

**BEST PRACTICE GUIDE FOR THE EXCHANGE OF REGULATORY
AND ADMINISTRATIVE INFORMATION REGARDING ORPHAN
MEDICINAL PRODUCTS BETWEEN THE EMA
AND THE NATIONAL COMPETENT AUTHORITIES**

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1 – INTRODUCTION AND SCOPE

This best practice guide (BPG) is intended to describe the duties of both EMA and national competent authorities, in order to fulfil the obligations laid down in Article 8 of Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products (OMPs).

With the adoption of Regulation (EC) No 726/2004, from 20th November 2005, all marketing authorisation for products designated as orphans have to be granted in accordance with the centralised procedure.

Considering that:

- the request for designation as an orphan medicinal product is always made to the EMA,
- the application for marketing authorisation of a medicinal product designated as orphan must use the centralised procedure since 20th November 2005,
- any ‘similar’ medicinal product may be granted a marketing authorisation by national competent authorities (not designated as orphan) or the European Commission (orphan or not),
- the procedures for marketing authorisation of similar medicinal products may go on simultaneously through the centralised and the national systems

It is essential to set up systematic ways of exchange of regulatory information between the EMA and national competent authorities in order to guarantee that the obligations laid down in Article 8 of Regulation (EC) No 141/2000 are fulfilled and to avoid future legal challenges.

This BPG should be read in conjunction with:

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products,
- 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”,
- Regulation (EC) No 726/2004 of the European Parliament and of Council of 31 March 2004,

- 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, 29 July 2003): <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2003:178:0002:0008:en:PDF>
- 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 (2008/C 242/08): <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:242:0012:0016:EN:PDF>
- 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): <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:242:0008:0011:EN:PDF>

The legal framework on the basis of which this BPG was developed may be found in the annex II together with some important definitions.

2 – TIMING OF EXCHANGE DEPENDING ON THE STATUS OF THE DOSSIER

2.1. Validation of the procedure for a new application for marketing authorisation or extension of indication

Where a marketing authorisation has been granted to an orphan designated medicinal product by the Community (through the centralised procedure) or by **all** Member States (through the mutual recognition procedure), the Member States shall not, for a period of 10 years after the granting of this marketing authorisation, **accept another application** for a marketing authorisation (or an application to extend an existing marketing authorisation), for the **same therapeutic indication**, in respect of a **similar medicinal product** (Article 8(3) - Regulation (EC) No 141/2000).

For any marketing authorisation application or type II variation modifying or extending therapeutic indications, potential similarity with an authorised orphan medicinal product should be checked by the National Competent Authority (NCA) prior to validating the application.

In all cases, the EMA should be kept informed (see section 3). Before validation of the procedure, it is therefore recommended to check the community register of designated orphan medicinal products available on the website of the European Commission: http://ec.europa.eu/health/documents/community-register/html/index_en.htm, which also indicates marketing authorisation status.

In accordance with Article 8(3) of Regulation (EC) No 141/2000, **where a marketing authorisation has already been granted to a previous similar orphan designated medicinal product by the Community or by all Member States**, the application will be refused except:

- where the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant,
- or,

- where the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product,
- or,
- where the 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 as defined in Article 3 of Regulation (EC) N° 847/2000 (this check should be part of the validation step).

2.2. Before granting a marketing authorisation for a new application, or an extension of indication

Where a marketing authorisation has been granted to an orphan designated medicinal product by the Community (through the centralised procedure) or by **all** Member States (through the mutual recognition procedure), the Member States shall not, for a period of 10 years after the granting of this marketing authorisation, **grant another marketing authorisation** to a similar medicinal product for the same therapeutic indication (Article 8(1) - Regulation (EC) No 141/2000).

Due to the fact that considerable time may elapse between the validation phase and the granting of a marketing authorisation, checking of potential similarity will be repeated prior to granting a marketing authorisation, as another orphan medicinal product may have been authorised for the same indication in the mean time. Before granting the marketing authorisation, it is therefore recommended to check the community register of designated orphan medicinal products (see web address above).

- In accordance with Article 8(3) of Regulation (EC) No 141/2000, **where a marketing authorisation has been granted to a previous similar orphan designated medicinal product by the Community or by all Member States**, the marketing authorisation should be refused except:

- where the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant,
- or,
- where the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product,
- or,
- where “clinical superiority” is demonstrated in the marketing authorisation application dossier. Assessment of clinical superiority may be performed following an opinion of the Committee for Human Medicinal Products (CHMP). It may be also performed at the national competent authority level.

