Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products

(2008/C 242/07)

1. INTRODUCTION

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products ([1]) 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) and 8(4) of Regulation (EC) No 141/2000, the Commission adopted Commission Regulation (EC) No 847/2000 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' ([2]).

In July 2003, following the first three years of application of Regulation (EC) No 141/2000, the Commission published a Communication ([3]) that sets out general considerations on certain matters relating to the application of that Regulation.

In accordance with Article 10 of Regulation (EC) No 141/2000, the Commission services adopted in June 2006 a general report on the experience acquired as a result of the application of Regulation (EC) No 141/2000 ([4]).

This guideline sets out the general principles and procedures by which the period of market exclusivity of orphan medicinal products is reviewed and may be reduced to six years. If necessary, this guideline will be updated when further experience is gained on the application of Article 8(2) of Regulation (EC) No 141/2000 ([5]).

2. BACKGROUND AND LEGAL BASIS

Designation as an orphan medicinal product is governed by Articles 3 and 5 of Regulation (EC) No 141/2000. The designation criteria are laid down in Article 3(1), which reads:

'A medicinal product shall be designated 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 no more than five in 10 thousand persons in the Community when the application is made (so-called "**prevalence**" criterion), **or**

that 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.' (emphasis added).

According to Article 8(1) of Regulation (EC) No 141/2000, where a marketing authorisation in respect of an orphan medicinal product is granted in all Member States, the Community and the Member States shall not, for a period of ten years ([6]), accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Article 8(2) of the same Regulation provides that this period may be reduced to six years ([7]) if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the designation criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity.

([1]) OJ L 18, 22.1.2000, p. 1.
([2]) OJ L 103, 28.4.2000, p. 5.
([3]) OJ C 178, 29.7.2003, p. 2.
([4]) Commission staff working document of 20 June 2006, on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained — Document on the basis of Article 10 of Regulation (EC) No 141/2000, SEC(2006) 832, available at: http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/orphan_en_06-2006.pdf
([5]) Certain principles for this review and possible reduction of market exclusivity were already contained in Section D.4 of the above-cited Commission Communication of 2003. However, following additional experience gained with the application of Regulation (EC) No 141/2000, the Commission developed its interpretation of Article 8(2) further, as set out in the present guideline. Consequently, the present guideline supersedes Section D.4 of the 2003 Communication.
([6]) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1) provides in its Article 37 that for medicinal products designated as orphan medicinal products, if specified criteria in the paediatric Regulation are met, the **ten-year period** referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be **extended to twelve years** (two-year extension as reward for compliance with paediatric investigation plan).
([7]) For products falling under Article 37 of the above-cited paediatric Regulation the **reduced period** under Article 8(2) of Regulation (EC) No 141/2000 will be equally **six years**; Article 37 of the paediatric Regulation only affects the calculation of the period referred to in Article 8(1) of Regulation (EC) No 141/2000.

Article 8(5) provides the legal basis for the Commission to draw up detailed guidelines for the application of Article 8. This guideline fulfils part of that requirement as it relates specifically to Article 8(2).

3. GENERAL PRINCIPLES FOR THE REVIEW UNDER ARTICLE 8(2)

The review procedure of Article 8(2) is triggered by information received from a Member State relating to a specific designation of an orphan medicinal product. The initiation of the procedure established in Article 8(2) is not intended to be systematic for all orphan designated products; on the contrary, Member States should only inform the European Medicines Agency (hereinafter 'the Agency') if they have sufficient indications suggesting that the designation criteria are no longer met; in that case, they have to do so. The review procedure under Article 8(2) is therefore expected to be the exception.

If and when the procedure is triggered by a Member State, an assessment will be carried out within the Agency by the Committee on Orphan Medicinal Products ('COMP'), according to the procedure laid down in Article 5(4) to 5(8) of Regulation (EC) No 141/2000. COMP will provide an opinion as to whether the market exclusivity should be maintained or reduced. For a given product, all authorised therapeutic indications falling within the scope of the same orphan designation will be assessed in the same procedure.

The review of market exclusivity by COMP will be based, in a first step, on the same set of criteria on which designation was granted according to Article 3 of the same Regulation. The period of market exclusivity will not be reduced to six years, if at the end of the fifth year the original designation criteria are still met. If the original criteria are no longer met, COMP will also review, in a second step of its assessment, the situation of the product concerned as regards the other designation criteria of Article 3(1) of Regulation (EC) No 141/2000.

The guidance provided in Section 5 below should be read jointly with the existing provisions and guidance as regards the factors that should be considered when initially assessing the designation criteria and the documentation relevant to that effect, and when re-evaluating the designation criteria before granting marketing authorisation. These factors and documentation will apply by analogy at the time of the review of the period of market exclusivity. In particular, they are laid down in the following texts:

— Regulation (EC) No 847/2000 and the Commission communication of 2003, referred to above, which contain various rules on the evaluation of the designation criteria, and

— the Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designation from one sponsor to another [1], which contains practical advice on how to compile the documents substantiating fulfilment of the designation criteria.

