COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 19.9.2008
C(2008) 4077 final

COMMUNICATION FROM THE COMMISSION

Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

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1. INTRODUCTION

Paragraph 5 of Article 8 of Regulation (EC) No 141/2000 requires the Commission to draw up detailed guidelines for the application of Article 8 of that Regulation. This guideline fulfils part of that requirement, providing guidance on the application of Articles 8(1) and 8(3) of that Regulation.

This guideline should be read in conjunction with:

– Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products,

– Commission Regulation (EC) No 847/2000 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",

– 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)[1], hereafter "Commission Communication".

According to Article 8(1) of Regulation (EC) No 141/2000, where a marketing authorisation in respect of an orphan medicinal product is granted either by centralised procedure or in all Members States, the Community and the Member States **shall not**, for a period of 10 years, **accept another** application for a **marketing authorisation**, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a **similar medicinal product (so-called 10 year market exclusivity)**.[2] The scenarios "application for a marketing authorisation" and "application to extend an existing marketing authorisation" will hereafter be referred to together as "application for a marketing authorisation".

With regard to Article 8(1), the present guideline provides guidance on the following questions:

What are the relevant criteria for assessing similarity of a medicinal product? See under section 2 below.

What is the procedure used by the competent authorities for assessing similarity? See under section 3. below.

Article 8(3) of Regulation (EC) No 141/2000 describes three types of derogations from the market exclusivity provided under Article 8(1) of that Regulation: (a) consent of the original

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1 Official Journal C 178/2 of 29 July 2003.

2 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 378/1 of 27.12.2006) provides 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 (see Article 37 of that Regulation).

marketing authorisation holder; (b) inability of the original marketing authorisation holder to supply sufficient quantities; (c) the second medicinal product is safer, more effective or otherwise clinically superior.

With regard to Article 8(3) of Regulation (EC) No 141/2000, the present guideline provides guidance on the following questions:

What is the relevant procedure for assessing whether one of the derogations applies? See section 3. below.

2. GENERAL PRINCIPLES FOR ASSESSMENT OF SIMILARITY

Article 3 of Commission Regulation (EC) No 847/2000 provides the following definitions:

– "***Similar medicinal product***" means a medicinal product containing a **similar active substance** or substances as contained in a currently authorised orphan medicinal product, and which is intended for the **same therapeutic indication**;

– "***Similar active substance***" means an identical active substance, or an active substance with the **same principal molecular structural features** (but not necessarily all of the same molecular features) and which acts via the **same mechanism**. The Commission Regulation (EC) No 847/2000 then provides specific examples;

– "Active substance" means a substance with physiological or pharmacological activity.

Based on the definitions set out in Article 3 of Regulation 847/2000, the assessment of similarity between two medicinal products under Article 8 of Regulation (EC) No 141/2000 takes into consideration principal molecular structural features, mechanism of action and therapeutic indication. If significant differences exist within one or more of these criteria, then the two products will be considered as not similar. These three criteria are further explained below.

The International Non proprietary Names (INN) may provide preliminary information in assessing the similarity of the molecular structural features and the mechanism of action. In the INN system, the names of pharmacologically-related substances may show their relationship by using a common "suffix"/substem.

2.1. Same principal molecular structural features

The following, general considerations should be taken into account for the assessment of the molecular structural features of the active substance (though for macromolecules, particularly complex biological medicinal products, not all of these considerations may be appropriate).

The applicant should demonstrate the proposed structure of the molecule as follows:

– The evidence relating to the demonstration of structure should be summarised in unambiguous two-and three dimensional graphical representations, whenever possible;

– Where possible, the active substance should be described precisely using systematic terminology, e.g. IUPAC [3]or CAS[4] nomenclature;

– Where the active substances have a recommended INN name, the World Health Organisation structures and reports should be provided.

If any of the above information is not provided or not available, a justification should be given.

The principal molecular structural features of the product should be described, based on evidence and compared to those of the authorised orphan medicinal product. It should be noted that certain observed differences in structure may appear major in the molecule's crystalline state (i.e. based on X-Ray data). However, since molecules exert their biological action in solution, these differences seen in the crystalline state may not be relevant for the assessment of similarity.

Software programs may be used to measure the degree of structural similarity between molecules; many of them allowing 'similarity searching' to identify molecules having common or similar molecular architectural features (2- or 3- dimensional).

