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Scientific Evidence Generation

Procedural advice for post-orphan medicinal product designation activities

Guidance for sponsors

Note:

IRIS | **Regulatory & Scientific Information Management Platform**, is a secure online portal for submitting and managing orphan medicinal product designation related applications.

The European Medicines Agency (EMA) is no longer able to process any orphan designation related submissions outside of the IRIS portal. For information and guidance on using IRIS, please visit the IRIS homepage.

All communication relating ongoing IRIS submissions should be done via the IRIS portal.

Any general queries can be submitted via the EMA send a question to the European Medicines Agency website.

[1] Removal of the information on publication of the COMP meetings outcome in monthly reports (which were abolished in September 2022).

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Introduction

Opinions on orphan designation are adopted by the Committee for Orphan Medicinal Products (COMP) at their monthly meetings at the European Medicines Agency (the Agency).

Following adoption of an opinion on orphan medicinal product designation by the COMP, the final COMP opinion (negative or positive) is forwarded to the European Commission (EC) and to the sponsor. Relevant information is published in the meeting minutes on the EMA website. The decision on the designation is adopted by the EC within 30 days of receipt of the COMP opinion and forwarded to the sponsor by the EC.

Upon a favourable decision by the EC, the designated medicinal product is entered in the Union Register and a public summary of opinion on orphan designation is published on the EMA website, which contains a searchable list of all opinions on applications for orphan medicinal product designation.

EC decisions on refusal of designation are published in the Union Register of refused orphan medicinal products. Relevant public summaries of the COMP negative opinions are published on the EMA website.

Orphan designations related procedures are described in the standard operating procedure 3534 SOP - Orphan procedures (europa.eu).

This guideline covers detailed information and procedures applicable to **orphan designated products**:

1. Incentives
2. Annual reports
3. Transfer of orphan designation
4. Change of sponsor's name or address
5. Amendment of designated condition
6. Marketing authorisation application

6.1 Review of the maintenance of orphan medicinal product designation at the time of marketing authorisation application

6.2 Review of the maintenance of orphan medicinal product designation at the time of extending the therapeutic indication post-authorisation

7. Removal of orphan designation
8. Review of the period of market exclusivity of orphan medicinal products.

1. Incentives

Sponsors of designated orphan medicines are eligible to benefit from incentives, including:

1.1 Protocol assistance with development of the medicine

1.2 Reduced fees

1.3 Access to centralised procedure

1.4 Protection from market competition once the orphan medicine is authorised

1.5 Additional incentives for micro, small and medium-sized enterprises (SMEs)

1.6 Grants

1.7 Incentives in Member States.

1.1. Protocol assistance

At any stage of development, sponsors can request protocol assistance. Protocol assistance is the special form of scientific advice available for companies developing designated orphan medicines for rare diseases.

The Agency gives protocol assistance by answering questions posed by companies. The advice is given in the light of the current scientific knowledge, based on the documentation provided by the applicant. Scientific advice is restricted to purely scientific issues associated with marketing authorisation applications such as quality, pre-clinical and clinical considerations. Applicants developing an orphan medicinal product can receive answers to questions relating to the criteria for authorisation of an orphan medicine. These include specific orphan designation issues such as:

- the demonstration of significant benefit within the scope of the designated orphan indication;
- similarity or clinical superiority over other medicines. This is relevant if other orphan medicinal products exist that might be similar to the product concerned and which have market exclusivity in the same indication.

This helps the applicants to ensure that the appropriate studies are performed, thereby reducing the possibility of major objections regarding the design of the studies which could be raised during evaluation of the marketing authorisation application. Such major objections may result in refusal of the maintenance of the orphan designation and of the eligibility for market exclusivity. Adherence to the Agency's advice, therefore, increases the probability of a positive outcome (Marketing authorisation of orphan medicines in Europe from 2000 to 2013, Hofer MP et al).

For human medicinal products, protocol assistance is given by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP) for quality, pre-clinical and clinical questions, and issues regarding similarity. The advice regarding the demonstration of significant benefit and maintenance of orphan designation is given by the COMP.

Protocol assistance is available at a reduced fee for designated orphan medicines, linked to a fee-reduction scale that depends on the status of the sponsor. The Agency updates this each year and makes it publicly available on the EMA corporate website. There is no restriction on the number of times a sponsor can request protocol assistance. The Agency offers assistance to applicants to appropriately prepare their scientific advice requests through free pre-submission meetings.

Detailed information on how to apply, including a template for notifying intent of submission, submission deadlines and details of the programme for EMA-FDA parallel scientific advice are available on the EMA corporate website:

- Scientific advice and protocol assistance
- European Medicines Agency guidance for companies requesting scientific advice and protocol assistance.

The Agency encourages sponsors to consider coordinating the timing of protocol assistance from the Agency with request for scientific advice from the United States Food and Drug Administration (FDA). Parallel scientific advice with the FDA is available:

- General principles: European Medicines Agency - FDA parallel scientific advice.