[1] Available at: http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm and regularly updated

After receipt of the opinion, the Commission will adopt a decision, according to the procedure laid down in Article 5(8) of Regulation (EC) No 141/2000. Where the decision is to reduce the period of market exclusivity, the product concerned will be removed from the Community Register of Orphan Medicinal Products, in accordance with Article 5(12) of Regulation (EC) No 141/2000.

The evaluation of the product by the Agency and the Commission will generally take place at the end of the fifth year from marketing authorisation in all Member States. If as a result of such evaluation the orphan status of the product is maintained, no other revision is foreseen between the sixth year and the end of the period of market exclusivity.

4. INFORMATION BY A MEMBER STATE

Article 8(2) of Regulation (EC) No 141/2000 establishes that a Member State shall inform the Agency that at least one of the designation criteria, on the basis of which market exclusivity was granted, may not be met.

According to Article 8(2) of Regulation (EC) No 141/2000, the period of market exclusivity may be reduced when appropriate evidence is established *at the end of the fifth year* of market exclusivity. To allow for the handling of Member States' information within this time frame, Member States are advised to submit this information by the end of the fourth year of market exclusivity.

The Member State in question should provide the rationale for its doubts and include appropriate data justifying why at least one of the original designation criteria of the orphan medicinal product concerned may no longer be met. In preparing its information to the Agency, the Member State may use data which supported the initial designation, held by the Agency.

5. ASSESSMENT BY THE AGENCY

Once the Agency has received information by one or more Member State(s) according to Article 8(2) of Regulation (EC) No 141/2000, the Agency will inform the Commission and the marketing authorisation holder before the assessment procedure is initiated. The market authorisation holder shall be provided with the Member State's reasons why at least one of the designation criteria on the basis of which market exclusivity was granted may not be met; he shall be given the opportunity to submit its views and appropriate data in writing, and may be invited to a hearing in front of COMP.

COMP will issue an opinion as a result of the assessment, justifying whether or not the orphan status of the product should be maintained. In its assessment, COMP will review the relevant designation criteria based on the evidence available to it, in particular provided by the sponsor and the referring Member State. If the available evidence is insufficient to establish with reasonable confidence whether or not the designation criteria continue to be met, COMP will recommend that the period of market exclusivity is not reduced.

The assessment will be done in two steps. In a **first step** (see under 5.1 below), COMP will review the initial designation criteria. If the initial designation criteria are still met, COMP *will adopt* an opinion recommending that the period of market exclusivity is *not reduced*.

If the original criteria are no longer met, **step two** will be performed (see under 5.2): after receiving the necessary information from the sponsor COMP will review whether the *other* designation criteria of Article 3(1) of Regulation (EC) No 141/2000 are met.

If the other designation criteria of Article 3(1) of Regulation (EC) No 141/2000 are fulfilled, COMP *will adopt* an opinion recommending that the period of market exclusivity is *not reduced*.

If none of the criteria for designation under Article 3(1) of Regulation (EC) No 141/2000 are met, COMP will adopt an opinion which *may* recommend that the period of market exclusivity shall be *reduced*.

5.1. **First step**

COMP will review the *initial* designation criteria, i.e. the criterion under Article 3(1)(a) and the criterion under Article 3(1)(b) of Regulation (EC) No 141/2000 which led to the designation as an orphan medicinal product.

5.1.1. *Alternative criteria of Article 3(1)(a) of Regulation (EC) No 141/2000*

5.1.1.1. Products initially designated on the basis of prevalence

For products initially designated on the basis of the prevalence criterion of Article 3(1)(a), first subparagraph, the Agency's assessment will include an evaluation of the prevalence of the orphan condition at the time of the review of market exclusivity.

The prevalence in the Community will be calculated for the designated orphan condition under review following the same standards as the ones used at the moment of designation.

The sponsor will be requested to provide a critical review of possible changes in the estimated prevalence of the condition, including a discussion on the impact of the product on the prevalence in comparison with the natural development of the prevalence of the condition. The prevalence estimate may in principle rise over time either because the prevalence was previously underestimated (e.g. better estimates due to increasing awareness of the condition) or because the true prevalence of the condition has risen (e.g. increasing incidence or increased survival).

A prolongation of patient survival attributable to the effect of the drug would not be used as a reason to reduce market exclusivity. However, an increase in the prevalence of the condition due to improved survival as a result of other advances in the management of the condition *not directly related* to the product or due to increased incidence would need to be taken into consideration.

5.1.1.2. Products initially designated on the basis of insufficient return on investment

For products initially designated on the basis of the insufficient return on investment criterion of Article 3(1)(a), second subparagraph, the Agency will use the same methodology at the time of the review of market exclusivity as the one used at the moment of designation.

