Orphan Medicine Designation and development in Rare Diseases

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Orphan Designation split into Three Separate Areas for consideration

1. Orphan Medicinal Designation: conducted by the Committee for Orphan Medicinal Products (COMP):
   - **Granting of Orphan Medicinal Designation**

2. Use of Incentives obtained with Orphan Medicinal Designation (SAWP, PDCO, SME Office at EMA)
   - **Scientific Advice Working Party: Protocol Assistance, Paediatric Committee (PDCO) Paediatric Investigational Plan, Fee reductions and assistance at Small and Medium Enterprises Office**

3. Review of the Orphan Medicinal Designation at the time of Marketing Authorisation Application: conducted by the CHMP and COMP (Significant Benefit).
   - **Granting 10yr Market Exclusivity and if applicable +2yr extension for compliant PIP**
COMP: composition and responsibilities

- **Composition:** 1 elected chair, 1 representative per member state,
  3 patients’ Representatives appointed by the European Commission (EC),
  3 members appointed by EC on proposal from the Agency

- **Responsibilities:**
  - Give opinions to the Commission on products eligible for designation
  - Contribute to protocol assistance. Questions on significant benefit requirements exclusivity of the COMP
  - Give opinions to the Commission on review of the criteria for designation at the time of marketing authorisation (MAA) and assessment of significant benefit
  - Opinion on granting of 10yr marketing exclusivity at the time of MAA
  - Advise and assist Commission on orphan product policy and guidelines
  - Assist Commission in international interactions on orphan issues
Orphan Medicinal Designation considerations:
Situation in Europe

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Main characteristics orphan designation

- **Procedure are free of charge**
- Submissions can be for a product which is for the treatment, prevention or diagnosis of a rare disease
- A request for designation can be made at any stage of development before the application for an MAA. The product must not have a previous MAA
- The sponsor can be a company, Non-governmental organisation, Academic centre or a private individual who is established in the EEA (EU, Iceland, Liechtenstein)
- The COMP assesses the application and sends a recommendation to the Commission who grants the designation thereby opening the incentives
- Key incentives are: protocol assistance, fee reductions, centralised procedure for MAA, access pending assessment of 10yr and +2yr (if PIP) Market Exclusivity
- Designated products are entered into the Community register of OMPs
Application package

- Application form (if intention to file with the FDA there is a Joint Application form).
- Scientific sections A-E of the application (A-E Template)
- Proof of establishment of the sponsor in the EU (passport for private person, certificate of company registration).
- Translations of the name of the product and the proposed orphan indication into the official languages of the European Union, plus Icelandic and Norwegian
- Bibliography
- If applicable, letter of authorisation from the sponsor for the person/company acting on their behalf during the procedure
How to apply for orphan designation


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


Application procedure
Sponsors should use the forms below to apply for orphan designation:

- Application form for orphan-medicinal-product designation
- Common European Medicines Agency / Food and Drug Administration (FDA) application form or application form for orphan medicinal product designation
- Template for sections A to E for the scientific part of the application for orphan designation
- Translations required with the submission of an application for orphan medicinal product designation

Refer to these documents for assistance completing these forms:

- 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, 27 March 2014
- Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation
- Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation
- Data providers and sources to identify existing authorised medicinal products in the European Union and European Economic Area

In particular, when completing section A.3.2 'Plausibility of the orphan condition; rationale for use of the medicinal product', sponsors should clearly identify studies with the substance in a relevant model(s) of the condition and, if possible, preliminary clinical data in patients with the condition.

Each application is assigned two coordinators:

- one member of the Committee for Orphan Medicinal Products (COMP);
- one scientific administrator from the Agency secretariat.

Once the application form and sections A to E are complete, the sponsor should submit the complete application electronically to the Agency.

The application should include full copies of the bibliographical references. The application form and sections A to E should be supplied in Word format (compatible with version 97-2003). References and the signed application form should be supplied as PDF files. In the application, sponsors should clearly substantiate the claims and support the statements made, with references where possible.

Deadlines for submission of applications for orphan designation are available under submission deadlines.

Applications for orphan designation are free of charge.
Key Considerations: EC Guideline on the format and content of applications as OMPs (ENTR/6283/00)

- Medical Condition under the orphan legislation:
  - Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)
  - Must be chronically debilitating and/or life-threatening.
  - Different degrees of severity - stages not acceptable
  - Subset of patients where positive B/R is expected generally neither sufficient to define a distinct condition.

- Prevalence must be BELOW 5 in 10,000.

- Authorised pharmacological treatments in Europe/Member States should be listed if there are any and European Guidelines highlighted.