1.2. Fee reduction

Medicines that have been granted orphan designation by the EC on the recommendation of the COMP are eligible for fee reductions for a range of regulatory activities. These include pre-authorisation activities such as protocol assistance, the marketing authorisation application (MAA) and inspections. The fee reduction is dependent of the status of the applicant. For detailed information please refer to Fee reductions for designated orphan medicinal products.

The Agency needs no specific information from the sponsor before submitting an application eligible for fee reduction for orphan medicines.

1.3. Access to the centralised authorisation procedure

All designated orphan medicines are assessed for marketing authorisation **centrally** in the European Union (EU). This allows companies to make a single application to the European Medicines Agency, resulting in a single opinion and a single decision from the European Commission, valid in all EU Member States. Sponsor's may also have access via orphan designation to conditional approval, which is conducted under the centralised procedure.

For more information, see central authorisation of medicines.

1.4. Market exclusivity

As per the Article 8(1) of the Regulation (EC) No 141/2000 (Orphan Regulation), medicines that still meet the criteria for orphan designation at the time of applying for marketing authorisation (MA) benefit from the incentive of ten years of market exclusivity once they are approved in the EU. This protects them from market competition of similar medicines and is intended to encourage the development of medicines for rare diseases.

The exclusivity is awarded by the EC and is linked to one specific orphan designation for which a MA has been granted.

Each orphan designation carries the potential for one ten-year market exclusivity for a particular indication. A medicine that has received several separate orphan designations for different indications can obtain more than one market exclusivity if these refer to separate designated conditions.

Sponsors of medicines with orphan designation should also remember to apply for a paediatric investigation plan (PIP), deferral or waiver once phase-I clinical studies are complete.

For products which have obtained a paediatric investigation plan (PIP) in the orphan designated condition(s) there is the possibility of extending the marketing exclusivity by an additional two years per orphan condition which has obtained ten-year market exclusivity.

The following conditions have to be fulfilled:

- the applicant complied with all the measures contained in the agreed completed paediatric investigation plan and this is demonstrated in the application through a compliance check conducted by the Paediatric Committee (PDCO);
- a statement indicating compliance of the application with the agreed PIP has been included in the marketing authorisation;
- a review by the CHMP which amends the summary of product characteristics, and if appropriate the package leaflet, reflects the results of studies conducted in compliance with that agreed PIP;

- the EC reviews and agrees to grant the two-year market exclusivity extension based on the recommendation from the CHMP.

For more information, see:

- Paediatric medicine development.
- Questions and answers on the procedure of PIP compliance verification at EMA, and on paediatric rewards.

Orphan medicinal products to which the extension was granted will contain a statement in the body of the relevant Commission decision, mentioning the extension of the duration of the market exclusivity: "The market exclusivity period referred to in Article 8(1) of Regulation (EC) No 141/2000 is extended to twelve years in accordance with Article 37 of Regulation (EC) No 1901/2006." This could be either part of the initial marketing authorisation or a subsequent variation. Commission decisions are published on the Union Register. Those products will be maintained in the Union Register of orphan medicinal products for an additional period of two years.

When the period of market exclusivity for an indication ends, the orphan designation for that indication expires and is removed from the Union Register.

Once all of the orphan designations associated with an approved medicine have expired or been withdrawn by the sponsor, the medicine ceases to be classified as an orphan medicine and no longer benefits from the orphan incentives.

1.5. Additional incentives for micro, small and medium-sized enterprises (SMEs)

The Agency encourages companies developing orphan medicines to check whether they can be classified as a micro, small or medium-sized enterprise (SME). Companies classified as SMEs benefit from further incentives when developing medicines with orphan designation. These include administrative and procedural assistance from the Agency's SME office and fee reductions. For more information, see SME office.

1.6. Grants

The Agency does not offer research grants for sponsors of orphan medicines, but funding is available from the EC and other sources via e.g.:

- Horizon Europe the EU Framework Programme for Research and Innovation
- E-Rare ERA-NET for research programmes on rare diseases.

Grants are also available for sponsors considering research in the United States or Japan:

- United States: Food and Drug Administration: Orphan products grants program
- Japan: National Institute of Biomedical Innovation - Orphan Products Development Support Programme

1.7. Incentives in Member States

Incentives for designated orphan medicines are available in the EU Member States. For more information, applicants should contact the medicines regulatory authority in their country:

- National competent authorities (human).

2. Post-designation procedures

2.1. Annual reports

Article 5(10) of Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products requires sponsors to submit annual reports on the state of development of designated medicinal products to the Agency.

Calendar for submission of annual reports

These reports must be prepared and submitted to EMA annually until the first application for marketing authorisation within the scope of the orphan condition is submitted in the EU or subsequently upon a specific request from the Agency. In case of a negative outcome of the MA evaluation procedure (i.e. withdrawal or refusal), submission of annual reports should resume.

