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Human Medicines, Scientific Evidence Generation

Procedural advice for orphan medicinal product designation

Guidance for sponsors

[1] Links updated- 4. General advice Relevant sources for orphan disease prevalence data (EMA/452415/2012) removed

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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. 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

IRIS | **Regulatory & Scientific Information Management Platform** is a new secure online portal for sponsors to submit applications for orphan medicinal product designation and to manage post-designation activities, operational from June 2018 as part of an EMA-wide programme to improve the way it records and manages master data and interacts with external stakeholders. All orphan applications should be created and submitted via the IRIS portal, which also contains the relevant procedural advice.

Sponsors should follow one of the two options below:

Submit directly an application to the EMA, through the online web portal

Pre-submission 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 and the possibility to intervene in case of technical problems. For further details on the submission of an orphan drug application for designation see point 3.2. below.

Request a pre-submission meeting/teleconference

If a Sponsor feels they could benefit from a preliminary discussion before the submission of an orphan drug application to the EMA, they can request a pre-submission meeting/teleconference at least two months prior to their planned submission date via the IRIS portal. For further details see point 3.1.1 below.

3.1.1. Pre-submission meeting

- The EMA 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 via tele/video conference. Follow-up calls are also possible. The following

information should be made available to the EMA via the online web portal one week prior to the meeting date:

  - draft information in the submission sections within the IRIS portal;
  - draft scientific document (sections A-E), as a Word or RTF file in the portal folder for the draft application for orphan designation);
  - short presentation about the application (approx. 15 min) (PowerPoint file, located as above);
  - list of participants and roles, and dial-in number and password for teleconference where applicable (Word/RTF file, located as above).

- 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 aspects:
  - the draft submission data in the portal;
  - the scientific document (sections A-E) as attached to the submission.
- Sponsors will be invited to take minutes of the meeting, which should be provided to the EMA within one week after the meeting (please upload them in the portal folder for the draft application for orphan designation). The Agency will subsequently review the minutes within one week and post the final (amended) version in the presubmission meeting request folder.

3.1.2. Appointment of rapporteurs

- A Rapporteur (COMP member), an EMA scientific officer and an EMA assistant will be identified for each application. COMP members may 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 Rapporteur, as appropriate.

3.2. Submission

- The deadlines for submission of an orphan medicinal product designation application are published on the EMA website;
- The sponsor should submit the application via the secure online web portal, IRIS;
- The complete application should include:

Document	Format
General administrative and scientific information completed online via the portal.	Web form
Scientific document (sections A-E) (To be uploaded in the portal folder of the submission).	Word/RTF file (docx format preferred)
Proof of establishment of the sponsor in a country of the European Economic Area (EEA): **If the sponsor is an organisation** should have a permanent physical address in one of the countries of the EEA 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, if needed. The proof of establishment e.g. certification of company incorporation, should be uploaded in the portal folder of the submission. **If the sponsor is a natural person** of a country of the EEA, in order to respect data protection rights and freedoms, they should not include proof of establishment in the portal folder of the submission. Once EMA receives the application, the Orphan Office will e-mail the individual sponsor outside the submission portal to verify their citizenship of a country of the EEA e.g. copy of passport. At the end of the validation process all personal data are deleted from EMA's systems. Please refer to Privacy Statement for proof of establishment of natural persons in orphan designation.	PDF
Translations of the active substance and proposed orphan condition into the official languages of the European Union, plus Icelandic and Norwegian should be uploaded via the online portal as part of the submission. **Note to sponsors established in Ireland** Sponsors established in Ireland, should either: - request a language waiver if they want English to be the authentic language of the product information and of the EC decisions. Such waiver request should be sent to IrishWaiver@ema.europa.eu with completed form. The request should also be uploaded via the online platform as part of the submission package OR - provide the Irish translation Sponsors are advised to check translations from previous orphan designations in the Community Register of Orphan Medicinal Products. If an active substance or a proposed orphan condition have been accepted it is advisable to use these translations in future submissions. **Note to sponsors with active SME status** SME applicants are not required to submit translations. EMA provides assistance with translations of product information into all official European Union languages to those sponsors that at the time of applying for an application for orphan medicinal product designation have their SME status confirmed. However, sponsors are recommended to submit as many translations they can complete with their submission. Sponsors are advised to search the Community Register as indicated	Word (docx format preferred)