The test used under Article 3(1)(a) at the time of designation is whether '*without incentives* it is *unlikely* that the marketing of the medicinal product in the Community would generate *sufficient return* to justify the necessary investment' (emphasis added). The criterion is thus based on a prognosis: the unlikelihood that the expected return would justify the required investment. The test is fulfilled, if it appears unlikely that a sponsor would be prepared to make the investment as the expected return would not be sufficient to compensate for the sponsor's risks.

The corresponding test at the time of the review of market exclusivity would use the same principles. Therefore, the criterion would still be fulfilled if the marketing of the medicinal product in the Community, without the incentive, would not generate *sufficient* return on investment to balance the risks already taken or still to be taken by the sponsor. If, after subtraction of the financial benefits gained as a result of the incentives under the Regulation, the return on investment is insufficient, market exclusivity will not be reduced.

5.1.2. *Alternative criteria of Article 3(1)(b) of Regulation (EC) No 141/2000*

For the criteria of Article 3(1)(b) — inexistence of a satisfactory method *or* significant benefit — the Agency will take into account any changes affecting the treatment, prevention or diagnosis of patients within the designated condition since the date of the marketing authorisation.

The sponsor may be requested to provide a critical review of its product at the time of the review of market exclusivity. The critical review will include any available data, for instance:

— results of any comparative studies performed,

— a comprehensive and balanced bibliographic review,

— marketing studies, or

— patients' surveys.

However, sponsors will not be required to generate new comparative data against another treatment/treatment method that has become available since a marketing authorisation was granted for the designated product.

5.1.2.1. Products initially designated on the basis of inexistence of a satisfactory method

For products initially designated on the basis of inexistence of a satisfactory method (Article 3(1)(b), first part), information which may be requested from the sponsor includes a critical review of the place of the product in the therapeutic, diagnostic or prophylactic management of patients within the authorised therapeutic indication at the time of the review of market exclusivity.

5.1.2.2. Products initially designated on the basis of significant benefit

For products initially designated on the basis of significant benefit (Article 3(1)(b), second part), information which may be requested from the sponsor includes a critical review of the maintenance of the significant benefit of the product in the designated condition, in comparison with methods of treatment, diagnosis or prophylaxis at the time of the review of market exclusivity.

5.1.3. *COMP opinion*

If COMP comes to the conclusion that the initial designation criteria are still met, it *will recommend* that the period of market exclusivity is *not reduced*.

5.2. **Second step**

If COMP is of the opinion that the initial criteria for designation are no longer met, it will provide the sponsor with an opportunity to demonstrate that the market exclusivity can be maintained based on the *other* designation criteria of Article 3(1) of Regulation (EC) No 141/2000. The sponsor will be requested to provide the Agency with the information necessary for that purpose.

5.2.1. *Alternative criteria of Article 3(1)(a) of Regulation (EC) No 141/2000*

Where the initial designation was based on prevalence and it is concluded that this criterion is no longer met, COMP will assess the return on investment of the product at the time of the review of market exclusivity.

On the other hand, where the initial designation was based on return on investment and it is concluded that this criterion is no longer met, COMP will assess the prevalence of the product at the time of the review of market exclusivity.

5.2.2. *Alternative criteria of Article 3(1)(b) of Regulation (EC) No 141/2000*

Where the initial designation was based on the inexistence of a satisfactory method and it is concluded that this criterion is no longer fulfilled, COMP will assess the significant benefit of the product at the time of the review of market exclusivity.

On the other hand, where the initial designation was based on significant benefit, and it is concluded that this criterion is no longer fulfilled, there would normally not be an alternative test available. However, COMP would assess the inexistence of a satisfactory method at the time of the review of market exclusivity in exceptional cases; this could for instance be the case if a method existing at the time of designation had in the meantime disappeared.

5.2.3. *COMP opinion*

If the COMP assessment under step two shows that the alternative designation criteria of Article 3(1)(a) and Article 3(1)(b) are met, COMP *will adopt* an opinion recommending that the period of market exclusivity *is not reduced*.

If following the assessments in steps one and two it turns out that neither the initial, nor the alternative designation criteria of Article 3(1)(a) and Article 3(1)(b) are met, COMP will adopt an opinion which *may* recommend that the period of market exclusivity *shall be reduced*. Relevant criteria for the COMP, on whether or not to recommend a reduction of market exclusivity, would include the extent according to which a designation criterion is not fulfilled. Furthermore, COMP should consider insufficient profitability as an argument against the reduction of market exclusivity.

6. **DECISION BY THE EUROPEAN COMMISSION**

The Commission will take a decision on whether market exclusivity is to be maintained or reduced, on the basis of the opinion of COMP. According to Article 5(8) of Regulation (EC) No 141/2000, this decision shall be adopted within 30 days of receipt of the opinion.

According to Article 5(8) of Regulation (EC) No 141/2000, the Commission may in exceptional circumstances adopt a decision which is not in accordance with the opinion of COMP. In exercising this discretion, the Commission will take into account the specific circumstances of the product concerned in the light of the Regulation's key objectives, i.e. improving the availability of orphan medicinal products and ensuring appropriate and effective incentives for research and development in this sector.