

## **Draft Guideline on the format and content of applications for designation as orphan medicinal products, revision 18/4/00**

### **Introduction**

This draft guideline is intended to provide supplementary advice to sponsors wishing to apply for orphan medicinal product designations on how to compile the documents that should be provided. They are intended to expand on the legal texts mentioned in the section “legal basis” below, but where the legal texts are in themselves sufficiently descriptive, the relevant extracts have been provided for ease of reference. This guideline is intended to form the basis for the format and content of a submission for designation, and should be followed unless otherwise justified. This draft version may be followed by applicants until a finalised guideline is available. In the light of experience, it is expected that this guideline will be expanded considerably to include more detailed explanation and examples.

### **Legal Basis**

Article 5 of Regulation 141/2000<sup>1</sup> on Orphan Medicinal Products requires the Commission in consultation with the Member States, the Agency and interested parties to draw up detailed guidelines on the required format and content of applications for designation of medicinal products as orphan medicinal products. Article 4 of the same Regulation states that one of the tasks of the Committee for Orphan Medicinal Products is to assist the Commission in drawing up detailed guidelines. Commission regulation XX of 27 April 2000<sup>2</sup> sets out, inter alia, the provisions for implementing the criteria for designation of a medicinal product as an orphan medicinal product and is intended to be supported further guidelines as referred to in Article 5 of Regulation 141/2000. The present guideline is intended to fulfil the obligations laid down in this article.

### **Scope**

The scope of this guideline is to describe the format and content of the applications that sponsors should submit for designation of medicinal products as orphan medicinal products to the EMEA.

Each application for orphan medicinal product designation for a medicinal product for a specified rare disease or condition shall be submitted to the EMEA using the form and table of contents provided in the Annex and containing the information described in this guideline.

### **Definitions**

The definitions of Directive 65/65/EEC, Regulation 141/2000 and Commission Regulation XX are applicable.

The relevant definitions are reproduced in the annex to this guideline.

### **Timing of submissions**

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<sup>1</sup> OJ n° L 18 of 22.01.2000

<sup>2</sup> draft text available on <http://pharmacos.eudra.org>

A sponsor applying for designation of a medicinal product as an orphan medicinal product shall apply for designation at any stage of the development of the medicinal product before the application for marketing authorisation is made. This means that if a marketing authorisation for the same medicinal product (in respect of the same therapeutic indication and submitted by the same sponsor) has already been submitted in any Member State within the Community, whether or not the marketing authorisation has been granted, that this medicinal product is no longer eligible for designation.

A sponsor may apply for designation of a medicinal product as an orphan medicinal product for an already approved medicinal product provided the orphan designation concerns an unapproved therapeutic indication. In this case, the marketing authorisation holder shall apply for a separate marketing authorisation which will cover only the orphan indication at the time of application for a marketing authorisation.

More than one sponsor may obtain designation as an orphan medicinal product for the same medicinal product intended to prevent, treat or diagnose the same disease or condition, provided that a complete application for designation as laid down in this guideline is submitted.

### **Language**

The application should normally be submitted in English.

### **Documentation to be supplied**

A sponsor shall submit one original and two copies of a completed dated and signed request for designation to the EMEA.

Sponsors are encouraged to submit one additional copy of the application in electronic form and submission of partial/complete copies using electronic storage media is encouraged.

Details of the number of copies which should be provided to Members of the Committee will be specified at a later stage and where possible this communication will be by electronic means.

If more than one indication is applied for, separate applications should be submitted for each indication.

The application should be signed and dated by the sponsor indicating that the documentation provided is complete and accurate.

### **Information to be included in the application form:**

Section I and III of the application form contain a series of tick boxes which should be completed as appropriate by the applicant. When completing section II, the following information should be included:

#### 1. Name of the active substance

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances

not having an exact scientific designation should be described by a statement of how and from what they were prepared.

Where the active ingredient is of herbal origin, the declaration of the active substance should be in accordance with the Note for Guidance on *Quality of Herbal Medicinal Products*.

## 2. Proposed indication and ATC code

The sponsor should submit details of the proposed therapeutic indication for which designation is applied. Where an ATC code has been assigned, this should be included.

## 3. Proposed details of the medicinal product (if available)

Details of the proposed tradename, the strength (quantitative particulars of active ingredient), pharmaceutical form and route of administration for the orphan medicinal product should be provided. For products that are in the early stages of development it may not be possible to complete this section.

## 4. Name or corporate name and permanent address of the sponsor and contact person

The name or corporate name and permanent address of the sponsor shall be provided.

The sponsor must be established in the Community, and must provide documentation indicating that he has a permanent address in the Community. The sponsor may be an individual or a company. For sponsors whose main business is operated from outside of the Community, the address of those premises and a contact name should be provided.

