



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Research and Development Support

Procedure for orphan medicinal product designation

Guidance for sponsors submitting an application via the current existing submission process until 19 Sept 2018

¹Revision of text for 'Parallel application with international regulators', p.7



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1. Legislative background

The legislation on orphan medicinal products, [Regulation \(EC\) No 141/2000](#) of the European Parliament and of the Council, was adopted on 16 December 1999 and published in the Official Journal of the European Communities on 22 January 2000 (Ref. L18/1). This Regulation lays down a Community procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the development and placing on the market of designated orphan medicinal products. The Regulation also establishes the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA), which is responsible for examining applications for orphan medicinal product designation.

On 27 April 2000, the Commission adopted [Regulation \(EC\) No 847/2000](#) laying down implementing rules and setting out definitions essential for the application of Regulation (EC) No 141/2000 (Ref. L103/5). As of 28 April 2000, the date this Regulation entered into force, sponsors have been able to submit applications for orphan medicinal product designation to the EMA.

On 31 March 2004, the European Parliament adopted [Regulation \(EC\) No 726/2004](#), which provides the legal framework for the centralised authorisation and supervision of medicines for human and veterinary use and establishes the European Medicines Agency (EMA). It determines that all marketing authorisations for orphan medicines in the EU should follow the [centralised authorisation procedure](#) and that the CHMP can issue guidance regarding [compassionate-use](#) programmes.

On 15 December 2005, the European Commission adopted [Regulation \(EC\) No 2049/2005](#) regarding the payment of fees to, and receipt of assistance from, the EMA by micro, small and medium-sized enterprises (SMEs). It determines that scientific advice and scientific services for designated orphan medicines shall be provided by the EMA to SMEs free of charge.

On 29 March 2006, the European Parliament adopted [Regulation \(EC\) No 507/2006](#), which provides the legal framework for the granting of a [conditional marketing authorisation](#) to medicines that fall within the scope of Regulation (EC) No 726/2004. It establishes that orphan medicines can be granted a conditional marketing authorisation within this legal framework.

On 12 December 2006, the European Parliament adopted [Regulation \(EC\) No 1901/2006](#) on medicinal products for paediatric use. It establishes that the usual period of market exclusivity for orphan medicines may be extended to twelve years if study results are submitted in compliance with an agreed paediatric investigation plan at the time of marketing authorisation.

On 19 September 2008, the Commission adopted a [Guideline on aspects of the application of Article 8\(1\) and \(3\) of Regulation \(EC\) No 141/2000](#): assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity, C(2008) 4077.

On 23 September 2008, the Commission published a [Guideline on aspects of the application of Article 8\(2\) of Regulation \(EC\) No 141/2000](#): review of the period of market exclusivity of orphan medicinal products, 2008/C 242/07.

On 18 November 2016, the Commission adopted [Commission notice on the application of Articles 3, 5 and 7 of Regulation \(EC\) No 141/2000 on orphan medicinal products](#) setting out its interpretation on certain matters relating to the implementation of the designation and the market exclusivity provisions. This notice replaced previous Commission Communication (2003/C/178/02 adopted on 29 July 2013).

On 29 May 2018, the Commission adopted [Commission Regulation \(EU\) 2018/781 amending Regulation \(EC\) No 847/2000 as regards the definition of the concept 'similar medicinal product'](#).

2. Objectives

In examining an application for orphan medicinal product designation the COMP will focus on determining whether the sponsor has established that the designation criteria are met, i.e.:

- the life-threatening or debilitating nature of the condition;
- the medical plausibility of the proposed orphan indication;
- that the prevalence of the condition in the European Union is not more than five in 10,000; or
- that it is unlikely that marketing the medicinal product in the European Union, without incentives, would generate sufficient return to justify the necessary investment;
- that no satisfactory method of diagnosis prevention or treatment exists, or if such a method exists, that the medicinal product will be of significant benefit to those affected by the condition.