Should development of a medicinal product for a designated orphan condition be terminated for any reason, the sponsor should inform the Agency and may request to the European Commission the removal of the designated orphan medicinal product from the EU Register of Orphan Medicinal Products, in accordance with Article 5(12) (a) of Regulation (EC) No 141/2000. Once a medicinal product is removed from the Union Register, annual reports submission will no longer be required.

Timelines for submission of annual reports

Annual reports for orphan medicinal products designated by the EU should be submitted within 2 months following the anniversary of the grant of the designation or at World Rare Disease Day (last day of February). If for any reason, the sponsor is unable to follow those timelines, a submission at any point in time, in a given year will be also accepted.

Procedural steps

- Annual reports are specific to each designation. As a consequence, when one active substance is the subject of several designations, a separate report should be prepared for each designation.
- Sponsors are required to make a submission **Annual Report** via the IRIS portal. Sponsors are not requested to submit any documents; it is sufficient to complete the requested IRIS fields. Note that the fields on "compassionate use", "marketing authorisation" and "new orphan designation" relate to global development (not only in the EU).
- Optionally, additional documents can still be uploaded if appropriate, and can contain information about:
  - ✓ a review of ongoing clinical studies,
  - ✓ a description of the investigation plan for the coming year,
  - ✓ any anticipated or current problems in the process, difficulties in testing and potential changes that may have an impact on the medicine's orphan designation.

Note: If the sponsor wishes to change the name or address of a sponsor or transfer an orphan designation, this should not be done in the annual report. A relevant application should be submitted via the IRIS portal.

2.2. Transfer of an orphan designation

A transfer of the orphan designation is the procedure by which the orphan designation is transferred from the current orphan designation holder to a new sponsor which is a different person/legal entity.

Such transfer may result from the designation holder's commercial decision to divest the orphan designation or be needed in anticipation of the designation holder ceasing to exist as a legal entity and orphan designation being taken over by another legal entity.

In a context of merger based on a universal succession the possibility of self-transferring orphan designations of centralised medicinal products may be considered by the Agency, performing a thoughtful review of the particularities of each case. The applications for the referred self-transfers of orphan designations will be reviewed on a case-by-case basis. The burden to demonstrate that the purchaser is the legal successor of the acquired company is on the transferor.

A transfer of the orphan designation can only be initiated once a designation has been granted by the EC. If there is a need to change the sponsor during validation or evaluation of the application for orphan designation, the applicant who initially applied for the orphan designation should inform the Orphan Medicines Office.

Transfers of orphan designations are free of charge. A transfer of an orphan designation does not include a transfer of MA since this is subject to a different procedure (see: Transfer of marketing authorisation: questions and answers).

According to 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) it is not possible to transfer an orphan designation to a sponsor who already holds a marketing authorisation for the same medicinal product and condition. Any additional pharmaceutical forms should be granted by varying the existing marketing authorisation. When a sponsor submits a separate marketing authorisation in order to distinguish between two pharmaceutical forms and avoid medication errors, this separate marketing authorisation will be subject to the same market exclusivity period.

Procedural steps

- A current orphan designation holder is required to make a submission **Transfer of Orphan Designation** via the IRIS portal together with the documents described in the Checklist for sponsors applying for the transfer of orphan medicinal product designation.
- The Agency can only provide an opinion on the transfer if all of the documentation required is complete and satisfactory. The Agency will issue an opinion within 30 days of the submission of the documentation and the opinion will be forwarded to the existing sponsor and to the EC.
- If the EC agrees with the transfer, it will amend the decision granting the designation as an orphan medicine. The transfer is accepted from the date of the EC notification of the amended decision. Sponsors will relevant communication directly from the EC. It is important that receipt of such communication is confirmed by sponsors via return e-mail.

A change of name and/or address of the orphan designation holder are not a transfer if the holder remains the same person/legal entity. Such change should be notified through a change of name and/or address of the orphan designation holder procedure.

2.3. Change of sponsor's name and/or address

A change in the name and/or address request should be used only once a designation has been granted by the EC. If there is a need to change the sponsor's name and/or address during validation or evaluation of the orphan designation application, the applicant should inform the Orphan Medicines Office via relevant IRIS submission.

A change in the name and/or address of the existing sponsor for an orphan designation does not require a new legal act, provided that the sponsor remains the same person or legal entity. A request to change the address to another country will be invalidated. In such case a transfer application should be submitted instead.

Procedural steps

- Prior to submitting the name and/or address change application, the sponsor should **update their organisation details** within the **change request** functionality in the Organisation Management Services (OMS) on the EMA SPOR portal, in accordance with the guideline "E-OMS change request" available under the published guidance. Sponsors - individuals (not registered in OMS) need to update their details in the EMA's Account Management Portal.
- Following the sponsor's record update in OMS, the orphan designation(s) holder should submit a **Change of Name and Address** application in the EMA's IRIS platform. For information and guidance on using IRIS, please see the IRIS portal guidance.
- The application will be forwarded to the EC for relevant update of the Union Register.
- The EC will acknowledge the change directly to the sponsor.
- The Agency will update the sponsor's details published on the EMA website. If, in any point in time, the sponsor would like to request update of published telephone number or email address, this should be done via the EMA Service Desk.

