COMMISSION NOTICE

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

(2022/C 440/02)

INTRODUCTION

This guideline gives supplementary advice on the information sponsors must provide when applying for designation of a medicinal product as an orphan medicinal product. It covers both the format and content of the application, and should be followed unless good reasons are given for deviating from it.

The guideline should be read in conjunction with existing information and guidance on the format of applications, available on the European Medicines Agency (EMA) website ([1]). The EMA's online guidance explains in detail the steps that must be completed before submitting an online application via the EMA's 'IRIS' platform ([2]).

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

Section G of the guideline provides advice on transferring the designation of an orphan medicinal product to another sponsor, and changing the name or address of a sponsor.

Section H provides advice on amending an existing designation of an orphan medicinal product.

LEGAL BASIS

Article 5 of Regulation (EC) No 141/2000 ([3]) on orphan medicinal products requires 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 the designation of medicinal products as orphan medicinal products (Article 5(3)), and

— the form and content of applications to transfer designation to another sponsor (Article 5(11)).

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 ([4]) sets out how the designation criteria for orphan medicinal products are to be implemented and refers to further guidance drawn up under Article 5(3) of Regulation (EC) 141/2000. Commission Notice (2016/C 424/03) of 18 November 2016 ([5]) sets out the Commission's interpretations on certain matters relating to 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 (EC) 847/2000 are applicable.

([1]) https://www.ema.europa.eu/en.
([2]) https://iris.ema.europa.eu/.
([3]) OJ L 18, 22.1.2000, p. 1.
([4]) OJ L 103, 28.4.2000, p. 5.
([5]) OJ C 424, 16.11.2016, p. 3.

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. It must also be specified if the medicinal product 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 therapeutic indication granted by the marketing authorisation or the extended indication granted subsequently will depend on the outcome of an assessment of the quality, safety and efficacy data submitted with the marketing authorisation application. It may be different to the indication proposed at the time of orphan designation application.

TIMING OF APPLICATIONS

A sponsor can apply to have a product designated as an orphan medicinal product at any stage in the product's development *before* the application for marketing authorisation is made. However, if the same sponsor has already submitted a marketing authorisation application for the same medicinal product in any EU ([6]) Member State or centrally through the EMA, then the product is no longer eligible for designation for an orphan condition that includes the proposed therapeutic indication in the marketing authorisation application, even if the marketing authorisation has not yet been granted.

Sponsors are strongly encouraged to request a pre-submission meeting with the EMA, free of charge, before submitting the orphan designation application, especially if it is their first application 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 orphan designation of an already approved medicinal product, provided the application concerns a different orphan condition from the condition mentioned in the approved therapeutic indication. If the product already has a non-orphan marketing authorisation, the marketing authorisation holder must apply for a separate marketing authorisation (with a different invented name), which will cover only the orphan condition.

More than one sponsor may apply for designation for the same product, intended to diagnose, prevent or treat the same or a different condition. Each sponsor must complete a separate application.

LANGUAGE

The full application should be in English. For bibliographical references in other languages, a summary in English should be included where possible.

The following information should also be provided, when the application is made, in all official languages of the EU, plus Icelandic and Norwegian:

— the name of the active substance (international non-proprietary name (INN), if available, or common name),

— the proposed orphan condition.

([6]) Where reference is made to the EU, this should be read as including 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 for more than one orphan condition for the same product, separate applications should be submitted for each orphan condition. For these purposes, each different 'diagnosis', 'treatment' and 'prevention' for the same condition are considered as separate orphan conditions and separate applications should be made for designation.

Each application for designation must include full bibliographical references, in accordance with legal requirements and procedural advice published on the EMA website.

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

INFORMATION TO BE INCLUDED IN THE APPLICATION

1. *Name of the active substance(s)*

Before the application is submitted, each active substance should be registered as a controlled term in the appropriate EMA substance data management service, using its recommended international non-proprietary name (INN) and providing 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. In the absence of a common name, the exact scientific designation should be given. Substances that do not have an exact scientific designation should be described by a statement of how and from what they were prepared, together with 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 line with the note for guidance on the quality of herbal medicinal products.

