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Review Article

Orphan drug designation in Europe-Procedural guidance and challenges

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Abstract

The European legislative framework on orphan medicinal products was implemented to stimulate the development of medicinal products against rare diseases and to ensure the patient's adequate access to qualitative and specific treatment methods. Between 2000-2018, 3210 orphan drug designation applications were submitted in Europe out of which 2121 orphan designations have been issued by the European Commission. (1) Though the definitions for orphan medicinal products and the regulatory procedures are well defined, a high degree of regulatory knowledge is needed and strategic decisions on the development program must be considered at a very early stage of development: in fact, only 164 of the 2121 designated orphan development products have resulted in authorised orphan medicinal products since the orphan legislation was implemented.

In this article, the requirements and procedures for the orphan designation application and maintenance at the time of marketing authorisation application are discussed in the context of the European Regulation.

Keywords: Orphan designation application, Commission Regulation, European legislative, MAA, EEA, COMP, EMA

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1. Introduction

In 1999 the European Community issued the orphan drug legislation defining diseases as rare when affecting less than 5 in 10,000 citizens. (2) Though, rare diseases have a particularly low prevalence, almost 27 to 36 million people (i.e. 6 to 8%) of the European population are affected. (3) The majority of rare diseases affect children and almost 30% of these children die before the age of 5. (4) In view of these facts, research on the origin and mechanisms of rare diseases and in the field of the development of orphan medicinal products became of increasing importance for the European Commission and public health organisations. However, the commitment of the pharmaceutical industry to develop such products was scarce due to many well-known difficulties including (i) the relatively low number of patients affected, leading to increased efforts and costs in patient recruitment for clinical studies, (ii) the limited knowledge and monitoring of rare diseases and (iii) a generally high risk to fail during development. Specifically almost 27.8 % of all designated orphan molecules and medicinal products fail, the main reasons being safety and efficacy. (5) As a consequence, the European Commission has taken numerous steps in

many areas to address the issue of rare diseases, improve the access to medical care for patients suffering and to support the development of specific medicinal products. This includes incentives for sponsors/ the pharmaceutical industry to develop such orphan medicinal products such as (i) an up to 10 years market exclusivity after the granting of a marketing authorisation, (ii) fee reductions for all centralised activities (e.g., marketing authorisation applications [MAA], variations, inspections, and protocol assistance) and (iii) grants from European Union (EU) and Member states supporting the research and development of orphan drug products. For small and medium-sized enterprises (SMEs), even additional fee reductions are applicable.

2. The European orphan legislative

At the European level, there are currently three key documents establishing a legal framework for the development and marketing of orphan medicinal products:

The Orphan Medicinal Product Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products to promote the development of orphan

medicinal products for rare diseases, laying down the criteria for receiving an orphan designation, the role and implementation of the committee for orphan medicinal products (COMP) as well as defining the incentives for developing such products including fee reductions and a 10-year market exclusivity. (2) As outlined in Article 3 of EC No 141/2000 a medicinal product shall be designated as orphan “(...) (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community (...), or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition (...) that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition (...) or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition”. (2)

Commission Regulation (EC) No 847/2000 of 27 April 2000 defining the provisions for implementation of the criteria for designation of a medicinal product as orphan and laying down the definitions of the concepts “similar medicinal product” and “clinical superiority”. (6) Beside the description of the documentation to be provided to receive an orphan designation, the Regulation highlights the importance of demonstrating that there “exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition”. (6) This is particularly important once the orphan drug designation will be re-assessed whether the medicine continues to meet the designation criteria for maintaining the orphan status and benefit from market exclusivity in parallel to a marketing authorisation application by European Medicines Agency’s (EMA) COMP.

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”. (7) Though Commission Regulation No 847/2000 already provides a definition which active

substances are to be regarded as similar to substances contained in authorised products intended for the same therapeutic indication or with similar structural features and mechanisms, the European Parliament identified a need for a clearer definition of similarity in light of new scientific data, particularly regarding biological and advanced therapy medicinal products (ATMPs). (7)

Beside these three fundamental orphan Regulations a large number of procedural guidance documents are provided by EMA. (8)

3. Applying for orphan designation

Applications for orphan drug designations for medicinal products must be submitted to EMA following the procedural guidance on the content and format of orphan drug designation applications. (9)

From 19 September 2018, applicants need to submit applications for orphan designation and pre- and post-designation activities using EMA's novel secure online system IRIS.