Changing a contact person

If a contact person, manager or contributor for an existing designation leaves their function or the organisation, an **IRIS Industry Admin** user should consider removing his/her affiliation to the OMS organisation in EMA's Account Management Portal, otherwise the EMA account of that user will still be usable to modify IRIS on behalf of the affiliated organisation.

The IRIS platform also allows industry users to change the **contact person assigned to a regulatory entitlement** (e.g. orphan designation) by editing the regulatory entitlement record directly in the portal. The record includes fields for:

- contact person for entitlement (who must have an IRIS role and affiliation to the sponsor);
- contact email for general public enquiries (any email is acceptable);
- contact phone number for general public enquiries (any phone number is acceptable and should include a country code).

All these fields are editable in the **My Individual RE** and **My Organization RE** tabs in the IRIS platform.For more information about EMA accounts and affiliation, see the IRIS Quick Guide to Registration or contact EMA Service desk.

2.4. Amendment of an existing orphan designation

In exceptional cases, change of the designated condition is possible as foreseen in 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) and in the EC 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 (ENTR/6283/00).

During the development of the product, the classification of a disease may change, and the designated condition may need to be modified to better reflect the indication that the sponsor intends to request at the time of marketing authorisation. An application for amendment has to be initiated by the sponsor and is expected to be requested before the application for marketing authorisation is made. The purpose of the amendment is to align the designated orphan indication with the marketing authorisation indication in the case where the latter is covered by the existing orphan designation due to a change in the classification of the designated orphan condition. It is to be noted that this would not be needed when the envisioned therapeutic indication at the time of marketing authorisation is already contained in the designated orphan condition.

Amendment criteria

The following scenarios may apply:

- **There has been a change in the classification of a previously designated condition**

Such change needs to be justified by a well-recognised classification, e.g. WHO or the relevant scientific society for the specific condition. Examples are the WHO revision of hematologic malignancies (2008) and the reclassification of acute lung injury and acute respiratory distress syndrome with the Berlin consensus (2012).

- **There is a need to better reflect the indication that the sponsor intends to request at the time of marketing authorisation**

An amendment can be requested when the envisaged therapeutic indication for a marketing authorisation falls outside the designated orphan condition and there has been a change in the classification of the previously designated condition.

Proposals for including sub-populations not part of the designated orphan condition other than as described in the scenarios above are unlikely to qualify for an amendment.

Procedural steps

- A request for amendment of an existing designated condition will follow the same assessment process as a new designation application by the COMP i.e. a 90-day procedure. It will, therefore, be necessary to justify that all criteria for designation remain applicable.
- Sponsors are required to make a submission **Amendment of Orphan Designation** in the IRIS portal. A complete application should include:

Documents	Format
Online completed application form with general administrative and scientific information	Web form

Files to be uploaded in the "Input from Industry" folder in the "Documents" section of the submission:	
Scientific document (sections A-E)	Word file (docx format preferred)
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 including the name of a contact person at the sponsor premises. Sponsor applying as individuals instead of an organisation, should refer to the Privacy statement for validation of proof of establishment of natural persons).	PDF
Translations of the name of the product and the proposed orphan indication into the official the EU languages, plus Icelandic and Norwegian.	Word file (docx format preferred)
Full text of any scientific article cited in the bibliography, uploaded as 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 create a subfolder, named 'Bibliography' to contain all individual files for each reference.	PDF

- The validation and evaluation procedure and timelines are the same as for the initial designation. For further information please refer to the Procedure for orphan medicinal products designation, guidance to sponsor.
- Based on the COMP's favourable opinion on the request for amendment, the EC will then issue a new decision for the revised condition. The initial decision will be automatically repealed by the new decision.
- After amendment of the orphan designation, the Agency will update its published information to reflect the fact that the orphan designation has been amended at the request of the sponsor.

2.5. Marketing authorisation application and review of orphan designation criteria

Following submission and validation of an application for marketing authorisation (MA) to the Agency, a sponsor should also submit a request for maintenance of the orphan designation via the IRIS portal. The evaluation by the COMP enables the Agency to determine whether the medicine can maintain its status as an orphan medicine and benefit from market exclusivity.

When an application for orphan designation is still pending at time of submission of the application for MA, it is nevertheless possible for the medicinal product to be authorised as an orphan medicine provided that the orphan designation is adopted by the COMP and confirmed by the EC before the granting of marketing authorisation.

However, in such cases, the eligibility for the centralised procedure (which precedes the submission of the application for marketing authorisation) cannot be based on Article 3(1) and point 4 of the Annex to Regulation (EC) No 726/2004. Similarly, a fee reduction will not be applicable, as this can only be

considered if orphan designation has already been granted at the time of submission of the application for MA.

