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**Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another**

First Commission proposal	7 <sup>th</sup> April 2000
Revision 1: included points to consider on plausibility of conditions and information on transfer of designations	19 <sup>th</sup> December 2000
Revision 2: included reference to Icelandic and Norwegian participation in the designation process, EU Enlargement, and cross-reference to the Commission Communication (2003/C 178/02)	24 <sup>th</sup> February 2004
Update of Annex in view of enlargement	October 2006
Revision 3: ease of obligation to provide paper copies of application; additional electronic copy (CD-Rom)	July 2007
Revision 4: clarified how the sponsors should define the medical plausibly and the significant benefit of its product, made possible to submit an electronic application, the common FDA-EMA common application or an amendment to an existing designation	March 2014
Revision 5: addressed the EMA's new online platform to submit applications for designations as orphan medicinal products and clarifications introduced by the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)	July 2021

# **Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another**

## **Introduction**

This guideline is intended to provide supplementary advice on how to compile the information that should be provided by sponsors in an application for orphan medicinal product designation. 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.

After the new European Medicines Agency (EMA) electronic system for submission of applications (industry portal) came into operation, more information and guidance on the format of applications is available on the EMA website. Sponsors are advised to read this EMA guidance, which explains in detail the pre-requisite steps that have to be completed before submitting an application for orphan medicinal product designation via the industry portal.

Each application for orphan designation for a medicinal product shall be submitted to the EMA and shall contain the information described in this guideline.

Section G of this guideline provides advice to sponsors wishing to transfer the designation of an orphan medicinal product and/or to change the name or address of a sponsor.

Section H of this guideline provides advice to sponsors wishing to amend an existing designation of an orphan medicinal product.

## **Legal Basis**

Article 5(3) and (11) respectively of Regulation (EC) No 141/2000<sup>1</sup> on Orphan Medicinal Products require the Commission in consultation with the Member States, the EMA 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 and on the form in which applications for transfer of designation to another sponsor shall be made. Article 4 of the same Regulation states that one of the tasks of the Committee for Orphan Medicinal Products (COMP) is to assist the Commission in drawing up detailed guidelines. Commission Regulation (EC) No 847/2000 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 by guidance as referred to in Article 5(3) of Regulation 141/2000. Commission Notice (2016/C 424/03) of 18 November 2016<sup>3</sup> sets out the Commission's interpretations on certain matters relating to the implementation of the designation and marketing exclusivity provisions.

## **Definitions**

The definitions laid down in Directive 2001/83/EC, Regulation (EC) No 141/2000 and Commission Regulation 847/2000 are applicable.

For the purpose of this guideline, the following additional definitions apply:

- (a) Condition: any deviation from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
- (b) Orphan Condition: a condition as defined above that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000. The orphan condition must also specify if the medicinal product

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<sup>1</sup> OJ n° L 18 of 22.01.2000

<sup>2</sup> OJ n° L 103 of 28.04.2000

<sup>3</sup> OJ n° C 424 of 16.11.2016

subject to the designation application is intended for diagnosis, prevention or treatment of the condition.

- (c) Therapeutic Indication: the proposed indication(s) for the future marketing authorisation, based on the sponsor's expectations at the time of the orphan designation application. Any future therapeutic indication must fall within the scope of the designated 'Orphan Condition'. The granted therapeutic indication at the time of marketing authorisation or extension of indication will be the result of the assessment of the quality, safety and efficacy data submitted with the marketing authorisation application and may be different to the one proposed at the time of orphan designation application.

### **Timing of submissions**

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 application (MAA) for the same medicinal product (and submitted by the same sponsor) has already been submitted in any Member State within the Union<sup>4</sup> or centrally through the EMA, whether or not the marketing authorisation has been granted, that this medicinal product is no longer eligible for designation for an orphan condition that includes the proposed therapeutic indication in the MAA.

Sponsors are strongly encouraged to request a pre-submission meeting with the EMA, free of charge, prior to submitting the orphan designation application, in particular if it is the first submission for an orphan designation.