The orphan drug designation application comprises a briefing document (sections A to E) describing the concerned medicinal product, the proposed orphan indication and scientific data supporting the orphan drug designation application (Table 1). In addition, the name of the product (INN or common name) and proposed orphan indication must be provided in all official languages of the European Union including Icelandic and Norwegian and all scientific articles which are referenced throughout the application must be provided as full text articles. An application form is electronically available using EMA’s IRIS online system.

As outlined in Article 3 of EC Regulation No. 141/2000 an orphan drug designation application can either be based on the low prevalence and incidence rate in the EU or where a sufficient return of investment without incentives is questionable. (2)

In both cases, sufficient data must be provided which should be presented in the application following specific rules as outlined in Article 2 of EC Regulation No 847/2000 (6) and following supportive procedural guidance documents provided by EMA. (8)

Table 1 List of documents included in the orphan designation application

Sr. no.	List of documents	Description	Format
1	Application form	<ul style="list-style-type: none"> - Administrative information - Sponsor information - Corresponding contact person - OD number 	Web form in EMA’s online system IRIS
2	Scientific document: Section A to E	<ul style="list-style-type: none"> - Information on the medicinal product - Proposed orphan drug indication - Medical information - Justification of the life-threatening or chronically debilitating nature of the disease - Data on the prevalence of the condition or disease - Potential return of investment - Details on existing diagnosis, prevention or 	Word/RTF format

		treatment methods - Justification of significant benefit over existing methods - Description of the current status of development - References	
3	Proof of establishment of the sponsor in the EU	The sponsor must have a permanent physical address in the European Community.	PDF
4	Translations	Name of the product and the proposed orphan indication translated into all official languages of the European Union, incl. Icelandic and Norwegian.	Word
5	References	Scientific articles cited throughout the application as single PDF files	PDF (Zip file)

Applications based on the low prevalence and incidence rate

As outlined, where the orphan drug designation application is based on the argument that the medical disease is rare, i.e. there are less than 5 out of 10,000 people affected by the disease, sufficient scientific data must be provided supporting this claim. Following COMP's Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (10) the low prevalence rate should be based on epidemiological data from scientific articles and reference databases. Prevalence rates for individual European member states and a comprehensive prevalence rate for the Community should be presented, where applicable.

However, for certain rare diseases, especially those considered as *ultrarare* (150 cases per 100,000 people or even less) (11), or for subgroups of the recognised condition it will be difficult to obtain sufficient prevalence data. In these cases, the prevalence rates may be estimated based on scientific data to the overall prevalence of the recognised condition and should be appropriately discussed and statistically justified. An orphan indication will only be granted for the indication for which sufficient and justified data are presented. The company may develop the medicinal product also in other indications but receives only benefits and incentives for the orphan designation in connection to the granted indication.

For medical diseases for which the given prevalence rate is close to the 5 out of 10,000 threshold a more detailed review and statistical analyses may also be necessary to justify the orphan designation.

For indications with prevalence rates greater than 5 in 10,000 there may be the opportunity to apply for only a subgroup of the recognised condition.

Applications based on insufficient return of investment

Orphan designations may also be granted for medicinal products intended for the treatment of seriously debilitating or life-threatening conditions and with prevalence rates greater than 5 in 10,000 that “without incentives it is unlikely that the marketing of the medicinal product in the Union would generate sufficient return to justify the necessary investment” (Article 3(1) (b) of Regulation (EC) No 141/2000). (2)

In the case of applications which are based on the second paragraph of Article 3(1), the documentation provided should be in accordance with Article 2(2) of Commission Regulation (EC) No 847/2000: beside appropriate scientific and medical data on the condition, the documentation submitted by the sponsor shall include data on all costs that the sponsor has beard or expects to incur in the course of developing and marketing the medicinal product and on grants and incentives received for the development of the medicinal product. (6)

If the medicinal product is already authorised for other indications, the proportion of costs applicable among the various indications may be additionally considered, i.e. costs related to R&D, or production operations such as process or formulation development or stability studies may be proportionally included if these tasks also apply on the development of the medicinal product intended for the specific indication.