The evaluation process has a maximum duration of 90 days without clock stops and cannot be lengthened to accommodate for the lack of data or other omissions in the application submitted by the sponsor. In order to assist in the development of a policy on orphan medicinal products, an expert network will be built up by the Committee, with expert(s) identified as appropriate to be involved in the evaluation of applications for orphan medicinal product designation.

3. General principles

Sponsors are no longer required to send a notification of intent to file an orphan drug application for designation to the EMA. Sponsors should follow one of the two options listed below instead:

Submit the application to the EMA

Presubmission meetings are not mandatory and sponsors are most welcome to send an application for orphan drug designation without notice. However, we will appreciate that sponsors send the application preferably few days before any of the published submission deadlines available on the EMA website to allow more time for the validation process. For further details on the submission of an orphan drug application for designation see point 3.2.

Request a presubmission meeting/teleconference

If sponsors feel they could benefit from a preliminary discussion before the submission of an orphan drug application to the EMA they should request a presubmission meeting/teleconference at least two months prior to their planned submission date by sending an email to orphandrugs@ema.europa.eu. This should allow enough time for the organisation and any amendment of the application as recommended by the EMA. Sponsors should send the draft application for the presubmission discussions one week in advance. For further details see point 3.1.1.

In any of the cases mentioned above sponsors should submit the application to orphandrugs@ema.europa.eu via the secure system, Eudralink clearly indicating in the subject message if the application is:

- 'Draft application for presubmission meeting on <date>'
- 'Application for orphan drug designation submission deadline <date>'

Sponsors should contact the EMA Eudralink helpdesk at eudralink@ema.europa.eu to open an account.

3.1.1. Pre-submission meeting

- The EMA strongly encourages sponsors to request a pre-submission meeting prior to filing an application for orphan medicinal product designation. Pre-submission meetings for orphan designation are free of charge and are held mostly via teleconference, unless the sponsor has a strong preference to come to the Agency in person. Our experience has shown that pre-submission meetings via teleconference are highly appreciated by sponsors, who do not need to worry about travel arrangements and the related expenses. The quality of the meeting and its outcome is equivalent. Follow-up teleconferences are also possible.
- The following documents should be sent at least one week prior to the meeting/teleconference via Eudralink indicating clearly in the subject message 'Draft application for presubmission meeting/teleconference on <date>':
 - draft [EMA application form](#)
 - draft [scientific sections A-E](#);
 - short PowerPoint presentation about the application (approx. 15 min);
 - list of participants;
 - dial-in number and password for teleconference (if applicable).
- In order to obtain the best outcome the sponsor should focus their presentation on issues pertaining to the orphan designation process:
 - condition, scope of the application;
 - description of the active substance, its mode of action and supporting non-clinical (in vitro and in vivo if available) as well as clinical data (if available) which would support the hypothesis of its potential in treating, diagnosing or preventing the condition;
 - chronically debilitating and/or life threatening nature of the condition;
 - overview of the prevalence calculation;
 - if applicable the significant benefit that the product will offer over current approved therapies in the EU;
 - intention to submit the application for orphan designation to other Agencies (e.g. US/FDA, Japan/MHLW & PMDA).
- During the pre-submission meeting the EMA will also offer a quality check of two key documents:
 - application form;
 - sections A-E of the scientific part of the application.
- Sponsors will be invited to take minutes of the meeting, which should be provided to the EMA within one week after the meeting. The Agency will subsequently review the minutes within one week, and agree the final (amended) minutes with the applicant.

3.1.2. Appointment of coordinators

- Two coordinators (1 COMP member, 1 EMA scientific officer) will be appointed for each application. The sponsor will be informed accordingly via e-mail after the submission of the application.
- COMP members will be invited to propose experts to be involved in the evaluation as appropriate. The Committee may appoint one or more experts from the EU expert list to be involved in each application, in addition to the coordinators, as appropriate.