Where the sponsor is not the person or company responsible for the research and development of the medicinal product, details of the person or company responsible should also be provided.

The person/company authorised to communicate with the EMEA on behalf of the sponsor during the designation procedure, and after designation if applicable, should be provided.

## 5. Name of the manufacturer of the active substance and medicinal product

The name(s) and address(es) of the manufacturer(s) and site(s) of manufacture of the active substance(s) and of the medicinal product (if available) should be provided.

### **Information to be included in the remainder of the application:**

The table of contents and check-list provided in Annex can be used as a guide to complete the documentation submitted in an application for designation. The following information should be included:

#### **A. Description of the condition**

##### 1. Details of the condition

Details of the condition that the medicinal product is intended to diagnose, prevent or treat should be provided. A review of the relevant scientific literature should be included, supported by scientific or medical references. This information should provide a clear

description of the disease or condition in question. Details of the symptoms, causes, epidemiological data, and preventive measures should be provided if applicable.

## 2. Proposed therapeutic indication

The sponsor should submit details of the proposed therapeutic indication for which designation is applied.

Where an ATC code has been assigned, this should be included.

The therapeutic indication should define the target condition or disease distinguishing between treatment, primary prevention, secondary prevention and diagnostic indications.

Sponsors should note that the indication applied for may be modified during the designation process. In addition, a designated indication is without prejudice to the final indication included in the terms of the marketing authorisation.

## 3. Medical Plausibility (If applicable)

Where the therapeutic indication refers to a subset of a particular patient population, a justification of the medical plausibility of this population sub-set should be submitted. The methods or criteria used to delineate this population subset should also be described.

## 4. Justification of the life-threatening or debilitating nature of the condition

(i) For applications submitted in accordance with Article 3(1)(a) paragraph 1 of Regulation 141/2000, a statement justifying the life-threatening or chronically debilitating nature of the condition supported by scientific or medical references should be provided.

(ii) For applications submitted in accordance with Article 3(1)(a) paragraph 2 of Regulation 141/2000, a statement justifying the life-threatening or seriously debilitating or serious and chronic nature of the condition supported by scientific or medical references should be provided.

## **B. Prevalence of the condition<sup>3</sup>**

Where designation according to Article 3(1) (a) paragraph 1 of Regulation 141/2000 is sought, information on the prevalence of the condition or disease in the Community should be provided in accordance with the requirements laid down by Commission Regulation XX:

### 1. Prevalence of the orphan disease or condition in the Community

#### *1.1. Reference documentation*

The documentation should include appended authoritative references which demonstrate that the disease or condition for which the medicinal product would be administered, affects not more than five in 10,000 persons in the Community, where these are available. This

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<sup>3</sup> The word “condition” is used in the text of the regulation. This is intended to ensure that the regulation applies also to treatments for conditions which are not classical diseases, in particular genetic disorders.

documentation should, as far as possible, clearly illustrate the prevalence of the disease or condition in the Community at the time of application for designation.

If up-to-date references are not available, the sponsor should provide a clear basis for the assumption that the disease or condition will meet the orphan criteria.

### *1.2 Information from databases on rare diseases*

Information from relevant databases in the Community should be provided, if available. Where an existing database refers to the prevalence of the disease or condition in one Member State, an explanation as to why it is plausible to extrapolate this data to other countries should be provided taking into account possible ethnic and/or cultural differences.

In the absence of databases in the Community, reference may be made to databases available in third countries, provided the extrapolation to the Community population is made.

## 2. Prevalence and incidence of the condition in the Community

Where designation according to Article 3(1) (a) paragraph 2, is sought, information on the prevalence and incidence in the Community of the condition or disease at the time at which the application for designation is submitted should be provided.

## 3. Information on participation in other Community projects

Where a disease or condition has been considered within the framework of other Community activities on rare diseases, this information shall be provided.

In the case of diseases or conditions included in projects financially supported by the Community in order to improve information on rare diseases, such as the European information network on rare diseases, foreseen by *European Parliament and Council Decision No 1295/99/EC of 29 April 1999<sup>4</sup> adopting a programme of Community action on rare diseases (1999-2003)* a relevant extract from this information, including in particular, details of the prevalence of the disease or condition in question, shall be provided.

In the case of research projects supported by Community framework programmes, a brief summary of the project of no more than one page, together with the relevant dates shall be provided.

## **C. Potential for return on investment**

In the case of applications for designation which are based on Article 3(1) (a) paragraph 2 of Regulation (EC) No 141/2000, i.e. where, without incentives, it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment, the documentation provided should be in accordance with Article 2.2 of Commission regulation XX.

The documentation submitted by the sponsor shall include data on all costs, under the sub-headings listed below, that the sponsor has incurred or expects to incur in the course of developing and marketing the medicinal product.