The challenge of orphan drug designation applications and maintenance: Demonstrating the significant benefit

While the presentation of scientific data to the medicinal product, the conditions and usually the prevalence rates remain a straight forward concept, the biggest challenge for orphan designation applications and later for the maintenance of the orphan designation remain the demonstration of the significant benefit over currently existing methods.

At the time of orphan designation applications a significant benefit can be theoretically shown by a head to head comparison of safety and/or efficacy data, and/or the contribution to patient cares, such as improved treatment or administration methods, improved quality of life or reduced dosing schedules.

The majority of applications are based on improved efficacy and the assumption of a major contribution to patients, because it is difficult to demonstrate an improved safety (i.e. less undesirable effects, reduced risks) with a usually very small clinical dataset. For example, demonstrating a significant benefit based on safety data would be feasible for products already licensed for other indications and for which sufficient safety data have been gained throughout the life cycle management.

Applications may be submitted at an early stage of development when clinical or comparative data are limited or even not available, but the theoretical benefit over existing *satisfactory* methods should be thoroughly discussed and justified based on scientific data available at the time of the orphan designation application.

However, at the time of the marketing authorisation application all orphan designations will be re-evaluated by the COMP and a theoretical comparison of preclinical or clinical data will not be sufficient to maintain the orphan designation. At this stage, the assumption of a significant benefit needs to be substantiated and usually requires a higher level of evidence, i.e. the direct comparison of treatment methods in preclinical and also in clinical studies.

The criteria for demonstrating a significant benefit are strict, since it was implemented to stimulate the development of advanced medicinal products for patients with rare diseases. Therefore, discussing the clinical development program with experts from COMP through protocol assistance is strongly recommended.

Timelines

Once the orphan designation application is submitted following EMA's submission schedule the application will be validated and evaluated by EMA's designated scientific administrator and one member from the COMP. After positive validation and start of the procedure (day 1) a summary report will be prepared and forwarded to all COMP members for review and subsequently discussed at the next plenary meeting (day 60). The COMP will either issue a list of questions which will be sent to the sponsor for response or adopts a positive opinion, which will be forwarded to the European Commission for adoption. The European Commission issues a decision within 30 days of receipt of COMP's opinion (day 90) and the information will be published by EMA and at the Community register of designated orphan medicinal products.

However, if the outcome of the application procedure is negative, COMP informs the sponsor that a negative opinion will be issued. The sponsor may withdraw the application and should inform EMA in writing *before* the negative opinion is issued, i.e. before the end of COMP's plenary meeting. At this stage, no information on the procedure will be published. The sponsor may re-apply for orphan designation with revised or additional data anytime thereafter.

If a negative opinion is issued, the European Commission adopts a negative Commission decision unless the sponsor appeals the opinion *prior* to the adoption. After the COMP's meeting the sponsor should immediately inform the Agency that an appeal will be made to stop the adoption procedure. The detailed grounds for appeal based on the submitted data and particularly on new substantiating data must be submitted within 90 days. At this stage, the presentation of new data supporting the application is essential for a successful appeal. A re-discussion of initially submitted data will not be sufficient to receive a positive opinion.

These data will be circulated with all COMP members and re-discussed at the next plenary meeting. In certain cases, the sponsor is invited to an oral hearing to present the submitted data and discuss its position.

Typically immediately after the oral explanation, the sponsor will be informed about COMP's final decision. At this stage, a final positive or negative opinion will be issued, a summary of the opinion published on EMA's webpage and a European Commission decision adopted. If the sponsor withdraws the appeal, the previous opinion will become final.

4. Activities after orphan designation: annual reports

Following Article 5(10) of Regulation (EC) No 141/2000 the sponsor of an orphan drug designation is required to annually submit a report on the current state of development of the designated medicinal product using a template provided by the Agency. (2) The annual report contains a description of preclinical and clinical activities as well as information on the regulatory status of the medicinal product in non-EU countries and a list of incentives received for the designated medicinal products. Typically the preclinical and clinical information includes a list of completed and ongoing studies, a short description of the study status and results and a description of activities for the upcoming year. The regulatory information includes the global orphan designation and marketing authorisation status and named-patient and compassionate use programs.