In advance of submission of an application for MA, irrespective of whether the medicinal product in question has been designated as orphan or not, a sponsor is advised to check the Union Register for information on medicinal products designated as orphan which are under market exclusivity protection.

If any of the designated orphan medicinal products has been granted a MA in the EU, and a period of market exclusivity is in force, a sponsor should attach to the marketing-authorisation application a similarity report addressing the possible similarity between new medicinal products and the orphan medicinal product(s) which have received a MA. Detailed information on submission of a similarity report is available on EMA's pre-authorisation guidance web page (see questions 3.2.4 and 3.2.5).

This legal requirement arises from Article 8(1) of the Orphan Regulation which stipulates that where a marketing authorisation for an orphan medicinal product is granted, the Agency and the Member States shall not, for a period of 10 years, accept another application for a MA, or grant a MA or accept an application to extend an existing MA, for the same therapeutic indication, for a similar medicinal product. Point 3 of the Article 8 specifies that a MA may be granted, for the same therapeutic indication, to a similar medicinal product if:

- the holder of the MA for the original orphan medicinal product has given their consent to the second applicant, or
- the holder of the MA for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
- the second applicant can establish in the application that the second medicinal product, although, similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

Commission Regulation (EU) 2018/781 of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product' defines the concept of similar medicinal product and clinical superiority. Article 3 defines similar medicinal product as a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication.

It also defines "similar active substance" as an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular features) and which acts via the same mechanism.

Based on the above-mentioned definitions, the assessment of similarity between two medicinal products takes into consideration the following criteria:

- principal molecular structural features;
- mechanism of action;
- therapeutic indication.

If significant differences exist within one or more of these criteria, the two products will not be considered as similar. These criteria are explained in:

- EC Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000 on assessing similarity of medicinal products versus authorised orphan medicinal products

benefiting from market exclusivity and applying derogations from that market exclusivity (2008/C 242/08).

- EC Communication (C(2008) 4077).

Where the CHMP concludes that the application for MA is not similar to an authorised orphan medicinal product or, if similar, that one of the derogations provided for in the Article 8(3) of the Orphan Regulation claimed by the applicant applies, this will not prevent the granting of the MA/extension to the marketing authorisation, provided that the quality, safety and efficacy of the medicinal product are demonstrated.

Should the CHMP conclude that the product which is the subject of the application for MA is considered similar to an authorised orphan medicinal product and none of the derogations applies, the CHMP will adopt an opinion recommending the refusal of the granting of the MA/extension to the MA, irrespective of the demonstration of the quality, safety or efficacy of the medicinal product.

2.6. MA application for a non-orphan indication

Under certain circumstances a product already authorised for a non-orphan indication in the EU can receive orphan designation for another indication which is orphan. However, at the stage of applying for the MA for the orphan indication, the MA holder would be required to apply for a separate MA 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.

Accelerated review

The maximum timeframe for the evaluation of a MA 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.

In order to meet the expectations of patients it is possible to obtain a marketing authorisation via an 'accelerated assessment procedure' (that is, within up to 150 days instead of 210 days) for products which are of major public health interest, in particular from the viewpoint of therapeutic innovation.

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:

- Guideline on the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004.
- Accelerated assessment.

2.7. Review of the maintenance of orphan medicinal product designation at the time of marketing authorisation application

If a sponsor of a medicine with an orphan designation submits an application for an initial MA or an extension which introduces a new indication to an existing MA, they should submit a report on maintenance of the orphan designation. The orphan designation review based on such report, enables

the COMP to recommend to the EC whether a medicine can maintain its status as an orphan medicine and benefit from market exclusivity.

The COMP reviews the maintenance of orphan designation based on the data available at the time and a report on the maintenance of the designation criteria.

The report includes data on:

- the current prevalence of the condition to be diagnosed, prevented or treated, or the potential return on investment;
- the current life-threatening or debilitating nature of the condition;
- the current existence of other methods for the diagnosis, prevention or treatment of the condition;
- if applicable, a justification of the medicine's significant benefit.