2.2. Same mechanism of action

The **mechanism of action** of an active substance is the functional description of the interaction of the substance with a pharmacological **target** that elicits a pharmacodynamic **effect**. In case the mechanism of action is not fully known, it will be for the applicant to demonstrate that the two active substances do not act via the same mechanisms.

Two active substances may only be considered to have the **same mechanism of action,** provided that *both* share the same pharmacological target and pharmacodynamic effect.

Factors not relevant to the mechanism of action are differences between two substances in terms of:

– Mode of administration;

– Pharmacokinetic properties;

– Potency; or

– Tissue distribution of the target.

A prodrug is considered to have the same mechanism of action as its active metabolite.

A **pharmacological target** is usually a receptor, enzyme, channel, carrier or an intracellular coupling process.

The **pharmacodynamic effect** is the action of the active substance on the body (e.g. bradycardia). For the purpose of assessing similarity of the second product with an authorised orphan medicinal product, the pharmacodynamic effect relevant to the "mechanism of action"

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[3] IUPAC stands for International Union of Pure and Applied Chemistry.

[4] CAS stands for Chemical Abstracts Service, which is a division of the American Chemical Society.

is the *primary* pharmacodynamic effect of the active substance, which determines the therapeutic indication.

Two substances with the same pharmacological target may elicit a different pharmacodynamic effect depending on the location of the target, or depending on whether the target is activated or inhibited.

Two active substances with the same pharmacodynamic effect may act at different pharmacological targets. In case these two active substances act at multiple targets (including subtypes of the same receptor) and *share at least one common target*, it should be considered whether the common target(s) explain the primary pharmacodynamic effects which determine the therapeutic indication.[5]

2.3. Same therapeutic indication

The therapeutic indication of an orphan medicinal product is determined by the marketing authorisation and has to fall within the scope of the (possibly broader) designated orphan condition, cf. Section C.1 of the Commission Communication.

If an orphan medicinal product has been granted a marketing authorisation for an indication which is a subset of the designated condition, an application for marketing authorisation of a second product, which claims to cover a different therapeutic indication, and thus another subset of the same designated orphan condition, will have to establish that the difference between the two subsets is clinically meaningful. If there is an overlap of the target populations of two allegedly different therapeutic indications, the second applicant would have to provide the authority with an estimate of its extent. The extent of the overlap will be a relevant factor for the authority to establish whether the claim for two different therapeutic indications can be upheld.

3. PROCEDURE FOR ASSESSING SIMILARITY AND FOR APPLYING THE DEROGATIONS IN ARTICLE 8(3)

3.1. Competent authority

According to Article 8(1) of Regulation (EC) No 141/2000, **the Community and the Member States** shall not, for a period of 10 years, accept a marketing authorisation application for a medicinal product (hereafter also "second product") which is similar to an authorised orphan medicinal product (hereafter also "first product").

The competent authority for providing the assessment of similarity, and if applicable the fulfilment of the criteria for one of the derogations set out in Article 8(3), ("competent assessing body") is to be determined depending on the route of marketing authorisation of the

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[5] For example: atenolol and propranolol would be considered to have the same mechanism of action regarding their indication in hypertension, even if they have different selectivity and potency at β1-receptor and β2-receptor levels. On the other hand, for example carvedilol and metoprolol would not be considered to have the same mechanism: although they share β-receptor blocking activity, their mechanisms of action differ for the treatment of severe congestive heart failure due to the additional α-receptor blocking activity of carvedilol.

second product. The second medicinal product may be authorised either nationally (non-orphan product[6]) or centrally (either orphan or non-orphan product).

For **centralised** marketing authorisation applications of a second product to be compared with an authorised orphan medicinal product, the competent assessing body is the Agency.

For applications filed through **National, Mutual Recognition or Decentralised** Procedures, the competent assessing body/ies is/are the national competent authority/ies concerned.

3.2. Validation

The applicant for a marketing authorisation of a ("second") product potentially similar to an authorised orphan medicinal ("first") product will have to provide appropriate documentation on his position regarding similarity of the second product with the first product and, if relevant, a justification that one of the derogations set out in Article 8(3) applies (see Section 3.3 "information to be submitted by the applicant" and Section 3.4 "identification of relevant products…").

The application for the second product will be validated by the competent assessing body if this documentation/justification is contained in the application. Applicants should be aware that validation implies a formal check (all relevant documents have been submitted) but does not give any indication as to the outcome of the material assessment of their application.