3.2. Submission

- Deadlines for submission of an orphan medicinal product designation application are published on the [EMA website](#).
- The sponsor should submit the application to orphandrugs@ema.europa.eu via Eudralink indicating clearly in the subject message 'Application for orphan drug designation submission deadline <date>'.
• The complete application should include:

Document	Format
Cover letter	signed PDF
EMA application form The application should be signed by no other than the sponsor. If the sponsor does not have the Unique Product Identifier (UPI) to complete the form the EMA will allocate one on receipt of the application.	e-signed PDF ²
Scientific sections A-E of the application	Word (97-2003)
Proof of establishment of the sponsor in the EU. The sponsor should have a permanent physical address in the EU and provide full details in the application form including the name of a contact person at the sponsor premises able to receive any documents in person.	PDF
If applicable, letter of authorisation from the sponsor for the person/company acting on their behalf during the procedure	signed PDF
Translations of the name of the product and the proposed orphan indication into the official languages of the European Union, plus Icelandic and Norwegian	Word
Bibliography saved as single publications and titled as first author and year, such as in 'Smith PH et al 2004.PDF'	PDF

² For general information on an electronic signature, please refer to <http://esubmission.ema.europa.eu/eSignatures.html>. For further information, including specific technical information, please contact ITServiceDesk@ema.europa.eu.

Important:

In preparing an application for orphan medicinal product designation, sponsors are requested to follow the [Commission guideline \(ENTR/6283/00\)](#) for the format and content of applications for designation as orphan medicinal products.

The Agency encourages parallel applications for orphan designation with **regulatory authorities outside the EU** and has special arrangements with regulators in the United States and Japan for this purpose:

- If an application has not been submitted to the United States before, the Agency advises sponsors to apply for orphan designation with the United States Food and Drug Administration (FDA). There are regular interactions and collaboration between EMA and FDA in the orphan and rare disease clusters.
- If an application has not been submitted to the Japanese authorities before, the Agency also encourages the sponsor to seek orphan designation from the Ministry for Health, Labour and Welfare (MHLW) in Japan. Under the Japanese orphan designation system, the MHLW provides consultation on orphan designations before submission, whereas marketing-authorisation applications submitted following an orphan designation are assessed by the Pharmaceuticals and Medical Devices Agency (PMDA). The MHLW generally seeks scientific counsel from the PMDA on the orphan designation.

If more than one indication is applied for the same product, separate applications should be submitted for each orphan indication. In this regard, 'treatment' and 'prevention' of the same condition are considered as two separate indications and should be the subject of two separate applications for orphan designation.

The sponsor should use the **recommended INN** if available at the time of submitting the application (proposed INNs will not be accepted). The INN should be used in the application form and throughout the entire scientific sections.

3.3. Validation

- The EMA Secretariat will complete the validation of the application and confirm whether sufficient data are provided that would allow for the evaluation of the application by the COMP as per Regulation (EC) No 141/2000. The EMA will also check that the application complies with the Commission guideline (ENTR/6283/00, rev 4) for the format and content of applications for designation as orphan medicinal products and Communication from the Commission on Regulation (EC) No 141/2000, 2003/C 178/02.
- EMA will check whether:
 - justifications are provided that the proposed condition may be acceptable for designation as per the abovementioned guideline,
 - whether data with the specific product in a relevant non-clinical model or in patients are included for the justification of medical plausibility,
 - whether a clear methodology and conclusion for the prevalence is provided, and
 - whether data are included to justify the significant benefit.

- In the event that the EMA requires additional data, information or clarification to complete its validation, the sponsor will receive a validation issues letter. The letter will be issued no later than one week before the start date of the procedure. The sponsor can at any time during the validation discuss with the scientific officer how to address the outstanding issues. The sponsor will be asked to respond within a maximum 3-month time limit. If no response from the sponsor is received within this time frame, the sponsor will be advised to withdraw the application and consider re-submission.
- Once the validation process is successfully completed, a timetable to start the procedure for the evaluation will be forwarded to the sponsor for information.