2. *Proposed orphan condition*

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

If, for the same product, more than one orphan condition is applied for, separate applications should be submitted for each 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 where possible. For products that are in the early stages of development, this may not be possible.

4. ***Sponsor / contact person***

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

The sponsor must be established in the EU, and must provide documentation indicating its permanent address in the EU.

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

The sponsor must indicate a person authorised to communicate with the EMA on its behalf during the designation procedure. The sponsor should provide contact details (telephone number in the EU and email address) for any queries arising from patients, health professionals or other interested parties after designation. 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***

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

The orphan condition may comprise a broader population than the population defined by the proposed therapeutic indication. This broader population should be the basis for estimating prevalence.

During the designation process, the COMP may amend the orphan condition applied for. 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, to be completed for all applications, should provide a detailed rationale for the use of the medicinal product in the proposed orphan condition. It should include a description of the medicinal product and a discussion of its mechanism of action, as far as it is known. To support the rationale for developing 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 involving the specific product in models of the specific condition cited in the application, and/or a discussion of preliminary clinical data in patients affected by the condition. The application should include, where available, study reports from the sponsor supporting the use of the product in the applied condition. The aim, methodology, results of all relevant studies, etc. should be submitted at the time of the application.

Where the proposed orphan condition refers to a subset of a particular condition, this section should justify why it is medically plausible to restrict use of the medicinal product to the subset. The methods or criteria used to delineate this population subset should also be described.

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

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. Alone, the mere existence of a subset of patients who would be expected to benefit from the product (as defined in the proposed therapeutic indication) would generally not be an acceptable defining criterion for a distinct condition.

The characteristics defining a distinct condition should determine a group of patients in whom the development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmaco-dynamic 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 meeting the designation criteria.

Special considerations

(a) Considering the above general requirements, convincing arguments would need to be presented to demonstrate 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 of greater than 5 in 10 000, could be exceptionally 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 this resulted in a certain new and evaluable characteristic that is essential for the pharmacological effect and the medical outcome.

(c) In rare cases, a particular treatment method could be considered to define a distinct condition. This could apply to products needed in medicinal procedures, regardless of the specific underlying condition.

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

(a) For applications submitted under the first paragraph of Article 3(1)(a) of Regulation (EC) 141/2000, a statement should be provided which explains the life-threatening or chronically debilitating nature of the condition, supported by scientific or medical references.

(b) For applications submitted under the second paragraph of Article 3(1)(a) of Regulation (EC) 141/2000, a statement demonstrating 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** ([7])

Where designation is sought under the first paragraph of Article 3(1)(a) of Regulation (EC) No 141/2000, information on the prevalence of the condition or disease in the EU should be provided in accordance with the requirements laid down by Commission Regulation (EC) No 847/2000. The application must state the prevalence of the condition (the number of people affected by a condition at a specified instant in time in a given population) affected by it in the EU ([8]) at the time of designation application), and, should be calculated for the condition as applied for in the designation application. The methodology for the calculation should be clearly described.

([7]) The word 'condition' is used in the Regulation.

([8]) For the purposes of orphan designation, the number of people affected in the EU should be calculated based on the population of the EU Member States plus Iceland, Liechtenstein and Norway.

Before completing this section of the application, sponsors are advised to consult the COMP guideline document 'Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation' ([9]).

1. ***Prevalence of the orphan disease or condition in the EU***

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 5 in 10 000 persons in the EU at the time of application. This information should, as far as possible, clearly illustrate the prevalence of the condition in the EU (in as many Member States as possible) and should include a conclusion on the estimated prevalence per 10 000 persons in the EU 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 both for identifying source data/information (peer-reviewed articles, databases and registries) and for calculating the prevalence (see 'Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation') ([10]).

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 are not available, the sponsor should provide a clear rationale for the assumption that the disease or condition will meet the orphan prevalence criteria at the time of application. For this, the sponsor should present and discuss trends over time in terms of incidence or increasing duration of condition due to improvement in treatment outcomes.