In all cases, this information should be communicated to the EMA (see section 3).

- Where a medicinal product has been designated as an orphan medicinal product but the marketing authorisation is granted in a different therapeutic indication. There is no legal obstacle to grant a marketing authorisation. However, in this situation also, the EMA should be informed.

3 – CHANNEL FOR EXCHANGING INFORMATION BETWEEN MEMBER STATES AND EMA

In order to identify and track marketing authorisation applications submitted through different registration procedures and to avoid any conflict with the market exclusivity of an orphan medicinal product in accordance with the provisions of the Regulation (EC) No 141/2000, Member States and EMA agreed the following rules for the exchange of information:

Member States actions

The Member States who identified a potential similarity of a product with an authorised orphan medicinal product during the validation phase of the procedure or before granting a new marketing authorisation or a new therapeutic indication should send a message to the CMDh and EMA Orphan Drug Section: orphandrugs@ema.europa.eu with the following heading: **Name of the product_Company_Potential Similarity Orphan Drug.**

The Member State should provide the rationale and all useful information regarding the potential similarity.

EMA actions

Once the EMA has received this information, the EMA will provide information to CMDh on centrally authorised orphan medicinal products to assist Member States about similarity issues and ensure a consistent approach between Member States.

Further information can be found in section “Special topics/Medicines for rare diseases” on the EMA website: <http://www.ema.europa.eu>

4 – SUBMISSION OF GENERIC APPLICATIONS

The market exclusivity is limited to the therapeutic indication for which marketing authorisation has been granted.

During the market exclusivity, similar medicinal products for the same therapeutic indication can only be authorised under article 8(3) of Regulation (EC) No 141/2000, irrespective from the legal basis chosen. This applies also to generics of an orphan medicinal product.

Therefore, generic applications cannot be submitted until expiry of market exclusivity of the orphan medicinal product chosen as reference product except if one of the derogations laid down in Article 8(3) of Regulation (EC) No 141/2000 is met and the period of data exclusivity of the reference medicinal product has expired.

