 24.8.1993, p. 1.

The Commission considers that, if a designated medicinal product is removed from the register after the procedure for authorisation in accordance with Regulation (EEC) No 2309/93 has commenced, it may still be granted a Community marketing authorisation in accordance with that Regulation. However, the medicinal product will not be entitled to the subsequent benefits provided for by the Orphan Regulation (e.g. market exclusivity and future fee reductions). On the other hand, none of the benefits enjoyed prior to the removal from the register, such as fee reductions, and which accrued prior to its removal shall be recovered.

C. COMMUNITY MARKETING AUTHORISATION — ARTICLE 7.3

1. Designated condition v authorised indication

Article 7.3 of the Regulation states that ‘the marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3’.

There have been questions regarding the possibility of having a therapeutic indication authorised in the framework of the marketing authorisation procedure, which is different from the condition that has been accepted in the designation procedure. The Commission considers that if orphan designation and its continuing benefits are to be maintained both the therapeutic indication applied for and the therapeutic indication finally authorised are required to fall within the scope of the designated orphan condition. In order to ensure this the sponsor may request a revision of the designation decision, prior to the submission of the MA application. If the amended designation is not accepted by Committee on Orphan Medicinal Products or if the applicant does not apply to amend the designation, the authorised indication will not be a designated ‘orphan indication’ and the product will not benefit from market exclusivity as foreseen in Article 8.

In cases in which the therapeutic indication approved through the marketing authorisation procedure is a subset of the designated orphan condition, the marketing authorisation holder will benefit from market exclusivity for this product, for this indication. If the same sponsor applies subsequently for a marketing authorisation for a second subset of the designated orphan condition, the product will not benefit from any additional period of market exclusivity, for that second authorised indication, i.e. the second authorised indication will be covered by the market exclusivity granted on initial authorisation. If, however, a different sponsor applies for a marketing authorisation for a second subset of the designated orphan condition, a new 10-year period of market exclusivity can be obtained for that second product, for that second authorised indication.

If it is considered that the second product (from a different sponsor) is similar to the one that is already authorised and that it is intended for the same therapeutic indication, i.e. the

same subset of the designated condition, the application can not be accepted (Article 8(1)), unless any of the derogations set out in Article 8(3) apply.

The designation as an orphan medicinal product and the grant of a marketing authorisation are subject to different criteria and procedures. Therefore, different decisions may be taken relating to, for example, the designated condition and the authorised therapeutic indication. As sponsors often apply for orphan designation at an early stage in the product development, the sponsor should provide a rationale for use in the proposed therapeutic indication. When evaluating an application for designation, the Committee on Orphan Medicinal Products will consider an orphan condition in broad terms in order to avoid designations related to artificial subsets of a particular condition.

2. Separate marketing authorisation

Article 7(3) provides for the possibility that a sponsor of an orphan medicinal product can ‘apply for a separate marketing authorisation for other indications outside the scope of this Regulation’. On the other hand it is also possible that a marketing authorisation holder of a non-orphan medicinal product may develop the product in a designated orphan condition and obtain orphan designation for this new indication. In both cases Article 7(3) requires that marketing authorisations for orphan medicinal products are handled separately from marketing authorisations for non-orphan medicinal products in order to provide legal certainty that the benefits of market exclusivity provided by the Regulation can be enforced.

D. MARKET EXCLUSIVITY — ARTICLE 8

1. MA applications running in parallel for the same orphan indication

1.1. Both products subject to marketing authorisation applications according to Chapter I of Regulation (EEC) No 2309/93

According to Article 8, a marketing authorisation granted for a designated orphan medicinal product will benefit from a ten year period of market exclusivity provided that certain conditions continue to be met.

If two applications for marketing authorisation for the same orphan condition with respect to similar designated orphan medicinal products are received by the Agency at different times, they will be evaluated according to the relevant provisions of the pharmaceutical legislation. This implies that the Committee on Proprietary Medicinal Products (CPMP) provides, as part of its opinion on the MAA, an opinion on the similarity of the two products and on whether or not they are intended for the same indication, for example, where there is a significant overlap of the target population. Following from

Article 5(12), prior to the grant of a marketing authorisation the Committee on Orphan Medicinal Products will have to review, where appropriate, the decision for designation. In other words, the Committee on Orphan Medicinal Products will have to verify whether the criteria for designation are still met. If this is not the case, the designated orphan medicinal product shall be removed from the Community Register.

It follows from Article 8(1) of the Regulation, that if a marketing authorisation in respect of an orphan medicinal product has been granted pursuant to Council Regulation (EEC) No 2309/93, neither the Community nor the Member States shall '(. .) grant a marketing authorisation for the same therapeutic indication in respect of a similar medicinal product' unless any of the derogations set out in Article 8(3) apply. Therefore after a Community marketing authorisation has been granted for one of the products, the other application will have to be refused unless the second applicant can establish in the application that the second product is safer, more effective or otherwise clinically superior.

1.2. Both products running in national procedures

The same rules apply in the cases where national procedures are used. According to Article 8.1, an orphan medicinal product does not benefit from market exclusivity until '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'.

Therefore, if two similar designated orphan medicinal products are subjects of procedures for mutual recognition running in parallel, the first product which has been granted marketing authorisations in all Member States will be the one to enjoy the benefits of market exclusivity preventing any further marketing authorisations from being granted for the second product unless any of the derogations set out in Article 8(3) apply.