1.2. *Information from databases on rare diseases*

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

Where, in the absence of epidemiological data or databases and registries, only case reports of the disease are available in the EU, reference may be made to epidemiological data and databases available in non-EU countries, provided an explanation is given of the extrapolation to the EU population.

2. ***Prevalence and incidence of the condition in the EU***

Where designation under the second paragraph of Article 3(1)(a) is sought, the sponsor should provide data on the prevalence and incidence of the condition in the EU at the time at which the application for designation is made should for information purposes.

C. **Potential for return on investment**

For applications 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 EU would generate sufficient return to warrant the necessary investment, the information provided should be in accordance with Article 2(2) of Commission Regulation (EC) No 847/2000.

([9]) 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.

([10]) See footnote 7.

Costs and revenue should be detailed under the sub-headings listed below.

1. Grants and tax incentives – grants, tax incentives or other forms of cost recovery received in the EU or in non-EU countries.

2. Past and future development costs – details of costs already incurred in developing the medicinal product, and a statement and explanation of all development costs that the sponsor expects to incur after submitting the application.

The details of past costs should include, but not be limited to: pre-clinical studies, clinical studies, formulation studies, stability studies, literature searches, meetings with regulatory authorities, costs of supplying the medicinal product, and preparation of the application. The information provided should include 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 work-hours involved.

Where the medicinal product is already authorised for an indication or is being considered for one or more other indications, the statement of costs should give a clear statement and explanation of the method used to apportion the development costs among the various indications.

3. Production and marketing costs – a statement and explanation of all production and marketing costs that the sponsor has incurred in the past and expects to incur in the first 10 years after authorisation.

4. Expected revenue – an estimate and explanation of the expected revenue from sales of the medicinal product in the EU in the first 10 years after authorisation.

5. Certification by registered accountant – a signed statement to the effect that all cost and revenue data have been calculated in accordance with generally accepted accounting practices and have been certified by a registered accountant in the EU.

D. **Other methods for diagnosing, preventing or treating the condition**

Under Article 3(1)(b) of Regulation (EC) No 141/2000 and Article 2(3) of Commission Regulation (EC) 847/2000, it is the responsibility of the sponsor to establish that there is no existing satisfactory method for diagnosing, preventing or treating the condition in question or, if there is already such a method, that the medicinal product will be of significant benefit to those affected by the condition.

Section D.1 ('Details of any existing diagnosis, prevention or treatment methods') must be filled in for all applications. 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***

Under Article 2(3)(a) of Commission Regulation (EC) 847/2000, if any medicinal products already exist for diagnosing, preventing or treating an orphan condition, justification should be provided as to why the existing methods are not considered satisfactory or why the new medicinal product will be of significant benefit to those affected by the condition.

In this part of the application, the sponsor should review available diagnosis, prevention or treatment methods in the EU, 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 (e.g. surgery, radiotherapy or medical devices) with no marketing authorisation 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 for the value of such methods. The assessment as to whether a particular method may be considered satisfactory should take account of experience with the method, documented results, and other factors including whether or not the method is invasive or requires hospitalisation.

The review should include, where relevant:

— medical devices (including active implantable medical devices) on the EU market, in accordance with the relevant legal framework ([11]),

— magistral or officinal formulations, if they are well known and safe and this is a general practice in the EU ([12]),

— where possible, other approaches to diagnosing, preventing or treating the disease or condition in question, such as diet or physical means, which are commonly used in the EU.

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.

For authorised medicinal products, the review should include those authorised nationally in at least one Member State (decentralised or mutual recognition procedures) or by the European Commission (centralised procedure), for the condition as such, for a broader condition which includes the condition to which the application relates, or for the same set of symptoms. An overview table of all relevant authorised medicinal products should be provided, including:

— invented name,

— Member States where authorised,

— holder of the authorisation, and

— authorised indication.

For medical devices, the name and the approved uses should be provided.

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 clinical information or on scientific literature.

Where medicinal products have already been authorised for the proposed orphan condition, these 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 EU, the sponsor is expected to address those methods in this section and to discuss why they are not considered 'satisfactory methods'. If this section is completed, there is no need to complete Section D3 ('Justification of significant benefit').