- If any are available then the sponsor must show Significant Benefit (either *clinically relevant advantage* or *major contribution to patient care*.)
Prevalence

• The starting point for any prevalence estimation is the definition of a medically plausible condition that is generally recognised.

• The best and most reliable sources of epidemiological data will vary depending on the condition of interest and there is no unique best source.

• Standard sources of information typically consist of primary epidemiological and medical literature from peer-reviewed journals and, where available, databases and registries.

• There is a Guidance document available on the EMA website regarding prevalence calculation for orphan conditions.

Significant benefit (Exclusive for Europe)

Significant benefit: “A clinically relevant advantage or a major contribution to patient care”

Based on assumptions at the time of orphan designation

- Significant benefit over “satisfactory methods” generally understood to mean authorised medicines for the indications.
- Current European Guidelines regarding how to treat patients with the condition.
- COMP to assess whether or not assumptions are supported by available data/evidence supplied by applicant
- Sign benefit to be confirmed at the time of marketing authorisation to maintain orphan status. Data to demonstrate the SB.
- Recommendation document on data for SB and plausibility
The Designation Process in the EU

1. Intent to file letter
2. Application submission
   - In parallel with FDA and/or Japan?
3. Pre-submission meeting with EMA staff
4. Appointment of COMP- and EMA Coordinators
5. Validation
6. Evaluation: Max 90 days

- DAY 1
- DAY 60 (COMP meeting)
- DAY 90 (COMP meeting)
- List of questions
- Oral discussion
- Opinion
- Decision (European Commission) 30 days
Incentives and regulatory considerations:

Situation in Europe

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Post-designation is complex field

- European legislation regarding post-designation is spread over several pieces of legislation.
- Covers support for:
  - Product development.
  - Small to medium enterprises.
  - Licencing
    - Post-licencing: 10yr Market Exclusivity +2yr Market Exclusivity with endorsed PIP.
- Specific regulatory considerations for Orphan Medicines;
  - Orphan Similarity
Product Development

• Product development for Rare Diseases offers challenges which are unique.

• In order to foster development, Europe offers assistance through its incentives mechanisms enshrined in EU regulations.

• Development support through:
  - Protocol Assistance
  - Paediatric Investigational Plan
  - Compassionate Use Guidance

• These are centralised services which are operated by the EMA involving SAWP, PDCO, COMP and CHMP primarily.
Protocol Assistance.

- Article 6 of EC Regulation No 141/2000 is the basis for Protocol Assistance before submitting for a Market Authorisation.
- The EMA operates a centralised Protocol Assistance system for these products through the SAWP.
- Sponsors can submit questions on quality, pre-clinical and clinical development.
- SAWP meets once a month and operates a 70 Day procedure. **Fee reductions** are applicable on status. *There is no limit to the number of times a sponsor can request this service.*
- CHMP endorses quality, pre-clinical and clinical development answers
- COMP endorses Significant Benefit answers.
- The EMA operates a parallel Scientific Advice Service with the FDA on request.
The European Medicines Agency (EMA) can give scientific advice and protocol assistance to companies involved in developing medicines. For human medicines, scientific advice and protocol assistance are given by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP).

**Scientific advice** is when the Agency gives advice to a company on the appropriate tests and studies in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients.

Companies can request scientific advice from the EMA at any stage of development of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not.

Scientific advice helps the company to make sure that it performs the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing-authorisation application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of
Paediatric Investigational Plan

- *EC Regulation (EC) No 1901/2006 Article 37 states that* “a Marketing Authorisation Application for an Orphan Medicinal product which includes the results of all studies conducted in compliance with an agreed paediatric investigation plan will be eligible for a *2yr extension* onto the 10yr Market Exclusivity.”

- Sponsors’ should come and establish the need for a Paediatric Investigational Plan (**PIP**) with the PDCO.

- The PDCO operates a 120Day procedure with clock-off periods for a PIP. The service is **free**.

- Sponsor’s should integrate this consultation into their development planning as failure to have a PIP may invalidate their application at the time of submission for MAA.
Dedicated webpages to Paediatric Investigation Plans


The European Medicines Agency has a number of important tasks and responsibilities relating to the development of paediatric medicines. These were brought in by the Paediatric Regulation in January 2007.

This legislation concerns the development and authorisation of medicines for use in children aged up to 17 years and introduced sweeping changes into the regulatory environment for paediatric medicines, designed to better protect the health of children in the European Union (EU). The main change introduced was the creation and operation of the Paediatric Committee within the Agency to provide objective scientific opinions on development plans for medicines for use in children.

This section of the website provides information for companies or individuals wishing to develop a paediatric medicine and requiring guidance for the approval of a paediatric investigation plan (PIP), together with other information relating to paediatric medicines.
Compassionate Use Advice.