Document	Format
above.	
Full text of any scientific article cited in the bibliography, saved in individual PDF files titled as first author and year, such as in 'Smith PH et al 2004.PDF'. While there is no maximum number of files or global size, there is a size limit of 50 Mb per file. Please include a Zip folder, named 'Bibliography' to contain all individual files for each reference.	PDF
A description of the mechanism of action of your medicine in lay language in 100 words maximum. This text should describe as simply as possible the clinically relevant principal mechanism of action, in relation to the condition applied for. If the medicine is granted an orphan designation, this text will be included in a public overview of the orphan designation to be published on the EMA website following the European Commission decision. The draft overview will be shared with you before publication. You can use previously published orphan designations overviews as a basis: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_orphan	Word (docx format preferred)

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 orphan condition is applied for the same product, separate applications should be submitted for each orphan condition. In this regard, 'treatment' and 'prevention' of the same disease are considered as two separate conditions and should be the subject of two separate applications for orphan designation.

The sponsor should use the **recommended** INN of the active substance(s), if available at the time of submitting the application. Otherwise, an appropriate chemical name or scientific name can be used, when registering the substance(s) in EUTCT. Proposed INNs and company codes are not acceptable for the purpose of orphan designation.

3.3. Validation

The EMA Secretariat will review the submission of the application within a month from the submission deadline, 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) for the format and content of applications for designation as orphan medicinal products and Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products.

- 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 supplementary information (VSI) letter. The sponsor can at any time during the validation discuss with the EMA Scientific Officer how to address the outstanding issues. If the application cannot be considered valid, the sponsor may submit a new application at any time, in agreement with the published deadlines.
- Once the validation process is successfully completed, the timetable to start the procedure for the evaluation will be confirmed.

3.4. Evaluation

- During the evaluation phase the EMA Scientific Officer will work very closely with the COMP Rapporteur and appointed expert(s) if appointed.
- The COMP rapporteur and the EMA Scientific Officer may gather information from other COMP members on the disease state, availability of treatments, research status, etc.;
- The EMA Scientific Officer, in association with the COMP Rapporteur, 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 made available to the COMP members for comments. Members of the COMP will provide 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 whether an opinion or a list of questions has been adopted by the Committee. The list of questions will be made available 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;

- The oral explanation is held 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;
    - PowerPoint presentation (in the interest of time, the presentation should focus only on the questions outlined in the list of questions).
- The sponsor is given 20 minutes to present and the oral explanation lasts around 1 hour in total including 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 is allowed to 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 via the IRIS portal before 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 (see 3.7 below).

3.6. Follow-up to the COMP opinion

- Following finalisation of relevant documents, the EMA forwards the COMP opinion to the European Commission for the Decision process and to the sponsor via the online portal;
- The sponsor is requested to confirm in writing (via e-mail) the receipt of the COMP opinion within the online portal. The minutes of the COMP meetings reflecting on the outcome for the opinions and the grounds are published on the EMA website (usually 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.3);

- The appeal is requested in the IRIS portal as a separate submission, linked to the initial submission. The submission of the appeal request, including detailed grounds, should be made 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 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 as well as in the minutes. This is done to increase transparency on previous designations.
- 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 ,
- Sponsors are welcome to address any general queries related to orphan medicines sending a question via the following link https://www.ema.europa.eu/en/about-us/contact/send-question-european-medicines-agency.

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 non-clinical 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 request 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 the application, 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 website 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 submission, including 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 website 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 only 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.