In order to synchronise evaluation of applications for orphan designation with the meetings of the COMP, deadlines for submission of applications have been fixed and are published on the website of the EMA.

A sponsor may apply for designation of a medicinal product as an orphan medicinal product for an already approved medicinal product provided the designation applied for concerns a different orphan condition as compared to the approved therapeutic indication. If the medicinal product has already a non-orphan marketing authorisation, the marketing authorisation holder shall apply for a separate marketing authorisation (with a different invented name) which will cover only the orphan condition(s).

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

### **Language**

The full content of the application should be submitted in English. If the bibliographical references submitted are not in English, a summary in English should be included where possible.

At the time the application is made, the following elements should be translated in the official languages of the Union plus Icelandic and Norwegian:

- the name of the active substance (INN, if available, or common name)
- the proposed orphan condition.

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<sup>4</sup> Where reference is made to the Union, this should be read as including the EU Member States and Iceland, Liechtenstein and Norway.

## **Information to be supplied**

The application should be signed electronically by the sponsor indicating that the documentation provided is complete and accurate. The scientific document provided with the application (parts A-E) should generally be relatively short and concise (maximum 30 pages).

If designation is sought in more than one orphan condition for the same product, separate applications should be submitted for each orphan condition. In this regard, 'diagnosis', 'treatment' and 'prevention' of the same condition are considered as separate orphan conditions and should be subject to separate applications for designation.

A sponsor shall submit to the EMA the complete application for designation including full bibliographical references, in accordance with legal requirements and procedural advice published on the EMA website.

Prospective sponsors should consult available procedural advice on the EMA public website, and contact EMA for any outstanding question or clarification.

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

### 1. Name of the active substance(s)<sup>5</sup>

Before submitting the application, the active substance(s) should be registered as a controlled term in the appropriate EMA substance data management service by recommended International Non-proprietary Name (INN), accompanied by its salt or hydrate form if relevant. If no recommended 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, supplemented where appropriate by any relevant details. Where the active substance has a biological origin, please specify the cells or expression system used.

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 orphan condition

The sponsor should submit details of the proposed orphan condition for which designation is being applied for, specifying whether the medicinal product is for diagnosis, prevention or treatment of the condition. It should be noted that the proposed orphan condition, which is requested here, may be broader than the proposed therapeutic indication (see definitions above).

If more than one orphan condition is applied for the same product, separate applications should be submitted for each orphan condition.

### 3. Invented name, strength, pharmaceutical form and route of administration

Details of the proposed invented name, the strength (quantitative particulars of active ingredient), pharmaceutical form and route of administration for the orphan medicinal product should be provided

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<sup>5</sup> Only medicinal products can apply for an orphan designation in accordance with Article 2 of Regulation (EC) No 141/2000. The orphan designation is granted on the basis of the claims submitted by the sponsor and should not be taken as advice on classification as a medicinal product or as a qualification of active substance(s) in a medicinal product.

where possible. For products that are in the early stages of development it may not be possible to complete this section.

#### 4. Sponsor / contact person

The name or corporate name and registered address of the sponsor shall be provided as a controlled term in the EMA organisation data management service before application. Applicants belonging to the same group of companies have to be taken as one sponsor.

The sponsor must be established in the European Union, and must provide documentation indicating its permanent address in the Union. For sponsors whose main business is operated from outside of the Union, the address of those premises and a contact name should be provided.

A contract research organisation can be the sponsor of an orphan medicinal product as long as it is established in the Union, as required in Regulation (EC) No 141/2000.

The person authorised to communicate with the EMA on behalf of the sponsor during the designation procedure should be provided. The sponsor's contact point (telephone/ -and e-mail, in the Union) should be indicated to respond to queries arising from patients, health professionals or other interested parties in the post-designation period should they arise. For these post-designation interactions, it is advisable to provide a non-personalised/general corporate email address rather than one associated with a specific person.

