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Human Medicines Research and Development Support

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 sponsors to submit applications for orphan medicinal product designation and to manage post-designation activities.

Sponsors need to use EMA's IRIS system to submit all post-designation activities. EMA will not be able to process any submissions outside of the IRIS portal. For information and guidance on using IRIS, please visit the IRIS system homepage.

In addition, sponsors should consult the European Commission's Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designation from one sponsor to another (ENTR/6283/00)

[1]Revision to update broken link

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1. Introduction

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

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 the sponsor. Relevant information is published in the COMP monthly reports and the meeting minutes on 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 via courier.

Upon a favourable decision by the EC, the designated medicinal product is entered in the Community Register and a public summary of opinion on orphan designation is published on 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 Community Register under orphan medicinal products refused. The relevant public summary of the COMP opinion is published on EMA website (negative opinions).

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

- incentives
- annual reports
- transfer of sponsorship
- change of sponsor's name or address
- amendment of designated condition
- marketing authorisation application
- review of the maintenance of orphan medicinal product designation at the time of marketing authorisation application
- review of the maintenance of orphan medicinal product designation at the time of extending the therapeutic indication post-authorisation
- withdrawal of orphan designation

2. Incentives

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

- protocol assistance with development of the medicine
- reduced fees
- access to centralised procedure
- protection from market competition once the medicine is authorised
- additional incentives for micro, small and medium-sized enterprises (SMEs)
- grants

- incentives in Member States

2.1. Protocol assistance

At any stage of development, sponsors can request protocol assistance from EMA. 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 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 publically 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

2.2. 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 application for marketing authorisation (MA) 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, EMA/622074/2013.

Academic units who have obtained an orphan designation who wish to have their fee reductions reconsidered, due to special requests made within the context of grant submissions, should write to the Executive Director of the Agency.

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

2.3. Market exclusivity

As per 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 Community Register. Those products will be maintained in the Community 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 Community 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.

Review of the period of market exclusivity of orphan medicinal products

Article 8(2) of the Orphan Regulation establishes the possibility for Member States to request that the market exclusivity is reduced to six years, under certain circumstances. On this topic, the European Commission has issued a 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. The review process is described in detail in the standard operating procedure: Review of the period of market exclusivity of orphan medicinal products in accordance with Art. 8(2) of Regulation (EC) 141/2000 (SOP/H/3526).

2.4. 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.

2.5. 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 2020, the EU Framework Programme for Research and Innovation - sponsors interested in submitting for a grant under this framework should visit the relevant European Commission webpage (see the theme Personalising health and care and Horizon 2020, Work Programme 2016-2017 which covers new therapies for rare diseases)
- E-Rare, a European transnational project 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: Services to promote development of medicinal products for rare diseases

2.6. Incentives in Member States

The incentives available for designated orphan medicines in EU Member States are detailed in the EC Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products — state of play 2015.

For more information, applicants should contact the medicines regulatory authority in their country:

- National competent authorities (human).

3. 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 European Medicines Agency (EMA).

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. These annual reports could provide:

- 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

Sponsors are not requested to submit any documents; it is sufficient to complete the requested fields in the IRIS portal. Optionally, additional documents can still be uploaded if appropriate.

Calendar for submission of annual reports

These reports must be prepared and submitted to the 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 EMA. In case of 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 EMA 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 Register, annual reports will no longer be required.

Timelines for submission – designations for EU

Annual reports for orphan products designated for the EU only should be submitted within 2 months following the anniversary of the grant of the designation.

Timelines for submission – designations for both EU and US

Annual reports for orphan products designated for both the US and EU can be provided in a single submission to the FDA and the EMA on World Rare Disease Day (last day of February) or, in alternative, on either the normal EU or US annual reporting date.

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. For this purpose it is necessary to undergo the procedure outlined in section G of the Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designation form one sponsor to another and explained below in section 4 and 5 respectively (ENTR/6283/00).

4. Transfer of the orphan designation

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

Such a 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.

To transfer an orphan designation, the sponsor needs to submit an application 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
- the sponsor to whom the designation will be transferred
- 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 notification of the amended decision.

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.

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

A change in the name and/or address 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 and send the revised application.

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.

Prior to the submission of the request the sponsor should update their organisation details within the 'change request' functionality in the Organisations Management Service (OMS) interface, in accordance with the published rules. Sponsors that are individuals will just need to update their details in the EMA's Account Management portal.

To apply for the change, the orphan designation(s) holder should submit a signed letter (PDF) via the IRIS portal and to the EC at SANTE-DL-H-STANDCOM@ec.europa.eu, listing EU designation(s) numbers and clearly indicating the new name and/or address and a statement that the identity of the company remains the same. If the company's name has changed, the sponsor should attach a copy of the certificate of incorporation.

