1 – INTRODUCTION AND SCOPE

This best practice guide (BPG) is intended to describe the duties of both EMEA and national competent authorities, in order to fulfil the obligations laid down in Article 8 of Regulation (EC) n°141/2000 of 16 December 1999 on Orphan Medicinal Products (OMPs), regarding in particular market exclusivity.

With the adoption of regulation (EC) No 726/2004, from 20th November 2005, all marketing authorisation for products designated as orphans will 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 EMEA,
- the application for marketing authorisation of a orphan medicinal product designated as orphan must use the centralised procedure since 20th November 2005,
- any ‘similar’ medicinal product (orphan or not) may be have been 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 EMEA and national competent authorities in order to guarantee that the obligations laid down in Article 8 of Regulation (EC) n°141/2000 are fulfilled and to avoid future legal challenges.

This BPG guideline should be read in conjunction with:
- 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”.
The European Commission has also published a communication (2003/C 178/02) on Regulation (EC) n°141/2000 which sets out the position of the Commission on certain matters relating to the implementation of the designation and market exclusivity provisions.

Considering that:
the request for designation as an orphan medicinal product is always made to the EMEA
the application for marketing authorisation of an orphan medicinal product may be submitted to either the EMEA (centralised procedure), or national competent authorities (national marketing authorisation and subsequent mutual recognition procedure(s))
any ‘similar’ medicinal product (orphan or not) may have been granted a marketing authorisation by national competent authorities or the European commission
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 EMEA and national competent authorities in order to guarantee that the obligations laid down in Article 8 of Regulation (EC) n°141/2000 are fulfilled and to avoid future legal challenges.

The legal framework on the basis of which this BPG was developed may be found in the annex 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 8.1 - Regulation (EC) n°141/2000) (whatever the orphan status of this second similar medicinal product).

For example, an application for a similar medicinal product cannot be accepted except in the cases described under 2.1.1.
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 EMEA should be kept informed. 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/enterprise/pharmaceuticals/register/index.htm, which also indicates marketing authorisation status. The register is available on the European Commission’s website at the following web address: http://dg3.eudra.org/F2/register/alforphreg.htm

Different situations may be encountered: In accordance with Article 8.3 of Regulation (EC) n°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,

- where the applicant informs that, in the dossier, it is demonstrated that the second medicinal product is not “similar” or, if similar, that it brings about “clinical superiority” as defined in article 3 of Regulation EC n°847/2000 (this check should be part of the validation step).

In all cases, this information should be communicated to the EMEA (see also points 3, 4 and 5 below).
2.1.2 – a previous similar medicinal product has been designated as an orphan medicinal product but the marketing authorisation has not been granted by the Community nor by all member states: the application can be validated and this information should be communicated to the EMEA. Before granting the marketing authorisation, it will be important to be in close contact with the EMEA.

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) n°141/2000), (whatever the orphan status of this second similar medicinal product).

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).

Different situations may be encountered:
- In accordance with Article 8.3 of Regulation (EC) n°141/2000, 2.2.1 – 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,
  - where the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product,
  - where “clinical superiority” is demonstrated in the MA application dossier. Assessment of clinical superiority may be performed following an opinion of the Committee for Human Proprietary Medicinal Products (CHPMP). It may be also performed at the national competent authority (NCA) level.

In all cases, this information should be communicated to the EMEA.

Once a first orphan medicinal product is currently under market exclusivity, no further MA can be granted for a similar medicinal product in the same therapeutic indication: in particular, if ongoing and/or repeat-use MR procedures are running and if marketing authorisations have not been granted in all member states, it is important to specify that, from the date of this first orphan MA, no further authorisations can be granted in respect of a similar product in the same therapeutic indication. The repeat-use mutual recognition procedures cannot be undertaken or finalised.

2.2.2 – a previous similar medicinal product has been designated as an orphan medicinal product but the marketing authorisation has not been granted by the Community nor...
If the medicinal product currently assessed by the NCA has not been designated as an orphan medicinal product, the marketing authorisation may be granted but this information should be communicated immediately to the EMEA. The orphan status of the first similar product will be revised by the COMP, i.e. the significant benefit should be confirmed (see paragraph 4) before the granting of the marketing authorisation.

If the medicinal product currently assessed by the NCA has also been designated as an orphan medicinal product, the marketing authorisation may be granted. Nevertheless, the market exclusivity will be given only when this medicinal product will be authorised through mutual recognition procedure in all Member States of the European union (see also point 3 below).

- **2.2.3** – Where a similar 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 granting a marketing authorisation; however, in this situation also, the EMEA should be informed.
3 — MARKET EXCLUSIVITY

3.1. Market exclusivity will be given for a period of 10 years (Article 8.1 of Regulation (EC) n°141/2000, paragraph 1).

- Centralised medicinal products: the market exclusivity starts on the date of decision of the marketing authorisation by the European Commission (i.e., not on the CPMP opinion date).

- Mutually recognised medicinal products: the market exclusivity starts as soon as and only if marketing authorisations have been granted by all member states of the Community.

3.2. In order to challenge the orphan exclusivity, a medicinal product in the same therapeutic indication will have to demonstrate that it is not “similar” to the first authorised orphan medicinal product or, if “similar”, that it is “safer, more effective or otherwise clinically superior”. The orphan exclusivity may also be challenged with the consent of the holder of the first authorised orphan medicinal product or in the case of insufficient supply of the authorised orphan medicinal product (Article 8.3 of Regulation (EC) n°141/2000).

3.3. In addition, the period of exclusivity may be reduced to 6 years if, at the end of the fifth year, it is established that the criteria for orphan designation are no longer met (in practice: significant benefit where appropriate), or where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity (Article 8.2 of Regulation (EC) n°141/2000). To that end, a Member State shall inform the EMEA that the criterion on the basis of which market exclusivity was granted may not be met. The review will be carried out by COMP.

4 — RE-EVALUATION OF ORPHAN DESIGNATION CRITERIA (COMP)

At the time of granting marketing authorisation, sponsors of designated orphan medicinal products are required to demonstrate that the criteria laid down in Article 3 of Commission Regulation (EC) n°847/2000 are still met in order to maintain orphan status.

Prior to the granting of the marketing authorisation, a designated orphan medicinal product shall be removed from the Community Register if it is established that those criteria are no longer met.

Those criteria may also be reviewed by COMP at the end of the fifth year of the period of exclusivity.

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) n°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.

35.3. 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.

35.4. 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 EMEA should be informed.

For further information, see also the European Commission guideline on aspects of the application of Article 8 of Regulation (EC) No 141/2000: Assessment of similarity and/or clinical superiority of orphan medicinal products when assessing marketing authorisation applications and variations

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Decision tree before validating an application and granting a MA to a medicinal product B

(1) - Is there a consent?
(2) - Is the MAH unable to supply?

Has a first MA been granted to ‘A’ by the Community or by ALL MS?

Is the MP ‘B’ similar to ‘A’?

Yes

Validation of the application

No

Granting of the MA*

No

(3) - Is the MP clinically superior?

Yes

No

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MP = medicinal product
MA = marketing authorisation in the same indication
A = Designated authorised orphan medicinal product

* 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.
ANNEX

Legal basis
Article 8 of Regulation (EC) n°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) n° 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) n°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) n°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.