### **Information to be included in the scientific part of the application**

An abbreviations list must be provided with each application. A review of the relevant scientific literature should be included, supported and cross-referenced to published references. The following information should be provided:

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

##### 1. Details of the orphan condition

Details of the condition that the medicinal product is intended to diagnose, prevent or treat should be provided. This information should provide a clear description of the disease or condition in question and should be based on published references. Details of the causes and symptoms should be provided.

The orphan condition may comprise a broader population than the population defined by the proposed therapeutic indication and should thus be the population on which the prevalence is estimated.

Sponsors should note that the orphan condition applied for may be modified by the COMP during the designation process. In addition, a designated orphan condition is without prejudice to the final therapeutic indication(s) to be agreed in the terms of the marketing authorisation.

##### 2. Medical Plausibility

This section should be completed for all applications with details of the rationale for the use of the medicinal product in the proposed orphan condition. This should include a description of the medicinal product and a discussion of its mechanism of action, as far as it is known. In order to support the rationale for the development of the product in the proposed condition non-clinical or preliminary clinical data are generally required. It is important to include, as far as possible, a discussion of the results of non-clinical studies with the specific product in models of the specific condition as applied for designation, and/or a discussion on preliminary clinical data in patients affected by the condition. Where available, reports of studies from the sponsor supporting the use of the product in the applied condition should be

included in the orphan designation application. The aim, methodology, results of all relevant studies, etc. should be submitted at the time of the application.

In addition, for applications where the proposed orphan condition refers to a subset of a particular condition, a justification of the medical plausibility for restricting the use of the medicinal product in the subset should be submitted in this section. The methods or criteria used to delineate this population subset should also be described.

The following points should be taken into account when considering the definition of condition. These points address, in particular, what constitutes a valid condition as opposed to what would be considered as invalid subsets within a condition and how these elements are linked to existing treatment(s), significant benefit of new treatments and to the proposed therapeutic indication(s).

#### General requirements

Recognised distinct medical entities would generally be considered as valid conditions. Such entities would generally be defined in terms of their specific characteristics, e.g. pathophysiological, histopathological, genetic subtype/genomic and clinical characteristics. The fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk (as defined in the proposed therapeutic indication) would generally not be sufficient to define a distinct condition.

The characteristics defining a distinct condition should determine a group of patients in whom development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions. Different degrees of severity or stages of a disease would generally not be considered as distinct conditions. It is the broader condition that should be considered for the purpose of justifying the criteria of designation.

#### Special considerations

- (a) Considering the above general requirements, convincing arguments would need to be presented to justify the medical plausibility of any proposed subset and the rationale for excluding the larger population. A subset of a condition which, when considered as a whole, has a prevalence greater than 5 in 10,000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action. In particular, the genetic subtype/profile and/or pathophysiological characteristics associated with this subset should be closely linked to the diagnostic and/or preventive and/or treatment action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population suffering from the condition.
- (b) Patients may be affected by more than one condition. Generally, the coexistence of two (or more) concomitant conditions would not be considered as a valid condition. However, it could be acceptable, if such intersection resulted in a certain new evaluable characteristic essential for the pharmacological effect and the medical outcome.
- (c) Exceptionally, a particular treatment modality could be considered to define a distinct condition. This could apply to products needed in medicinal procedures, but regardless of the specific underlying condition.

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

- (a) For applications submitted in accordance with the first paragraph of Article 3(1)(a) 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.

- (b) For applications submitted in accordance with the second paragraph of Article 3(1)(a) 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>6</sup>**

Where designation according to the first paragraph of Article 3(1) (a) of Regulation (EC) No 141/2000 is sought, information on the prevalence of the condition or disease in the Union should be provided in accordance with the requirements laid down by Commission Regulation (EC) No 847/2000. Prevalence (i.e. the number of persons affected by a condition at a specified instant in time in a given population) affected by the condition in the European Union<sup>7</sup> at the time of designation application, should be calculated for the condition as applied for in the designation application. The methodology for the calculation should be clearly described.

Sponsors are advised to consult the COMP Points to Consider document on “Points to consider document on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation” prior to completing this section of the application.