3.4. Evaluation

- During the evaluation phase the EMA coordinator will work very closely with the COMP coordinator and appointed expert(s).
- The coordinators may gather information from other COMP members on the disease state, availability of treatments, research status, etc.
- The EMA coordinator, in association with the COMP coordinator, will prepare a summary report on the application. The summary report will include data reported in the sponsor's application, a critical review, and a conclusion.
- The summary report will be circulated to the COMP members for comments. Members of the COMP will forward comments to the Agency in accordance with the adopted timetable.
- At the meeting(s) following circulation of the summary report, the COMP will discuss the application together with the comments raised. Where possible the expert(s) involved in the application will be invited to attend the COMP discussion.
- Following on the outcome from the COMP's first discussion on the application, the sponsor will be informed about adopted positive opinion or a list of questions. The list of questions will be forwarded to the sponsor with the draft summary report within 3 working days following the COMP meeting. The sponsor may be asked to respond in writing only or in addition the sponsor may be invited to attend an oral explanation at the next COMP meeting held in the EMA.
- Depending on the sponsor's preference the oral explanation can be held in a face to face meeting or via a teleconference. The COMP after discussing the sponsor's written response to the list of questions, may agree on a positive opinion before the oral explanation. This is done at the first day of the plenary meeting. In such case the oral explanation would be cancelled.
- For the oral explanation the sponsors will be requested to provide the EMA (one week before the meeting at the latest) with:
 - list of participants;
 - individual dial-in numbers for the sponsor's representatives/experts wishing to participate via teleconference.
- On the day of the oral explanation the sponsor should arrive to the EMA at least half an hour before the start of the discussion and bring:
 - PowerPoint presentation (in the interest of time, the presentation should focus only on the questions outlined in the list of questions);

- 50 printouts of the presentation (in a case of the teleconference, the printouts should be delivered to the EMA one day before the start of the COMP meeting the latest).
- The oral explanation lasts around 1 hour and includes the COMP discussion with the sponsor. The outcome of the discussion will be communicated to the sponsor immediately after the Committee has reached a conclusion.

3.5. Opinion

- Before day 90, the COMP adopts its opinion (in English).
- The opinion may be obtained during a COMP meeting or exceptionally by written procedure. The COMP opinion, which may be favourable or unfavourable, is, wherever possible, reached by consensus. If such consensus cannot be reached, the opinion shall be adopted by a majority of two-thirds of all COMP members.
- The EMA, taking into account the discussion within the COMP and the conclusions reached, will revise the summary report, which once adopted by the COMP will become the final summary report.
- If a negative outcome of the review of the application appears likely the sponsor may withdraw the application before the COMP adopts the opinion. In such case the sponsor will be informed immediately about the negative trend and advised on a possibility to withdraw the application by sending an e-mail requesting the withdrawal by the end of the on-going COMP meeting.
- If a negative opinion is adopted the sponsor receives the COMP negative opinion with the information about the appeal procedure.
- The detailed grounds for the appeal should be sent to the Agency within 90 days of receipt of the opinion. The grounds for the appeal should be based only on the original information provided in the application for orphan designation, but may include new analyses.

3.6. Follow-up to the COMP opinion

- The information on the adopted COMP opinions is published in the [COMP monthly reports](#) on the EMA website within a week of the end of the COMP meeting.
- Following finalisation of relevant documents the EMA forwards the COMP opinion to the Commission for designation process and to the sponsor.
- The sponsor is requested to confirm in writing (via e-mail) the receipt of the COMP opinion.
- The minutes of the COMP meetings reflecting on the outcome for the opinions and the grounds are published on the EMA website approximately one month after the COMP opinion. The published minutes will not identify the name of the product or the name of the sponsor for the withdrawn procedures, which did not receive an opinion.

3.7. Appeal

- In case of a negative opinion, the sponsor may appeal. Please refer to the [Procedural advice on appeal procedure for Orphan Medicinal Product Designation](#) (EMEA/2677/01 Rev.1).
- The grounds for appeal must be forwarded to the Agency within 90 days of receipt of the opinion.