3. ***Justification of significant benefit***

Where methods already exist for diagnosing, preventing or treating 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 definitive and preliminary comparative studies. If this section is completed, there is no need to complete Section D2 ('Justification as to why methods are not considered satisfactory').

([11]) 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 (OJ L 117, 5.5.2017, p. 1).

([12]) See Commission Notice (2016/C 424/03) of 18 November 2016.

At the time of designation, the assumption of significant benefit could be based on non-clinical or preliminary clinical data in the specific context of the 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 supporting 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. Where 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 determine whether or not these assumptions are plausible and supported in the application by appropriate evidence.

Since 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, explaining why significant benefit can be assumed. This review should consider the limitations and risks of the available methods and focus 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 maintaining orphan status than for the initial designation.

Protocol assistance is highly recommended to ensure 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 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 EU, e.g. preliminary research, brief details of pharmaceutical development, tabular format of pre-clinical investigation, clinical investigation, final preparation of a marketing authorisation file. Details of the proposed development plans for the orphan condition should be provided. Information on any proposed developments for other indications should be supplied. This information should be supplied in the form of an 'investigator brochure' style summary. Full study reports of non-clinical and clinical studies 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 in 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 non-EU 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 for the product in other countries. 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 the website was 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 or address of the sponsor**

1. ***Transfer of the orphan designation to another sponsor***

The designation of an orphan medicinal product can be transferred to another sponsor under Article 5(11) of Regulation (EC) No 141/2000.

When the marketing authorisation is submitted, the marketing authorisation applicant and the sponsor of the orphan medicinal product need to be the same to benefit from the orphan fee incentive. For this, where necessary, the sponsor can request a transfer before the marketing authorisation application is submitted. Both the applicant and the sponsor need to be established in the EU.

When submitting a transfer application, the current sponsor should follow the procedural guidance on the EMA website. The EMA will not be able to give an opinion on the transfer if the application is incomplete or filled in incorrectly.

Within 30 days of the request being submitted, the EMA will send its opinion to the current sponsor and to the Commission.

If it agrees to the transfer, the Commission will amend the decision granting the designation as an orphan medicinal product. The transfer is valid from the date when the Commission gives notice of the amended decision. The Commission will also publish the decision on the community register of orphan medicinal products ([13]).

2. ***Change in the name or address of the sponsor***

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

The sponsor should submit the request in accordance with the procedural guidance on the EMA website. In particular, the sponsor must first amend the relevant data in the list of controlled terms in the EMA's organisation data management service).

This information is kept by the EMA and the European Commission. Name changes are recorded in the community register on orphan medicinal products.

H. **Amendment of an existing designation**

In exceptional cases, the designated condition may be changed, in line with 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 the sponsor intends to request at the time of marketing authorisation. The amendment procedure is used only for changes to the classification of a disease. It cannot be used to broaden or narrow the orphan condition at the sponsor's request. For this, the sponsor should submit a revised orphan designation application before applying for a marketing authorisation. The sponsor should update any relevant sections accordingly e. g. prevalence. The sponsor should specify the reference for the existing designation under Section I.1.3.

This procedure cannot be used for any other changes (e.g. new salt or new INN) that do not affect the condition. For this, a new application must be submitted.

A request to amend an existing designated condition undergoes the same assessment process as a new designation. The requester will need to demonstrate that all criteria for designation are still met. If the COMP agrees to the amendment request, the Commission will issue a new decision and the initial decision will be automatically repealed.

([13]) https://ec.europa.eu/health/documents/community-register/html/index_en.htm.

ANNEX

Section I

History of the document

Version	Comment	Date
First Commission Proposal		7 April 2000
Update 1	— Included points to consider on plausibility of conditions and information on transfer of designations	19 December 2000
Update 2	— Addition of reference to Icelandic and Norwegian participation in the designation process, EU Enlargement, and cross-reference to the Commission Communication (2003/C 178/02)	24 February 2004
	— Update of Annex in view of enlargement	October 2006
Update 3	— Ease of obligation to provide paper copies of application; additional electronic copy (CD-ROM)	July 2007
Update 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
Update 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)	December 2021