Procedural steps

- Sponsor should submit the **maintenance of orphan designation** application via the IRIS portal and:
  - ✓ around day 121 of the full MA procedure (210 days), or
  - ✓ after validation of the application for MA in a case of approved accelerated review (150 days) and only after the sponsor received the confirmation that the validation of the application for MA has been completed and a centralised procedure number is available, which is needed to create the maintenance submission.
- The submission should include the maintenance report and full text of any scientific article cited in the bibliography, uploaded as individual PDF files, titled as first author and year, such as in 'Smith PH et al 2004.PDF'. Please create a subfolder, named 'Bibliography' to contain all individual files for each reference.
- The sponsor can request a pre-assessment virtual meeting with EMA to discuss the maintenance report and other queries regarding the COMP review procedure. To do so, the sponsor must first make an IRIS submission **Maintenance of Orphan Designation** and upload the draft maintenance report. Once receipt of the submission is confirmed, an e-mail requesting a pre-assessment meeting with proposed dates and timeslots can be sent through the system. After the pre-assessment meeting the sponsor will be able to upload a revised version of the maintenance report to be assessed by the COMP.
- The COMP's review is carried out independently of, but in parallel with, the evaluation of the MA application by the CHMP. The COMP will assess the maintenance to be able to deliver an opinion at the COMP meeting following adoption of the CHMP positive opinion. The following cases are reviewed by the COMP one month in advance of scheduled CHMP opinion to facilitate adoption of the COMP opinion (via written procedure) immediately after the CHMP final opinion:
  - ✓ products without significant benefit;
  - ✓ products under accelerated procedure;
  - ✓ products for final CHMP opinion in July or December (to accommodate the EC timely MA decision making process during holiday months).
- In a case of the CHMP negative opinion or withdrawal of the MAA, the COMP review of the maintenance ceases.

- During review, the COMP may adopt a list of questions and invite the sponsor to an oral hearing at the following Committee meeting.
- During the post-oral hearing debriefing and in case of a negative trend expressed by the COMP the sponsor will be presented with the following two administrative steps scenarios for consideration:

  1. Sponsor may decide to request a removal of the orphan designation from the Union Register prior to adopting a negative opinion on the review of the orphan designation criteria by the COMP:

  - ✓ the intention to request the removal should be expressed by a return e-mail as soon as possible after the oral hearing. To request the removal the sponsor should proceed with a new IRIS submission **Removal of an Orphan Designation from the EU register**. Please refer to section 8 of this guidance below;
  - ✓ **the removal request should be submitted by the end of the ongoing COMP meeting.** The orphan designation maintenance submission **should NOT be withdrawn** by the sponsor, and it will be closed by EMA in due course.

  2. The COMP adopts a negative opinion. The opinion with a 90-days appeal deadline will be forwarded to the sponsor following the COMP meeting. The EC will be informed accordingly, and the MA decision-making phase will be put on hold. The sponsor may choose:

  - ✓ To appeal. In such case the sponsor should make a new IRIS **Appeal** submission, where the grounds for appeal should be uploaded by the set deadline. The appeal oral hearing will be held at the COMP meeting following submission of the grounds for appeal. The COMP will adopt their final opinion at the same meeting. The final opinion will then be forwarded to the EC.
  - ✓ Not to appeal. It should be noted that during the COMP review of the orphan designation, the EC decision on the MA is on hold. Therefore, it is essential that sponsors inform the Agency if they do not intend to appeal, so the COMP opinion can be forwarded to the EC for the MA decision making procedure. In the event that no communication is received, the opinion will be forwarded to the EC after the appeal deadline expires.
- For the appeal discussion, the sponsor is usually invited for another oral hearing at the meeting following receipt of the appeal. To allow appropriate time for evaluating the grounds for appeal, it is recommended that a sponsor submits the grounds for appeal at least two weeks before forthcoming COMP meeting.
- In the event of the negative outcome following the appeal, the COMP's recommendation to remove the designation from the Union Register is forwarded to the EC. In a case of a positive outcome, the COMP opinion recommending that the orphan designation should remain in the register is sent to the EC.

The outcome of the COMP review is published on the EMA website in the COMP meetings reports and minutes; and a report on whether the medicine still meets the criteria of orphan designation (orphan maintenance assessment report - OMAR) is published together with an European Public Assessment Report (EPAR) on the medicine's orphan designations page. The sponsor will be given an opportunity to review the report and identify any commercially confidential information not suitable for publication.

2.8. Review of the maintenance of orphan medicinal product designation at the time of extending the therapeutic indication post-authorisation

When the sponsor applies, post-authorisation, for an extension of the therapeutic indication, in order to ensure that the marketing authorisation only covers indications that fulfil the orphan designation

criteria foreseen in the Article 3 of the Orphan Regulation, a review by the COMP may be required for the following:

- for a new therapeutic indication falling **within a new orphan designation**, i.e. an orphan designation other than the one(s) related to the already approved indication(s), the COMP will have to confirm the maintenance of the orphan designation before authorisation of the new indication. In this case, the sponsor should provide, at the time of applying, the orphan designation maintenance report. The sponsor should make the **Maintenance of Orphan Designation** submission via the IRIS portal, only after the sponsor receives the confirmation that the validation of the application for MA has been completed and a centralised procedure number is available, which is needed to create the submission;
- for a new therapeutic indication falling within **an already authorised orphan designation**, the COMP will have to consider if the specific scope of the application raises justified and serious doubts in respect to the fulfilment of the orphan designation criteria and indicate if a formal review process of the maintenance of the orphan designation is needed. Note, that the COMP will not reassess extensions of indications to new age groups (e.g. paediatric patients) or if the patient population stays the same (e.g. a new combination with other products). Hence submission of the maintenance report for such extension is not required.