The Agency and the EC will update their records with the new information.

- Template - sponsor's name and/or address change notification letter

6. 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 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 Rev 4).

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.

6.1. 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.

6.2. Procedural steps

A request for amendment of an existing designated condition will follow the same assessment process as a new designation by the COMP i.e. a 90 day procedure. It will, therefore, be necessary to justify that all criteria for designation remain applicable.

The sponsor should submit the completed application via the IRIS portal and 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 in the "Input from Industry" folder in the "Documents" section of the submission).	Word/RTF 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 able to receive any documents in person. (To be uploaded in the portal in the "Input from Industry" folder in the "Documents" section of the submission).	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. (To be uploaded in the portal in the "Input from Industry" folder in the "Documents" section of the submission).	Word (docx format preferred)

Document	Format
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 create a subfolder, named 'Bibliography' to contain all individual files for each reference.	PDF
Zip folders are not supported with the submission.	

The validation and evaluation procedure and timelines are the same as for the initial designation. For further information please refer to Procedure for orphan medicinal products designation, guidance to sponsor available on the EMA corporate website.

Based on the Committee'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.

7. Marketing authorisation application and review of orphan designation criteria

If the sponsor of a medicine with an orphan designation submits an application for marketing authorisation (MA) to EMA, it should also submit a request for maintenance of the orphan designation via the IRIS portal once the MA has been validated. The evaluation 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 Community 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 European Union (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 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.

7.1. 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.

7.2. 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

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

If the 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. This 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. This 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

The sponsor should submit the maintenance report using the template provided on EMA website with the application for MA in a case of approved accelerated review (150 days) or around day 121 of the normal MA procedure (210 days). The maintenance report should be submitted 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.

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 final opinion.

During review, the COMP may adopt a list of questions and invite the sponsor to an oral hearing at the following Committee meeting. In case of a negative trend the sponsor may either withdraw the orphan designation or accept a negative opinion. Withdrawal of the orphan designation has to be requested during an ongoing COMP meeting and by submitting a withdrawal request to the EC SANTE-DL-H-STANDCOM@ec.europa.eu and to the Orphan Medicines Office via the IRIS portal. In a case of the negative opinion the sponsor can appeal by sending the grounds for appeal within 90 days following receipt of the COMP opinion. It should be noted that during the COMP review of the orphan designation, the EC decision on 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 MA decision making procedure.

For the appeal discussion, the sponsor is usually invited for another oral hearing at the meeting following receipt of the appeal.

In the event of the negative outcome following the appeal, the COMP's recommendation to remove the designation from the Community 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 reports and minutes from the Committee meetings; 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.

Related template:

Sponsor's report on the maintenance of the designation criteria at the time of marketing authorisation for a designated orphan medicinal product.

7.4. 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 Article 3 of Regulation (EC) No 141/2000, a COMP review 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 submission a maintenance report using the template provided on the EMA corporate website. The maintenance report should be submitted to the Orphan Medicines Office 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

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

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 a maintenance report. The procedure for assessment will follow the usual procedure, as described in Review of orphan designation at the time of granting/varying a marketing authorisation (SOP/H/3190).

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 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 following link https://www.ema.europa.eu/en/about-us/contact/send-question-european-medicines-agency.

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)
- EMA Post-authorisation guidance

8. Removal of orphan designation

The sponsor of a designated orphan medicine can for the orphan designation to be removed from the Community Register.

To request removal, the sponsor should:

- prepare a letter requesting the removal of the orphan designation, signed by a person having the legal mandate to request a removal
- create and submit the removal request via the IRIS portal, selecting as submission type 'Removal of an orphan designation from the EU register'. An electronic copy of the letter above should be included with the submission

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

Upon receiving the submission, EMA will forward the request to the European Commission, who will confirm the removal to the sponsor in due course.

The removal of an orphan designation from the Community register is irreversible.

Removal of an orphan designation is in accordance with Article 5(12) of the Orphan Regulation.

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.

After removal of an orphan designation, the Agency will update its published information to reflect the fact that the orphan designation has been removed from the Community register at the request of the sponsor.

The EC will also update the Community register to reflect the removal of the designation.

9. 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. Sponsors are advised to check this page regularly for further guidance on the consequences of Brexit, as EMA and the EC are preparing a series of further guidance documents.

10. General advice

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

All procedures related to an application for orphan medicinal product designation and post designation activities should be submitted via the secure online portal IRIS. Please refer to guidance available at EMA website if it is the first time you will be submitting via the industry portal.