If the application concerns a generic medicinal product, similarity is assumed. Consequently, the application cannot be validated before the end of the period of market exclusivity unless justification is provided to support one of the derogations laid down in Article 8(3).

3.3. Information to be submitted by the applicant

Information to address potential "similarity" and, where applicable, to justify that one of the derogations laid down in Article 8(3) of Regulation 141/2000 applies should be submitted in module 1.7 of the application for marketing authorisation.

3.3.1 Similarity

For **similarity**, a report should be included in module 1.7.1 comparing the product with authorised orphan medicinal products in the context of similarity as defined in Art. 3(3) of Regulation (EC) No 847/2000 and concluding on similarity or "non" similarity, addressing the three criteria for assessing similarity:

– Molecular structural features,

– Mechanism of action, and

– Therapeutic indication.

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[6] As of 20 November 2005, designated orphan medicinal products may only be authorised via the centralised authorisation procedure (Article 3(1) of Regulation (EC) No 726/2004). Thus, a second product can only be authorised nationally, if it is not an orphan medicinal product.

Particular emphasis should be made on the explanation of the first two criteria. If the applicant claims that the two products are not similar, he should provide reasons to support this claim.

3.3.2 Derogations

To support that **one of the derogations** laid down in Article 8(3), paragraphs (a) to (c) of the same Regulation applies, the following information should be submitted in module 1.7.2, as applicable:

3.3.2.1 Article 8(3)(a)

If the holder of the marketing authorisation for the original orphan medicinal product has given his **consent** to the second applicant:

A signed letter from the holder of authorised orphan medicinal product confirming his/her consent for the second applicant to file an application for marketing authorisation, in accordance with Art. 8(3)(a) of Regulation (EC) No 141/2000.

3.3.2.2 Article 8(3)(b)

If the holder of the marketing authorisation for the original orphan medicinal product is **unable to supply sufficient quantities** of the medicinal product:

A report describing why supply of the authorised orphan medicinal product is deemed to be insufficient, in accordance with Art. 8(3)(b) of Regulation (EC) No 141/2000.

The report should include details of the supply problem and an explanation as to why patients' needs in the orphan indication are not being met. All claims should be substantiated by qualitative and quantitative references.

3.3.2.3 Article 8(3)(c)

If 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**:

A critical report which justifies why the second product is deemed to be "clinically superior" to the authorised orphan medicinal product, in accordance with Art. 8(3)(c) of Regulation (EC) No 141/2000.

The report should include a comparison of the two products in the context of "clinical superiority" as defined in Art. 3(3)(d) of Regulation (EC) No 847/2000, with particular reference to:

– the results of clinical studies,

– the scientific literature.

3.4. Identification of relevant products to perform similarity check

For any application for marketing authorisation, the competent assessing body should check *which authorised orphan medicinal products* need to be taken into consideration for an assessment of possible similarity. This check should first be performed **prior to validating** the application.

If a competent assessing body identifies a possible similarity issue not addressed by the applicant before validation, the applicant will be asked to complete the application with information on "similarity" and, if applicable, on one of the derogations in Article 8(3). Validation of the application will only proceed once the applicant has submitted either a report justifying the lack of similarity or information justifying one of the derogations in Article 8(3), see above under 3.3 "information to be submitted by the applicant".

As considerable time may elapse between validation of an application and adoption of the opinion/granting of a marketing authorisation, the competent assessing body should repeat its check of possibly similar orphan medicinal products prior to the granting/amendment of the marketing authorisation: new orphan medicinal products may have been authorised for the same condition in the meantime.

For the **centralised procedure,** the Agency will repeat its check for possibly similar orphan medicinal products before the Committee for Medicinal Products for Human Use (CHMP) issues a positive opinion. Where additional possible similarity issues are identified, the applicant will be asked to submit further relevant documentation on similarity (and, if necessary, documentation to support that one of the derogations in Article 8(3) applies). The "procedural clock" will be stopped until this documentation is submitted.

Should a new issue of possible similarity be identified during the procedure at the level of the European Commission, during the preparation of a marketing authorisation decision, the latter may refer the CHMP opinion back to the Agency for further evaluation.

3.5. Procedure for assessing similarity and for applying the derogation based on "clinical superiority"

Following identification of the relevant products to perform the product similarity check, the competent assessing body will initiate the procedure for assessing similarity and, if its opinion on similarity is positive, the procedure for assessing whether a derogation under Article 8(3) is fulfilled.