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<sup>4</sup> OJ n° L 155 of 22.06.1999

These costs shall include, but are not limited to, pre-clinical studies, clinical studies, formulation studies, stability studies, literature searches, meetings with regulatory authorities, costs of supplying the medicinal product, preparation of the application for designation. The documentation provided shall indicate the number of studies or investigations performed in each case, the duration and timing of each study or activity, the number of patients or animals involved in each study or activity, and the number of man-hours involved.

In cases where the medicinal product is already authorised for any indication or where the medicinal product is under investigation for one or more other indications, a clear explanation of and justification for the method that is used to apportion the development costs among the various indications shall be provided.

#### 1. Grants and tax incentives

The documentation provided shall include details of any grants, tax incentives or other cost recovery provisions received either within the Community or in third countries.

#### 2. Past and future development costs

The sponsor shall provide data on all costs incurred in course of developing the medicinal product. In addition, a statement of and justification for all development costs that the sponsor expects to incur after the submission of the application for designation shall be provided.

#### 3. Production and marketing costs

A statement of and justification for all production and marketing costs that the sponsor has incurred in the past and expects to incur during the first 10 years that the medicinal product is authorised shall be provided.

#### 4. Expected revenues

An estimate and justification for the expected revenues from sales of the medicinal product in the Community during the first 10 years after authorisation.

#### 5. Certification by registered accountant

The sponsor is required to ensure that all cost and revenue data is determined in accordance with generally accepted accounting practices and that it is certified by a registered accountant in the Community. A signed statement to this effect should be included.

### **D. Existence of other methods of diagnosis, prevention or treatment**

This section must be filled in for all applications for designation.

The sponsor is required to establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question or that if such a method exists that the medicinal product will be of significant benefit to those affected by that condition.

#### 1. Details of any existing diagnosis, prevention or treatment methods

In order to complete this part of the application, the sponsor should review available diagnosis, prevention or treatment methods in the Community. If no other methods currently exist, this should be stated.

In the case of authorised medicinal products, this review should include those authorised nationally (national or mutual recognition procedures) or by the Community (centralised procedure). In the case of medical devices which come within the scope of Directive 93/42/EEC, this should include all medical devices placed on the market according to this directive or in the case of active implantable medical devices which come within the scope of Directive 90/385/EEC, medical devices which are placed on the market or put into service in accordance with this directive.

For authorised medicinal products details should include: tradename(s), Member State(s) where authorised, holder of the authorisation, and the authorised indication. For medical devices, the: tradename(s) and the approved use(s) should be provided.

The sponsor should include in his review, as far as possible, other approaches to diagnosing, preventing or treating the disease or condition in question, such as surgical interventions, radiological techniques etc which are commonly used in the Community. The review should make reference to scientific and medical literature or any other relevant information.

## 2. Justification as to why methods are not satisfactory

The sponsor should provide justification as to why the methods reviewed are not considered satisfactory. This may be based on either clinical information or on scientific literature.

## 3. Justification of significant benefit

Alternatively the sponsor should provide justification for the assumption that the medicinal product for which designation is sought will be of significant benefit to those affected by the condition. This justification should make reference to scientific literature or the results of comparative studies, whether of a definitive or preliminary nature.

In this context, significant benefit means a clinically relevant advantage or a major contribution to patient care. In general a demonstration of potential greater efficacy, less frequent and/or less severe adverse effects, and/or more favourable pharmacokinetic properties than existing methods may be considered to support the notion of significant benefit. Other compliance-promoting features or evidence to show fewer interactions with food or other medicinal products, where these are relevant may also be considered.

## **E. Description of the stage of development**

### 1. Summary of the development of the product

The applicant should describe the current development status of the orphan medicinal product within the Community, e.g. preliminary research, pre-clinical investigation, clinical investigation, final preparation of a marketing authorisation dossier, etc. This information should be supplied in the form of an “investigator brochure” style summary. Actual reports of non-clinical and clinical studies undertaken need not be provided unless requested.

This section should also include information on whether the sponsor intends to apply to the EMEA for protocol assistance and/or for fee exemptions with respect to applications for marketing authorisation. Expected dates for the application for protocol assistance and submission of the marketing authorisation application should be provided if known.

## 2. Details of current regulatory status and marketing history in non EU countries

A summary of the regulatory status and marketing history of the medicinal product in third countries should be provided. This should include, for example, clinical trials and marketing application status, details of other indications under investigation including the location of the relevant investigations, details of the indications for which the medicinal product is approved in third countries; details of any adverse regulatory actions that have been taken against the medicinal product in any country. This information should also include details of whether orphan status has been applied for or granted in other countries with respect to the medicinal product.

## **F. Bibliography**

This section should contain all published references referred to in section A to D above and should be submitted together with the application but as a separate volume(s).