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

#### *1.1. Reference information*

The information should include a comprehensive review of authoritative references (including sources such as epidemiological and medical peer-reviewed articles, databases and registries) 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 Union at the time of application. This information should, as far as possible, clearly illustrate the prevalence of the condition in the Union (in as many Member States as possible) and should include a conclusion on the estimated prevalence per 10,000 persons in the Union at the time the application for designation is made.

For medicinal products intended for diagnosis or prevention of a condition, the prevalence calculation should be based on the population to which the product is expected to be administered on an annual basis.

The sponsor should clearly explain how the estimated prevalence has been calculated, indicating the methods and results for identifying source data/information (peer-reviewed articles, databases and registries) and calculating the prevalence<sup>8</sup>.

References for medical and epidemiological literature, databases, registries and other sources of information used to estimate prevalence should be summarised in tabular format, giving the most relevant information and results of each study, such as characteristics and size of the study population, case definition, etc. If up-to-date evidence-based references (including sources such as epidemiological and medical peer-reviewed articles, databases and registries) are not available, the sponsor should provide a clear basis for the assumption that the disease or condition will meet the orphan prevalence criteria at the time of application by presenting and discussing trends over time in incidence or increasing duration of condition due to improvement in treatment outcomes.

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<sup>6</sup> The word “condition” is used in the text of the Regulation.

<sup>7</sup> For the purposes of orphan designation the number of persons affected in the Union should be calculated based on the population of the Member States of the European Union plus Iceland, Liechtenstein and Norway.

<sup>8</sup> Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation. 20 June 2019 EMA/COMP/436/01 Rev. 1

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

Information from relevant sources of data, including databases and registries in the Union 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 Member States should be provided taking into account possible ethnic and/or cultural differences.

In the absence of epidemiological data or databases and registries and when only case reports of the disease are available in the Union, reference may be made to epidemiological data and databases available in third countries, provided an explanation of the extrapolation to the Union population is made.

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

Where designation according to the second paragraph of Article 3(1) (a) is sought, information on the prevalence and incidence of the condition in the Union at the time at which the application for designation is made should be provided for information purposes.

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

In the case of applications for designation which are based on the second paragraph of Article 3(1) (a) of Regulation (EC) No 141/2000, i.e. where, without incentives, it is unlikely that the marketing of the medicinal product in the Union would generate sufficient return to justify the necessary investment, the information provided should be in accordance with Article 2(2) of Commission Regulation (EC) No 847/2000.

The information 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.

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 information 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 information provided shall include details of any grants, tax incentives or other cost recovery provisions received either within the Union 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.



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.

### 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 Union during the first 10 years after authorisation.

### 5. Certification by registered accountant

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

## **D. Other methods for diagnosis, prevention or treatment of the condition**

In accordance with Article 3(1)(b) of Regulation (EC) No 141/2000 and Article 2(3) of Commission Regulation 847/2000, it is the responsibility of the sponsor to establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition.

Please note that, in the Section D.1 (Details of any existing diagnosis, prevention or treatment methods) must be filled in for all applications for designation. Conversely, Section D.2 (Justification as to why the methods are not considered satisfactory) and section D.3 (Justification of significant benefit) are mutually exclusive and only one of them should be filled in.

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

In accordance with Article 2(3)(a) of Commission Regulation EC 847/2000 in case of existing medicinal products for the diagnosis, prevention or treatment of an Orphan Condition, justification should be provided either as to why the existing methods are not considered satisfactory **or** for the assumption that the new medicinal product seeking designation will be of significant benefit to those affected by the condition.

In order to complete this part of the application, the sponsor should review available diagnosis, prevention or treatment methods in the Union, making reference to scientific and medical literature or other relevant information. If no other methods currently exist, this should be stated.

Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (e.g. surgery, radiotherapy, medical devices) may be considered satisfactory if there is consensus among clinicians in the particular field as to the value of such treatment(s) or if there is scientific evidence as to the value of such method. The assessment as to whether a particular method may be considered satisfactory shall take into account the experience with the method in question, documented results, and other factors including whether or not the method is invasive and/or requires hospitalisation. In the case of medical devices, this should include medical devices (including active

implantable medical devices) placed on the EU market in accordance with the relevant legal framework.<sup>9</sup> In certain cases, magistral or officinal formulations could be considered as satisfactory treatment, if they are well known and safe and this is a general practice in the EU.<sup>10</sup> The sponsor should also include in the review, as far as possible, other approaches to diagnosing, preventing or treating the ~~disease~~ or condition in question, such as diet, physical means, etc., which are commonly used in the Union. The review should make reference to scientific and medical literature or any other relevant information e.g. clinical guidelines by European medical societies if available.

In the case of authorised medicinal products, this review should include those authorised nationally in at least one Member State (decentralised or mutual recognition procedures) or by the European Commission (centralised procedure). An overview table of all authorised medicinal products should be included in this section. Details provided should include: invented name(s), Member State(s) where authorised, holder of the authorisation, and the authorised indication (medicinal products taken into consideration should be authorised for the treatment of the ~~disease~~ condition as such or ~~authorised to~~ or for a broader condition which includes the condition which is subject of the application, or ~~address~~ the same set of symptoms). For medical devices, name(s) and the approved use(s) should be provided. Where medicinal products authorised in the proposed orphan condition exist they would be viewed as 'satisfactory methods' and the sponsor would be required to argue 'significant benefit'.

## 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. It should be noted that, where medicinal products authorised in the proposed orphan condition exist they would be viewed as 'satisfactory methods' and the sponsor would be required to argue 'significant benefit'. When there is evidence that magistral or officinal formulations are well known and safe and this is a general practice in the Union, the sponsor is expected to address those methods in this section and to discuss why they are not considered as 'satisfactory methods'. If this section is completed, it is not necessary to complete section D3 regarding justification of significant benefit and vice versa.

## 3. Justification of significant benefit

Where there already exist methods of diagnosis, prevention or treatment of the condition in question, 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 appropriate scientific literature or the results of comparative studies, whether of a definitive or preliminary nature. If this section is completed, it is not necessary to complete section D2 regarding justification as to why methods are not considered satisfactory and vice versa.

At the time of designation, significant benefit could be based on assumptions, which should be well justified by non-clinical or preliminary clinical data in the specific context of the sought condition. Assumptions of potential benefit(s) should be plausible and where possible based on sound pharmacological principles. Non-clinical data and preliminary clinical data should be added as supportive evidence. In general, a demonstration of greater efficacy and/or an improved safety profile (i.e. clinically relevant advantage) may be considered to support the notion of significant benefit. When significant benefit is argued on major contribution to patient care due to significantly improved adherence in treatment due to a change in pharmaceutical form, this should be accompanied by a discussion on the serious and documented difficulties with the existing formulation and data to demonstrate that the proposed product can overcome such difficulties. In all cases, the COMP will

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<sup>9</sup> Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

<sup>10</sup> See Commission Notice (2016/C 424/03) of 18 November 2016

determine whether or not these assumptions are plausible and supported in the application by appropriate evidence.

Acknowledging the fact that many sponsors will apply for orphan designation at an early stage in development, when comparative data are often not available, a critical review comparing satisfactory methods should be provided, justifying the assumption of significant benefit. This review should be based not only on the limitations and risks of the available methods but in particular on the benefit expected with the proposed product.

All orphan designations are reviewed to ensure maintenance of the criteria prior to the grant of a marketing authorisation at the time of adoption by the Committee of Human Medicinal Products of EMA. At this stage, sponsors of designated orphan medicinal products will be required to demonstrate significant benefit over currently satisfactory methods in order to maintain orphan status. To this end, the COMP will require a higher level of data/evidence for the orphan status to be maintained than at the time of designation.

Protocol assistance is highly recommended to ensure an appropriate clinical development of the orphan medicinal product. Protocol assistance should also include guidance to demonstrate significant benefit over satisfactory methods of diagnosis, prevention or treatment.

Further information and examples are available in the Commission Notice (2016/C 424/03).