The competent assessing body should assess "similarity" and, if applicable the fulfilment of the derogation "clinical superiority" in parallel with the evaluation of the quality/safety/efficacy of the medicinal product.

Should the competent assessing body come, only during the quality/safety/efficacy evaluation, to the conclusion that there is similarity between the product under evaluation and an authorised orphan medicinal product, the applicant will be requested at that time to submit a justification that one of the derogations in Article 8(3) is fulfilled.

3.5.1. Centralised Procedure

The CHMP opinion on "similarity" and, where applicable on "clinical superiority" will be part of the overall opinion on quality/safety/efficacy. Where clinical superiority is assessed, the basis for clinical superiority will be described in the European Public Assessment Report.

Re-examination of CHMP opinion

Once the CHMP has concluded its assessment of similarity and, if applicable, of the fulfilment of the criteria for the derogation "clinical superiority", the applicant may ask for a re-examination of the CHMP Opinion according to the principles set out in Article 9(2) of Regulation (EC) No 726/2004.

Scientific advice or protocol assistance on similarity and clinical superiority

Applicants seeking to develop a product where an issue on similarity with an orphan medicinal product might arise can request Scientific Advice (or Protocol Assistance) from the CHMP. In its request for advice, the applicant will have to document its position regarding similarity and, if relevant, provide a justification for one of the derogations.

If the applicant intends to rely on the derogation of clinical superiority, Scientific Advice or Protocol Assistance can be requested, and is recommended, on the appropriateness of the study(ies) intending to demonstrate clinical superiority.

3.5.2 National, Mutual Recognition and Decentralised Procedures

It is highly recommended that the relevant national competent assessing body in a national, mutual recognition or decentralised procedure informs the Agency as soon as a potential similarity issue with an authorised orphan medicinal product is detected. In order to ensure consistency of the assessment of similarity and clinical superiority throughout the Community, it would be advisable to have a consultation process between the Agency's CHMP and the national authority.

In all cases, the Agency should be informed of the national authority's conclusions on similarity and, if applicable, clinical superiority.

3.6. Procedure for applying the derogation based on "inability to supply sufficient quantities"

For the derogation set out in Article 8(3)(b) of Regulation (EC) No 141/2000 – the holder of the marketing authorisation of the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product – the applicant of the second product will have to provide the competent assessing body with a report supporting this derogation (see above under 3.3 "information to be submitted by the applicant").

The competent assessing body should circulate the applicant's report to (other) Member States for comments. The competent assessing body should also liaise with the marketing authorisation holder of the original product, inviting him to submit comments in writing. The competent assessing body should issue a **position** on the fulfilment of the criteria for derogation, taking into account the applicant's report as well as comments received from Member States and the marketing authorisation holder. If the derogation is assessed in the framework of the centralised procedure, this position shall be part of the CHMP opinion.

3.7. Parallel assessment of two applications for the same orphan condition

3.7.1 Centralised Procedure

In case two procedures for granting marketing authorisations for possibly similar orphan medicinal products are running in parallel, having been received by the Agency at the same time, the following scenarios may arise:

In the *very exceptional case* where marketing authorisation applications for the same orphan indication are *received at the same time* and, being handled in accordance with the relevant provisions of the pharmaceutical legislation, the authorisation procedures *remain in parallel*, an opinion on similarity of the two products will not be necessary.

On the other hand, where for these simultaneous marketing authorisation applications, based on the examination of each application on its own merits, the two authorisation procedures *do not remain in parallel*, an opinion on similarity will be necessary: as soon as one of the products with orphan status obtains marketing authorisation, the applicant for the other (second) product will be informed that a marketing authorisation for a possibly similar orphan medicinal product has been granted. A report on "similarity" and, if applicable a justification for one of the derogations in Article 8(3) will be requested from this applicant.

3.7.2 National, Mutual Recognition and Decentralised Procedures

In case a medicinal product has been designated as an orphan medicinal product and its marketing authorisation is under assessment, but has not yet been granted by the European Commission, a parallel assessment of a possibly similar (non-orphan[7]) medicinal product can occur by a national authority. As there is no authorised orphan medicinal product yet, the marketing authorisation may be granted (without an opinion of similarity).

[7] See under 3.1. above: since 20 November 2005, designated orphan medicinal products may only be authorised via the centralised authorisation procedure.