- The EMA will refer the grounds for appeal to the COMP, who will consider whether its opinion should be revised at the first meeting following receipt of the grounds for appeal.

3.8. Decision

- The decision will be adopted by the Commission, within 30 days of its receipt of the COMP opinion and forwarded to the sponsor.
- Following the EC decision on the designation a public summary of opinion on orphan designation will be published on the [EMA website](#).

3.9. Publication in the Register

- Upon a favourable decision by the Commission, the designated medicinal product shall be entered in the [Community Register of Orphan Medicinal Products](#).

4. General advice

- Full information on the procedure for orphan medicinal products designation is available on the EMA [orphan designation website](#).
- The European Union (EU) offers a range of [incentives](#) to encourage the development of medicines intended for small numbers of patients.
- Sponsors are invited to consider the benefits of obtaining Small or Medium Enterprise status, if applicable; more information is available on the EMA [small and medium-sized enterprise office webpage](#).
- Every sponsor is requested to provide a prevalence calculation based on existing sources irrespective of the data already known and assessed by the COMP. Even though the assessment of the prevalence calculation is done on the merits of each application, sponsors can refer to previous COMP opinions and make use of published conclusions. In those cases sponsors should provide an updated estimate with regards to the submission date and based on its own calculations. The Agency publishes information on the prevalence conclusions in the product's public summary of opinion and keeps an updated table with relevant sources for conditions that have been subject of marketing authorisation. This is done to reduce the administrative burden for new applications and to increase transparency on previous designations. Please refer to the [Relevant sources for orphan disease prevalence data](#) (EMA/452415/2012).
- Sponsors with Advanced Therapeutic Medicinal Products (ATMPs) should consider submitting to the Committee for Advanced Therapies (CAT) for classification and naming of their product if possible before submission for Orphan Medicinal Designation. More information is available on the EMA [advanced therapies webpage](#).
- All confidential information should be sent to the EMA via secure system, Eudralink. Sponsors should contact the Eudralink helpdesk at eudralink@ema.europa.eu to open an account.
- Sponsors are welcome to address any questions with regards to the orphan medicines to orphandrugs@ema.europa.eu.

5. Frequently asked questions

Can an application for orphan medicinal product designation be submitted at any time in the development process?

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the sponsor may submit an application for orphan medicinal product designation to the Agency at any stage of development of the medicinal product as long as the criteria for designation may be justified. However, the designation application must be submitted before the submission of the application for marketing authorisation.

For the purpose of designation and to support the rationale for the development of the product in the proposed condition some preliminary preclinical and/or clinical data are generally required. A pharmacological concept, not supported by any form of evidence or results, would generally not be considered by the Committee for Orphan Medicinal Products (COMP) as sufficient justification for the designation of the medicinal product in the proposed condition.

A request for designation may be made for an already authorised medicinal product, if the designation request concerns a new orphan condition (please refer to the guideline on format and content of applications), which is not currently authorised.

Can an application for marketing authorisation be submitted before the application for orphan medicinal product designation has obtained an opinion and/or designation? If yes, can a fee reduction be granted on condition or refunded once the designation is obtained?

An application for marketing authorisation can be submitted after the application for orphan designation has been submitted, while designation is still pending. It should be noted, however, that a fee reduction for the application for marketing authorisation can only be considered if designation has already been granted at the time of application for marketing authorisation.

If the marketing authorisation application is submitted while the designation is pending, a fee reduction cannot be granted on condition or refunded.

Can a product already authorised for a non-orphan indication in the EU receive orphan designation for another indication which is orphan?

Yes, under certain circumstances. A request for orphan medicinal product designation may be made for a new orphan indication for an already authorised medicinal product. However, at the stage of applying for the marketing authorisation for the orphan indication, the marketing authorisation holder would be required to apply for a separate marketing authorisation for the orphan indication, using a different proprietary name. It will not be possible to extend the existing marketing authorisation to cover the new orphan indication. Orphan and 'non-orphan' indications may not be covered by the same marketing authorisation.