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

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

The applicant should concisely describe the current development status of the orphan medicinal product within the Union, e.g. preliminary research, brief details of pharmaceutical development, tabular format of pre-clinical investigation, clinical investigation, final preparation of a marketing authorisation dossier, etc. Details of the proposed development plans in the orphan condition should be provided. Information on any proposed developments in other indications should be supplied. This information should be supplied in the form of an “investigator brochure” style summary. The full study 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 EMA for protocol assistance. 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 the EU and non EU countries

A summary of the worldwide regulatory status and marketing history of the medicinal product should be provided. This should include, for example, clinical trials and marketing application status, details of the indications for which the medicinal product is approved in third countries; previous applications for marketing authorisation; and any adverse regulatory actions that have been taken against the medicinal product in any country.

This section should also include details of whether orphan status has been applied for or granted in other countries with respect to the medicinal product. If orphan status has been granted elsewhere, it is useful to append a copy of the decision on orphan designation to the application.

## **F. Bibliography**

All published references referred to should be submitted together with the application. Where information has been downloaded or extracted from a website, the date that the website has been accessed should be noted.

The preferred format for cross-referencing published literature in the application is by the lead author and year e.g. (Smith *et al*, 2002).

## **G. Transfer of the Orphan designation to another sponsor and change in the name of the Sponsor and/or the address of the Sponsor**

### 1. Transfer of the Orphan designation to another sponsor

Transfer of the designation of an orphan medicinal product is possible in accordance with Article 5(11), Regulation (EC) No 141/2000.

At the time of submission of a marketing authorisation, the applicant and the sponsor of the orphan medicinal product should be the same in order to benefit from the orphan fee incentive. When needed, a transfer will be requested by the sponsor in advance of the marketing authorisation application submission. Both the applicant and the sponsor need to be established in the Union.

The current sponsor should submit an application according to procedural guidance available on the EMA website. The EMA will not be in a position to provide an opinion on the transfer should the application be incomplete or unsatisfactory.

Within 30 days of the submission of the request, the EMA shall adopt an opinion to be sent to the existing sponsor and to the Commission.

In the case of agreement to the transfer, the Commission shall amend the decision granting the designation as an orphan medicinal product. The transfer is accepted from the date of notification of the Commission Decision. The Commission shall also publish the Decision on the community register on orphan medicinal products.

### 2. Change in the name of the Sponsor and/or the address of the Sponsor

A change in the name or address of an existing sponsor does not require a new legal act, provided that the sponsor remains the same person or legal entity.

The sponsor should submit the request according to procedural guidance available on the EMA website, including the amendment of relevant data first in the EMA's organisation data management service controlled term lists).

This information shall be maintained by the EMA and the European Commission. In the case of a change in the name, the community register on orphan medicinal products shall be updated accordingly.

## **H. AMENDMENT OF AN EXISTING DESIGNATION**

In exceptional cases, change of the designated condition is possible as foreseen in the Commission Notice (2016/C 424/03). During the development of the product, the classification of a disease may change and the designated condition may need to be modified to better reflect the indication that the sponsor intends to request at the time of marketing authorisation. Voluntary changes by the sponsor to broaden or narrow the orphan condition cannot be covered by the amendment procedure, which only applies in cases the classification of the disease changes. In such situation, the sponsor should submit a revised application. This request must be introduced before the application for a marketing authorisation is made. The sponsor should update any relevant sections accordingly e.g. prevalence. The sponsor should specify the reference to the existing designation under section I.1.3.

Any other changes (e.g. new salt or INN) not affecting the condition as reflected above are not concerned by this procedure and should either be addressed in the annual report or by submitting a new application for an orphan designation.

A request for amendment of an existing designated condition will follow the same assessment process as a new designation by the Committee for orphan medicinal product. It will therefore be necessary to justify that all criteria for designation remain applicable. Based on the Committee's favourable opinion on the request for amendment, the European Commission will then issue a new Decision for the revised condition. The initial Decision will be automatically repealed by the new Decision.