- **EC Regulation (EC) No 726/2004 Article 83 states that** “By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.”

- There is a guideline available for sponsors on the EMA website: **GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004**

- Sponsor’s can approach their National Competent Authorities to request that the CHMP provide Advice for compassionate use programmes for a given product. This coordinated by EMA.
Regulatory Support for Small to Medium Size Enterprises

- EC Regulation No 2049/2005 specifically addresses assistance of pharmaceutical SMEs in Europe.

- The EMA operates a Small to Medium Size Enterprises Office whose role is defined in Article 11 of the Regulation No 2049/2005.

- Companies who qualify need to register with the SME Office in order to benefit from these incentives more information is available on the EMA website.

- Article 7 of EC Regulation No 2049/2005 is the basis for free Scientific Advice and Scientific Services for Small and Medium Size Enterprises (SMEs) who have a product with an Orphan Medicinal Designation.
Dedicated Webpage to Small to Medium-sized Enterprises


Micro-, small- and medium-sized-enterprise (SME) office

The European Medicines Agency launched a micro-, small- and medium-sized-enterprise (SME) office in 2005. The office is dedicated to addressing the particular needs of smaller companies.

The establishment of the SME office followed the European Commission’s adoption of specific provisions on 15 December 2005. These provisions were aimed at promoting innovation and the development of new medicines for human and veterinary use by SMEs.

This section of the website provides information on the assistance that the SME office offers to SMEs:

- Incentives
- How to apply
- SME register
- Workshops
- Guidance
- Related information

Related documents

- SME Office - Addressing the needs of small and medium-sized enterprises (18/05/2015)

Related EU legislation

- Commission Regulation (EC) No 2049/2005

Contact point:

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SME office
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Orphan Fee Incentives

SMEs - 100% fee waiver for:
- scientific advice
- scientific services
- marketing autorisation application
- pre-authorisation GMP, GLP, GCP, PhVig inspections
- 1st year post-licensing fees (variations etc.)

Non-SMEs – 70% fee reduction for:
- scientific advice
## Letter from the Executive Director for Fee reductions

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<th>Fee reduction applicable to</th>
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Marketing Authorisation considerations:

Situation in Europe

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Key Considerations

• Centralised procedure through the CHMP for MAA.
  • Normal 210 day procedure
  • Accelerated Procedure
  • Exceptional circumstances
  • Conditional Licencing
  • Orphan Similarity where applicable.

• Review of the Maintenance of the Orphan Designation
  • Orphan condition, prevalence and if applicable Significant Benefit.
  • COMP gives an opinion on granting the 10yr exclusivity.

• Paediatric Exclusivity
  • PDCO responsible for giving an opinion on compliance of completed PIP which if positive opens granting of 2yr extension of Market Exclusivity per orphan condition.
Marketing Authorisation

- *EC Regulation (EC) No 726/2004* establishes the basis for the centralised procedure for products which have obtained an Orphan Medicinal Designation.

- Specific considerations for Orphan Medicinal Designation Products:
  - Centralised Procedure for Products with Orphan Medicinal Designation.
  - Conditional Licence
  - Orphan Similarity
Specific requirements

- Orphan on the market
- My designated product MAA
- Confirmation orphan status
- Similarity and derogations
- My MARKET EXCLUSIVITY
Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only centralised procedure: Regulation 2004/746
- CHMP responsible for assessment
- A completed valid PIP or waiver at the time of MAA submission if new active substance.
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)
Conditional Approval

- *EC Regulation (EC) No 507/2006* establishes the basis for the conditional marketing authorisation for products which have obtained an Orphan Medicinal Designation.

- MA on the basis of **less** complete data

  - subject to **specific obligations**

- Well motivated in CHMP

- B/R balance positive

- Benefits of immediate availability outweigh risk of incomplete data
Conditional Approval

- Only clinical part of the application dossier is less complete (Incomplete pre-clinical or pharmaceutical data only in the case of emergency situations)

- **Specific Obligations**: initiate or complete certain clinical studies

- Valid for 1 year and is renewable.

- Only for initial MAA

- Significant benefit is assessed by the COMP at the time of initial MAA.
Dedicated webpage for Conditional Licencing


This page lists questions that marketing-authorisation holders (MAHs) may have on annual renewals of conditional marketing authorisations. It provides an overview of the European Medicines Agency’s position on issues that are typically addressed in discussions or meetings with MAHs in the post-authorisation phase. Revised topics are marked ‘New’ or ‘Rev.’ upon publication.

A PDF version of the entire post-authorisation guidance is available:

- European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

These questions and answers have been produced for guidance only and should be read in conjunction with the rules governing medicinal products in the European Union, volume 2, notice to applicants.