1.3. One product subject to a marketing authorisation application made according to Chapter I of Regulation (EEC) No 2309/93 and one product subject to a marketing authorisation application in the national procedure

The same general rule applies as in the preceding paragraph. The application of market exclusivity depends on the timing of the grant of the Community marketing authorisation on the one hand and the grant of national marketing authorisations in all Member States on the other. The first of the two cases to be fulfilled will prevent any (further) marketing authorisation(s) for the second, unless any of the derogations set out in Article 8(3) apply.

1.4. Transparency regarding Marketing Authorisation applications for designated orphan medicinal products

In order to aid transparency, when a sponsor of a designated orphan medicinal product submits an application for a marketing authorisation to the EMEA or to a national competent authority, it is recommended that the competent authority publish the name (INN) of the active substance of the designated orphan medicinal product.

2. New orphan indications granted to an authorised orphan medicinal product

If a sponsor obtains a marketing authorisation for a designated orphan medicinal product within a particular designated orphan condition, the product will benefit from a 10 year period of market exclusivity for the authorised indication. If the MAH subsequently varies the marketing authorisation to include another, separate, designated orphan condition, then a second 10 year period of market exclusivity starting on the date of approval of the variation shall apply to the second orphan indication. The second period of exclusivity shall run in parallel to the first, while maintaining different start and finish dates.

3. Different orphan indications granted to similar orphan medicinal products with different sponsors

If two sponsors of similar designated orphan medicinal products apply at different times for the authorisation of different orphan conditions, then it is possible that one sponsor would be granted marketing authorisation for an orphan medicinal product in one orphan condition and the other sponsor would be granted marketing authorisation for a similar orphan medicinal for another orphan condition. In this case, each product would be granted market exclusivity for the authorised indication only.

4. Article 8(2) Review of market exclusivity at five years

Article 8(2) provides for a reduction in the period of market exclusivity to six years if it is established at the end of the fifth year that the criteria laid down in Article 3 are no longer met. This includes demonstrating, on available evidence, that the product is sufficiently profitable not to justify the maintenance of market exclusivity.

The Commission will put in place the necessary procedures and systems in order to monitor the prices of orphan medicinal products and in order to determine whether or not at the end of five years the product is sufficiently profitable not to justify maintenance of market exclusivity. An important element of the systems will be the drawing up of detailed guidelines for the application of Article 8, as required by Article 8(5) of the Regulation.

In any event, it is recommended that by the end of the fifth year of market exclusivity the competent authorities systematically check whether or not the criteria on which basis market exclusivity was granted are no longer met. In such cases, the competent authority shall inform the Agency in order to instigate the procedure laid down in Article 5.

As a further consideration, it is implicit that the criterion of non-profitability must have been met at the time of orphan designation. It follows that an orphan medicinal product should not benefit from market exclusivity if it enjoys raised profit levels from the time of marketing. The criterion of non-profitability should therefore be assessed whenever there is a review of the criteria for orphan designation, which may occur at any time.

In order to facilitate regular monitoring of the non-profitability criterion, the Marketing Authorisation Holder will be asked to submit information to the Commission and to the Committee on Orphan Medicinal Products on the marketing, prices and reimbursement, distribution costs, annual estimate of number of patients treated or prescriptions, and all other necessary economic data related to the authorised orphan medicinal products in all of the Member States.

5. Article 8(3)c — challenging the 10-year market exclusivity

Article 8(3) allows a derogation from the market exclusivity provision if a second applicant for a marketing authorisation for a similar medicinal product (be it designated or not) intended for the same therapeutic indication, can establish that the second medicinal product is 'safer, more effective or otherwise clinically superior'.

In this situation, once the second applicant with a designated orphan medicinal product succeeds in obtaining a marketing authorisation for his/her product, he/she will share the market exclusivity with the first holder for the remaining duration of the 10-year period of market exclusivity granted to the first product, until the review foreseen in Article 8(2) is triggered. If the second product is not designated, the second applicant will enjoy the benefits of the full period of data protection, but will not share market exclusivity.

If a third applicant wishes to obtain a MA for a similar product designated for the same therapeutic indication, he/she will have to demonstrate that his product is 'safer, more effective or otherwise clinically superior' than any designated products already authorised. Again, market exclusivity will be shared until the review foreseen in Article 8(2) is triggered.

6. Market exclusivity and Enlargement

When a designated orphan medicinal product has been authorised throughout the Community and therefore benefits from market exclusivity, this market exclusivity extends automatically to the acceding country on the day of accession, encompassing the same rights as in the Community.

National marketing authorisations granted in the candidate countries before accession do not conflict with the market exclusivity.

ANNEX 1

1. ENTR/6283/00 Revision 1

Guideline on the Format and Content of Applications for designation as Orphan Medicinal Products (October 2002) and Annex

2. COMP/436/01 Final

Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (COMP Adopted March 2002)

3. EMEA/14222/00

Procedures for Orphan Medicinal Product Designation — General Principles Revision 2 (25/10/02)

4. EMEA/4795/00

General Information for Sponsors of Orphan Medicinal Products Revision 1 (25/10/02)

5. COMP/50/01

Appeal Procedure for Orphan Product Designation

6. COMP/189/01 Final

Note for Guidance on the Format and Content of the Annual Report on the State of Development of an Orphan Medicinal Product, (Adopted by COMP April 2002)

7. EMEA/H/238/02

EMA Guidance for Companies requesting Protocol Assistance regarding Scientific Issues

All of these documents are available on the EMA website (www.ema.eu.int). In addition document ENTR/6283/00 is available on the DG enterprise website (pharmacos.eudra.org/F2/)