If a medicinal product has already been granted orphan drug designation in the US or Japan, would this be automatically accepted for the EU?

No, the EU Regulation does not foresee recognition of orphan status granted in other regions. In addition, the criteria for orphan designation are not internationally harmonised. Orphan designation can only be granted in the EU, by the European Commission, once an application for designation has been reviewed by the [Committee for Orphan Medicinal Products \(COMP\)](#), in accordance with the procedure laid down in Article 5, Regulation (EC) No 141/2000 of 16 December 1999.

Once orphan designation is granted, will it be possible to obtain a reduction in fees also for protocol assistance, variations and annual fee, or only for a reduction in fees for the marketing authorisation application?

For medicinal products which have been granted orphan designation (i.e. EC decision), reduction of fees or fee waivers will be considered for all types of activities including, fees for pre-authorisation activities such as protocol assistance, the application for marketing authorisation, inspections. For post-authorisation activities fee waivers apply to SME sponsors only. The extent of these fee reductions may vary annually, in accordance with the funding approved by the EU Commission for these activities.

Which are the sponsor's options in case of negative outcome for orphan designation? Which information is published in case of a negative opinion?

When the outcome for a designation application is negative, the COMP will adopt a negative opinion, unless the sponsor chooses to withdraw the application. The sponsor must inform the Agency in writing of the withdrawal before the COMP adopts an opinion, in other words, before the end of the COMP meeting. When the application is withdrawn, no information on the application is made public. The sponsor can re-apply for orphan designation with additional or complementary data at a later stage.

If the sponsor does not withdraw, a negative opinion is adopted by the COMP and is transformed into a Commission Decision, unless an appeal procedure is triggered. In this case the Decision has to wait for the outcome of the appeal. A summary of the negative opinion will be published on the Agency web-site and the decision will be entered in the [Community Register](#).

Can the sponsor appeal an opinion issued by the COMP?

Yes, a sponsor can appeal an opinion of the Committee. The detailed grounds for the appeal should be sent to the Agency within 90 days of receipt of the opinion. The grounds for the appeal should be based only on the original information provided in the application for orphan designation, but may include new analyses.

The COMP will discuss the grounds for appeal and will consider whether its opinion should be revised. Once a final opinion is adopted by the Committee, a summary of the opinion will be published on the Agency web-site and the resulting Commission decision will be entered in the Community Register. In case of withdrawal of the appeal by the sponsor, the previous opinion will become final.

At the stage of the application for marketing authorisation, does the sponsor of a designated orphan medicinal product have the choice between the centralised procedure and the Mutual Recognition procedure?

This was a possibility in the past. According to the Art. 3(1) of Regulation No 726/2004 of the European Parliament and the European Council, designated orphan medicinal products are required to apply through the centralised procedure. No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.

Are orphan medicinal products eligible to receive a marketing authorisation under exceptional circumstances?

As any medicinal product, a designated orphan medicinal product may be granted a marketing authorisation under exceptional circumstances, subject to annual re-assessment and certain specific obligations, in particular "when the indications for which the product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence" (Part II.6 of Annex I to Directive 2001/83/EC, as amended).

Do medicinal products designated as orphan medicinal products automatically qualify for accelerated review?

The maximum timeframe for the evaluation of a Marketing Authorisation Application under the centralised procedure is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP).

Designated orphan medicinal products will not automatically qualify for accelerated assessment. However, an accelerated evaluation might be initiated by the CHMP in exceptional cases, when a medicinal product is intended to meet a major public health need.

The justification for a request for accelerated assessment and further details on how to submit a request for accelerated assessment can be found in the CHMP 'Guideline on the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004' or the 'Pre-submission Guidance' document on the Agency website.

Does an orphan medicinal product designation in the EU qualify for designation outside Europe?

The Agency encourages parallel applications for orphan designation with regulatory authorities outside the EU, particularly with regulators in the United States and Japan. However, the processes are independent from each other and sponsors should liaise with each of the Authorities for the purpose of applying for orphan drug designation.