MAHs must in all cases comply with the requirements of Community legislation. Provisions that extend to Iceland, Liechtenstein and Norway by virtue of the European Economic Area agreement are outlined in the relevant sections of the text.

1. How long is my conditional marketing authorisation valid? New March 2013
2. When shall I submit my annual renewal application? Rev. September 2014
3. How shall I present my annual renewal application? Rev. September 2014
5. How shall my annual renewal application be handled (timetable)? New March 2013
Other Licencing Considerations

• Although Orphan Medicines are not specifically mentioned in the relevant legislation companies can consider:
  • An accelerated Centralised Procedure providing the Applicant submits adequate argumentation the CHMP to support the basis for this procedure.
  • A submission based on Exceptional Circumstances which can be considered in very rare conditions where very few patients have the condition.
Orphan Similarity

- Paragraph 3 of Article 8 of EC Regulation 141/2000 establishes the basis for Orphan Medicinal Similarity.
- Orphan Similarity involves a orphan designation product which is applying for an MAA where another Orphan Product already has an MAA for the same indication and has the 10yr Market Exclusivity.
- CHMP determines at any stage before EC approval whether there is Orphan Similarity.
- EC Guideline exists which is available on the EMA Orphan Designation legal basis webpage which explains how it works.
Guideline on Orphan Similarity

COMMUNICATION FROM THE COMMISSION

Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity
Assessment of Orphan Similarity

• Applies if other orphan medicines authorised for same designated condition
• Need to submit report in module 1.7
  – Molecular structure
  – Mechanism of action
  – Similarity of indication (“significant overlap of populations”?)
• Assessment by CHMP working party competent (BWP or QWP)
• Final opinion by CHMP
• Similarity can be triggered any time before EC decision on MAA.
• Proactive publication on-going procedures
Derogations to market exclusivity if Orphan Similarity applies

Applicable if product is considered similar by CHMP.

Assessed based on sponsor’s report

- Specific timetable (parallel to QSE assessment)

Three derogations (Art 8(2))

- First MAH’s consent (agreement market sharing)
- Insufficient supply: long term and clinical consequences (presumably)
- Clinical superiority: better efficacy, better safety or exceptionally major contribution to patient care
Specific requirements for an Orphan Medicinal MAA

Confirmation designation criteria

- Report to orphan medicines section
  - Use of standard template available on Website.
  - At time of submission MA
  - Possible to update

- Need to address all designation criteria:
  - Orphan condition, prevalence, significant benefit (if applicable)

- Standard set at time of authorisation

- Assessment by COMP; opinion in parallel with MA opinion by CHMP
Procedure

- Sponsor submits report at the same time submission marketing authorisation application
- Data with the product in the condition needed for significant benefit.
- Procedure allows two discussions at COMP:
  - First hearing and oral explanation is a list of questions.
- COMP adopts opinion only after CHMP has adopted opinion on marketing authorisation
- COMP opinion can be subject to appeal
- Final COMP opinion is sent to Commission
- The Commission grants the 10yr Market Exclusivity
Market Exclusivity

• The Commission grants the 10yr Market Exclusivity based on the recommendation of the COMP.

• Sponsors should ensure that Significant Benefit is adequately addressed at the time of MAA submission (Protocol Assistance answer from the COMP on Significant Benefit should be sought)

• A valid and completed PIP should be available at the time of Market Authorisation Submission for evaluation by the CHMP.

• In the event it isn’t the sponsor can submit at a later date when the data are available through a variation.

• Based on the recommendation from CHMP the Commission grants the additional 2yr Market Exclusivity.
How to obtain additional 2yr extension

- To obtain an additional 2yr Marketing exclusivity extension the sponsor must be compliant with the agreed PIP.

- Each separate orphan designation linked to an orphan condition has its own additional 2yr Marketing Exclusivity Extension.

- The Paediatric Committee conducts the compliance check to ensure that the PIP has been completed adequately.

- The COMP is not involved. The CHMP will assess the data in the PIP.

- A positive opinion from the Paediatric Committee is communicated to the European Commission who grants the 2yr extension for the indication(s) in the PIP.
Conclusions

- European Legislation provides the basis of the framework for Post-Orphan Medicinal Designation Incentives and Regulatory Guidance.

- Support of product development through Protocol Assistance, Paediatric Investigational Plans and Compassionate Use Guidance.

- Specific Regulatory support and fee reductions exist for SMEs.

- Centralised Marketing Authorisation with specific consideration to Conditional Authorisation, Orphan Similarity Issues, review of Orphan Designation and granting of 10yr+2yr Market Exclusivity.