To support this process, the sponsor is requested to provide, at the time of applying, either a justification that the application does not raise doubts on the fulfilment of the orphan criteria or a maintenance report to support that the orphan criteria are still met. The justification or the maintenance report should be submitted to the Orphan Medicines Office in the IRIS portal **Maintenance of Orphan Designation** submission.

Further to the COMP preliminary discussion based on the sponsor's justification/maintenance report, a formal review process of the maintenance of the orphan designation for the applied indication will be triggered if this raises justified and serious doubts on the maintenance of the orphan designation. In this case, if previously only a justification was submitted, the sponsor will be requested to provide the maintenance report. The assessment procedural steps are described under heading 2.7.

In order to define what is a new therapeutic indication or a modification to an existing one for the COMP review for post-authorisation extensions of indications, the EC Guideline on the elements required to support the significant clinical benefit in comparison to existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection should be followed.

Any applicant who is unsure about what is required may contact the Orphan Medicines Office in advance of a planned submission in order to clarify orphan requirements sending a question via the EMA website.

Further information:

- 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).

2.9. Removal of orphan designation

The sponsor of a designated orphan medicine can request a removal of the designation from the Union Register. The removal of an orphan designation is in accordance with the Article 5(12) of the Orphan Regulation and it is irreversible.

It should be noted that prior to requesting the removal via the IRIS portal, the sponsor should have acquired all IRIS access rights to complete the request. Details are included in the IRIS quick guide to registration.

Procedural steps

- To request the removal, the sponsor should:
  - ✓ prepare a letter requesting the removal of an orphan designation, signed by a person having the legal mandate to request a removal. It should be noted that the removal from the Union Register can only be requested by the orphan designation holder. Therefore, the removal request letter should originate from such entity;
  - ✓ make a **Removal of an Orphan Designation from the EU register** submission via the IRIS portal. An electronic copy of the letter above should be uploaded with the submission.
- Upon receiving the request, the Agency will forward it to the EC for update of the Union Register. The EC will confirm the removal to the sponsor in due course.
- Following the removal, the Agency will update its published information to reflect the fact that the orphan designation has been removed from the Union Register at the request of the sponsor.

Once all of the orphan designations associated with an approved medicine have expired or been removed by the sponsor, the medicine ceases to be classified as an orphan medicine and no longer benefits from the orphan incentives.

2.10. Review of the period of market exclusivity of orphan medicinal products

The Article 8(2) of the Orphan Regulation establishes the possibility for a Member States to request that the market exclusivity is reduced to six years, under certain circumstances. On this topic, the European Commission has issued the EC Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products.

Procedural steps

Pre-assessment

- A Member State (MS) notifies the Agency that at least one of designation criteria of the orphan medicinal product may no longer be met. Such notification must include a written justification.
- The Agency acknowledges receipt and checks if pre-requisites of the request are met in line with legislation e.g. time of request.
- The Agency prepares a 90-day procedure timetable for start at a forthcoming COMP meeting according to the following guide:

Day 1 – start of the procedure and adoption of a list of questions (LoQ) for Step 1 (review of initial designation criteria) and Step 2 (return on investment assessment)

Day 30 - preliminary COMP discussion as required

Day 60 - OE by a Marketing Authorisation Holder (MAH) for Step 1 LoQ and adoption of a positive opinion on the maintenance of orphan criteria

or, if applicable, discussion with MAH on Step 2.

Day 90 - Step 2: 2nd OE by MAH, adoption of a COMP opinion.

- The Agency informs in writing the EC and MAH about the procedure providing MS' reasons for triggering Art. 8(2) and procedure timetable.

Assessment

- At day 1 the COMP adopts a LoQ covering both Step 1 and Step 2.
- MAH receives a summary report with LoQ with a deadline for response (3 weeks prior to day 60 COMP meeting) and an invitation to an oral explanation (OE).
- At the day 60 COMP meeting MAH attends OE (firstly for Step 1 and on Step 2 only when applicable). MAH is not required to address Step 2 before Step 1 is concluded, however MAH can discuss response to Step 2 LoQ during the same plenary.
- If the COMP trend is positive, a positive opinion is adopted and forwarded to the EC and the MAH.
- If COMP trend is negative, another discussion is scheduled for day 90 COMP meeting to conclude on Step 2.
- MAH receives the updated summary report and an invitation to the 2nd OE. MAH can submit additional data in support to Step 2 discussion by 2 weeks before next - day 90 COMP meeting deadline.
- If, following the 2nd OE, the COMP opinion is negative, MAH have a possibility to appeal within 90 days of receipt of the opinion.
- In a case of an appeal MAH is invited to another OE at the meeting following sumbission of the grounds for apppeal.

Post-COMP opinion

- The Agency forwards the COMP final opinion to the EC and to MAH.

Following the EC decision the Agency will update its published product related information.