Annual reports must be submitted within 2 months following the anniversary of the approved designation. Alternatively sponsors have the opportunity to submit the annual report for granted designations in EU and US on the World rare disease day which is the last day in February.

5. Activities during marketing authorisation application: the maintenance of the orphan drug status and the evaluation of similarity

Following Article 3 (1) of Regulation (EC) No 726/2004 for orphan medicinal products it is required to apply for marketing authorisation through the centralised procedure. (12)

While the authorisation process is similar to other medicinal products there are two specificities which must be especially considered for orphan medicinal products: (i) the parallel assessment of the orphan designation maintenance and (ii) the assessment of orphan similarity.

The maintenance of the orphan drug status

When submitting a marketing authorisation application for a designated orphan medicinal product, sponsors are obliged to submit a report on the maintenance of the orphan drug status in parallel to the authorisation procedure. However, while the marketing authorisation application is reviewed by the CHMP, the orphan designation will be independently reviewed by the COMP. Similar to the initial application for orphan designation a report must be submitted discussing the medicinal condition, prevalence and incidence rates or insufficient return of investment and the justification for

orphan designation, i.e. either data on the significant benefit over existing methods or the lack of alternative treatment methods.

As mentioned earlier, if the application was based on the assumption that the medicinal product is significantly superior over existing methods the submission of sound experimental data is nearly always a prerequisite. A theoretical discussion of alternative treatment methods that was accepted for granting the orphan designation will not be sufficient for maintenance. However, if the significant benefit cannot be demonstrated and the orphan status is not sustained, the medicinal product can still receive a marketing authorisation - but not as an orphan medicinal product.

Importantly, the evaluation of the maintenance report is driven in parallel to the assessment of the marketing authorisation application and the coordinators of CHMP and COMP remain in close contact to discuss the current status of their review. A detailed description of the procedure of reviewing the maintenance application at the time of the initial MAA is laid out in EMA's SOP Review of orphan designation at the time of granting/varying a marketing authorization (SOP/H/3190) (13) and should be considered at the time of MAA to avoid any unexpected surprises which may delay the MA licensure procedure. As a matter of fact, the COMP adopts an opinion *after* the CHMP positive opinion at day 210 of the centralised procedure. Since the COMP opinion will also be forwarded to the European Commission for adoption the issuance of the marketing authorisation will be delayed as long as the orphan drug maintenance procedure is not completed. This fact is especially important if the COMP issues a negative opinion and the sponsor intends to appeal within 90 days. In this case a Commission decision will not be issued until the appeal is cleared and a final opinion is available.

The assessment of similarity

Table 2 Key considerations

At the time of orphan designation application
The condition is chronically or seriously debilitating or life-threatening.
The prevalence of the condition in the EU must be below 5 in 10.000 people affected or it must be unlikely that treatment methods will be development without incentives.
No satisfactory diagnosis, prevention or treatment methods exist or the orphan medicine has a significant benefit over existing methods.
For conditions with prevalence rates grater 5 in 10,000 an orphan designation can be filed for only a subgroup of the recognized condition.
Applications are made using EMA's online portal IRIS. The company and the active substance must be registered before applying for orphan designation.
The proposed orphan indication should match the future indication for Marketing authorisation. Otherwise the OD indication will be appropriately adapted.
Scientific studies to demonstrate a significant benefit over existing treatment methods must be planned at an already stage of development.
At the time of marketing authorisation application
Marketing authorisation applications of orphan medicines must be filed using the centralised procedure.
At the time of MAA an application for maintenance of the orphan designation must be filed and will be assessed by the COMP.
A significant benefit over existing diagnosis, prevention or treatment options must be usually demonstrated by a direct comparison.
A European Commission decision (license) will be issued once the CHMP opinion on the MAA <i>and</i> the COMP

Before submitting a marketing authorisation application, the pharmaceutical company is advised to check the Community register of orphan medicinal products (14) if medicinal product with orphan designations and market exclusivity protection are authorised in the European Union through the centralised procedure or in at least one Member state nationally or through a MRP or DCP. As outlined previously, Article 8 (1) of Orphan Regulation EC (No.) 141/2000 provides that "(...) *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*". (2) Based on the definitions set out in in Article 3 of Regulation 847/2000 medicinal products are considered similar, if the active substance is considered similar in terms of its molecular structural features, the mechanism of action *and* the therapeutic indication. (6) If the sponsor demonstrates a difference of one or more of these criteria, the medicinal product is not considered as similar to the authorised orphan product. The reasons for claiming a non-similarity should be presented as a similarity report in Module 1.7.1 of the MAA and will be assessed during the MA procedure.