5 – RECOMMENDATIONS REGARDING “SIMILARITY” AND ‘CLINICAL SUPERIORITY’ TO AN ORPHAN MEDICINAL PRODUCT

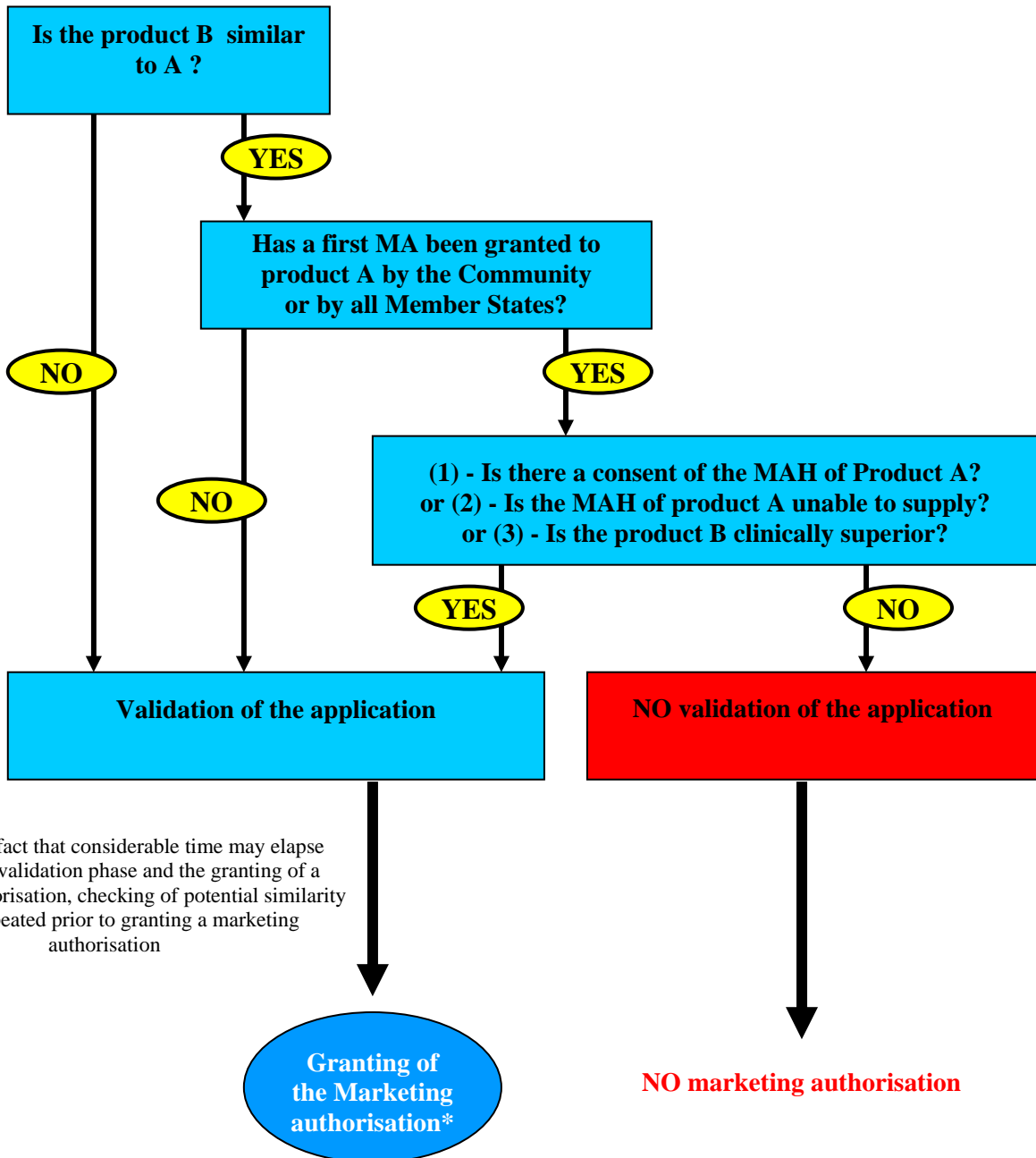
- 5.1.** “Similar medicinal product” and “Clinical superiority” are defined in Article 3 of Commission Regulation (EC) No 847/2000 (see Annex).
- 5.2.** In order to determine if a medicinal product is “similar” or not to an already designated orphan medicinal product, it is highly recommended seeking advice from the Quality Working Party (QWP) or the Biologics Working Party (BWP), according to the medicinal product.

- 5.3.** At the time of application for marketing authorisation, applicants of similar medicinal product(s) (designated as orphan or not) are required to demonstrate that the similar medicinal product is “safer, more effective or otherwise clinically superior” to orphan medicinal products authorised in the same therapeutic indication.
- 5.4.** To evaluate if the medicinal product is “safer, more effective or otherwise clinically superior” in a harmonised way, the opinion of the CHMP is sought on this matter prior to granting the marketing authorisation via the centralised procedure. The assessment of ‘clinical superiority’ may be performed at the NCA level for national procedures including mutual recognition and decentralised procedures. However, in all cases the EMA should be informed.

For further information, see also the 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 (2008/C 242/08).

ANNEX I – Decision Tree

Decision tree before validating an application and granting a marketing authorisation in the same indication to a medicinal product B



A = designated authorised orphan medicinal product

ANNEX II – Legal framework

Legal basis

Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products regards market exclusivity and requires that:

- *Paragraph 1*

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

- *Paragraph 2*

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

- *Paragraph 3*

“By way of derogation of paragraph 1, and without prejudice to intellectual property law or any provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

- (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or*
- (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or*
- (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.”*

Definitions

Article 3 of Commission Regulation (EC) No 847/2000 of 27 April 2000 lays down definitions of the concept of “similar medicinal product” and “clinical superiority” and in particular specifies the following:

- **“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 with the same principal molecular structural feature (but not necessarily all of the same molecular structural features) and which acts via the same mechanism.

NB All specific situations of similarity are described in the Commission Regulation (EC) No 847/2000 of 27 April 2000.

- ***"Clinically superior"** means that a medicinal product is shown to provide a significant therapeutic or diagnosis advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:*
 - *greater efficacy than the authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials)*
 - *greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary, or*
 - *in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.*
- ***"Significant benefit"** means a clinically relevant advantage or a major contribution to patient care.*