3. Information for sponsors with reference to the United Kingdom's withdrawal from the EU ('Brexit')

On 31 May 2017, EMA and the European Commission published a question-and-answer (Q&A) document concerning the location of establishment of a company in the context of centralised procedures and certain activities, including the location of **orphan designation holders**. The Q&A document and up-to-date guidance for sponsors is available on the EMA website.

4. Frequently asked questions

1. If an applicant submits a new MA application with 3 orphan designated indications and following receipt of a positive CHMP opinion, the COMP concludes that one of the indications no longer meets the orphan criteria, would the applicant need to submit a new MA application to register the non-orphan indication (i.e. register under a non-orphan MA) or

would it be possible for EMA to proceed to issue two MAs (i.e. MA for orphan indications and MA for non-orphan indication) within the same procedure?

In the event that the COMP does not confirm the maintenance for one of the indications the applicant can follow several routes:

- appeal the negative COMP outcome for a re-examination by the COMP. If not successful, the options are 1) and 2) above;
- withdraw all the orphan designations and keep all three indications under one MAA;
- withdraw the indication with the negative COMP outcome and resubmit this one as a stand-alone non-orphan MAA;
- generate more data to address the deficiencies of the COMP outcome if feasible and resubmit as an extension of indication to keep it under the same orphan MAA a-s the other two indications.

2. My company is developing an orphan drug, which is likely to be the second drug on the market because there is a competitor (similar molecule, similar/same indication, different mode of administration from ours) pending MA. It's understood that once the competitor gets marketing approval as an orphan drug, our product cannot be approved in the next 10 years.
On page 3 of (2008/C 242/08) at the bottom, it says that "As of 20 November 2005, designated orphan medicinal products may only be authorised via the centralised authorisation procedure. Thus, a second product can only be authorised nationally, if it is not an orphan medicinal product". Does it mean that we can still pursue national/mutual recognition procedure and are able to get marketing approval for the same indication (as that of the competitor) in some EU countries even after the competitor gets a marketing approval as an orphan drug via central procedure?

A product that is authorised as orphan benefits, in principle, from a 10-year period of market exclusivity. As set out in Article 8(1) of Regulation (EC) No 141/2000, "Where a marketing authorisation in respect of an orphan medicinal product is granted […] the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product".

The similarity is based on three cumulative criteria: principal molecular structural features, mechanism of action and indication but does not take into account whether a different pharmaceutical form.

In case your company develops a similar medicinal product to an already authorised orphan (that still benefits from market exclusivity), that new candidate product may only be authorised if your company can establish that one of the derogations of Article 8(3) of Regulation (EC) No 141/2000 applies.

In the case the new candidate product can be authorised due to an applicable derogation, then there are, in principle, three possible scenarios:

- under the first scenario, the new candidate product falls within the mandatory scope of Regulation (EC) No 726/2004 (in this respect, see Article 3(1) of Regulation (EC) No 726/2004 and Annex I to the same Regulation); in that case, it must be authorised via the centralised procedure;
- under the second scenario, the new candidate product falls within the optional scope of Regulation (EC) No 726/2004 (in this respect see: Article 3(2) and (3) of Regulation (EC) No 726/2004); in that case, it may be authorised either via the centralised or the national procedures;

- under the third scenario, the new candidate product does not fall within the mandatory or optional scopes of Regulation (EC) No 726/2004; in that case, it may only be authorised via the national procedures.

For more information on the eligibility of product to be authorised via the centralised or national procedures, please refer you to Questions 2.1, 2.2 and 2.3 of the "European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure" (available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf; version of 16 April 2021).

3. We have been granted an orphan designation and would like to know if this implies any specific obligations upon receiving an approval of the MA in a centralised procedure - i.e. more specifically, are we obliged to go to market in all of the countries in the procedure or only the ones we choose to? Are there any special obligations in this regards due to the orphan designation?

There is no special obligation for an orphan medicinal product with regards to the choice and number of countries to market the product, once it received marketing authorisation.
For the benefit of the patients across the EU it would of course be preferable if the product could be made available across all countries.

4. As development of a product occurs, it is understood that the ultimate indication submitted in an MAA may not encompass the broad disease state noted in the original orphan designation. It is also understood that acceptable methods for treatment for the orphan condition may have progressed significantly, thus potentially changing the assessment of "significant benefit".

Recognizing the above, when the COMP makes a re-assessment for orphan designation at the MAA stage, would data clearly be supporting significant benefit in a large subset (approximately 60%) of the submitted indication support maintenance of the orphan designation for the submitted indication? Please assume that the submitted indication is supported by strong clinical data and the CHMP has granted positive opinion.

At the time of MAA the COMP will check that the sought therapeutic indication falls underneath the designated orphan condition. For the purpose of the significant benefit (SB) discussion, only the therapeutic indication will be considered. The new product will only be asked to show SB over product which cover the same or a broader patient population. It would definitely be possible to support the SB justification by showing a benefit in a subset of a population.