If the medicinal product under assessment is considered as similar to an authorised orphan product, a marketing authorisation will not be granted unless the sponsor is able to demonstrate that the medicinal product under assessment is significantly safer or clinically superior. Besides, a similar orphan product may be authorised if supply shortages of the first orphan product can be demonstrated or if a written consent of the marketing authorisation holder of the first product is available. This information should be placed in Module 1.7.2 of the MAA.

opinion on the orphan maintenance are available.

An assessment of similarity with approved orphan medicines having 10-years market exclusivity must be included in Module 1.7.1 of the MAA.

6. The impact of the UK Brexit on orphan designations

At the time of this publication the negotiation period for United Kingdom's (UK) impending withdrawal from the European Union was extended until 31 October 2019. UK's leave irrespective of the outcome of the negotiations becomes apparent. For sponsors of orphan medicines and for those intending to apply for an orphan designation the upcoming Brexit causes some fundamental changes:

- As outlined in Article 2 of Regulation (EC) No 141/2000 the sponsor of orphan drug designations must be established within the European Economic Area (EEA). (2) The EEA includes the 28 EU Member States and three countries which are not in the EU: Norway, Iceland and Liechtenstein. Membership of the EEA has been suggested as a possible option for the UK after Brexit, however the British government ruled this out. For designated orphan medicinal products the holders located in the UK will therefore need to transfer its designation to a holder established in the Community using a template for changing the name and/or address of the sponsor which is accessible on EMA's webpage. Importantly, the notification must be sent to the European Commission by mail and to EMA via its online portal IRIS on the same time. Hence, as outlined before, access to EMA's IRIS is a prerequisite for any application related to orphan medicinal products.
- For orphan designation applications, annual reports or for its maintenance submitted after UK's withdrawal, data from the UK should no longer be considered for calculation of the prevalence of the disease or the discussion of the significant benefit over existing treatment methods.
- From the European perspective, orphan drug designations are no longer applicable for the UK and the British medicines agency MHRA would have exclusive responsibility for decisions around marketing authorisations and orphan designations. Though it is still not clearly communicated how authorisations are transferred to a pure national license, MHRA promised to retain a close working partnership with the EU and to guarantee sponsors to be able to take their products to the UK market as quickly and simply as possible.
- Following MHRA's further guidance note on the regulation of medicines, medical devices and clinical trials if there's no Brexit deal (updated 26 February 2019, (15) it is not thought to replicate the Community's orphan drug designation procedure since this procedure is well-established at EU level and it is doubted that sponsor's may benefit from a national UK procedure. However, in view of a UK-specific criteria for determining if a drug qualifies as

orphan in the UK (e.g. prevalence of the rare disease in the UK, the availability of existing treatment methods and the significant benefit of the orphan drug) the MHRA has committed to evaluate the incentives and establish a designation procedure if needed.

The procedure for maintaining the orphan drug designation at the time of a marketing authorisation application will be replicated and if an orphan MA is granted the product will also benefit from 10 years market exclusivity as in the European Community.

7. Conclusion

The availability of orphan medicinal products is fundamental for patients suffering from rare diseases. For this reason the European Commission established a legal basis supporting the development of orphan medicines by rewarding pharmaceutical companies with special incentives such as procedural fee reductions and market exclusivity for a given period after marketing authorisation. Three main regulations and numerous procedural guidances are available supporting companies when preparing orphan designation applications and maintenance reports. However, a lot of regulatory experience and finesse is needed to successfully apply and maintain the designation after marketing authorisation. Especially the demonstration of a significant benefit of the medicinal product over existing treatment methods presents one of the major hurdles. The majority of orphan designations are withdrawn because the sponsor fails to present sufficient experimental data confirming the claim. This can be avoided if the product's development plan is adequately set up already at an early stage.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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