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The orphan framework as a new opportunity: an expert opinion

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This is a review of the post-designation incentives framework that exists in Europe under its Orphan Medicinal Designation System. The aim of the article is to review and highlight specific regulatory mechanisms which are used or tailored to help in the development and licensing of products which receive an orphan designation. It is hoped that through this article there will be greater clarity of the post-designation incentives available to sponsors who obtain an Orphan Medicinal Designation.

Keywords: committee for orphan medicinal products, exclusivity, orphan, regulation

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In Europe efforts have been in hand to improve the development of therapies for rare diseases. The European Orphan Regulation (Regulation (EC) No 141/2000 of the European Parliament and of the Council) has led to the successful implementation of a European wide Orphan Medicinal Designation system [1]. Applications for the initial orphan designation are evaluated by the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA) [1]. The COMP also reviews the fulfillment of the designation criteria at the time of marketing authorization and makes a recommendation to the European Commission on maintaining the Orphan Designation and granting a 10-year market exclusivity. This incentive has been a very visible cornerstone in the effort to enhance the development and bring new medicines for rare diseases to the market.

Obtaining an orphan drug designation opens the door to a series of incentives offered by the European Orphan Regulation. In addition, the Member States and European Institutions also have several areas of support to facilitate research and development national incentives exist [2]. These are reported in a yearly communication from the Commission Expert Group on Rare Diseases. In the EMA, the incentives offered include fee reductions on the services and regulatory fees and protocol assistance [3].

Sponsors who obtain a designation should carefully consider and integrate these services into their development planning. In the following paragraphs, the interface between the orphan and other regulatory tools is emphasized, with the aim to increase the knowledge on the regulatory issues to be considered during the development of an orphan product.

1. Protocol assistance (scientific advice for orphan medicines) and parallel EMA/FDA advice

The development of products for rare diseases offers many challenges which can be different from those for products for common diseases. With this in mind the Member States and the European Institutions have worked to create a framework through several pieces of legislation to facilitate the support of the development process and licensing. This includes access to protocol assistance (Article 6 of the Regulation (EC) No 141/2000) which is provided by the Scientific Advice Working

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Party (SAWP) and reviewed, discussed and endorsed by the Committee for Human Medicinal Products (CHMP) [4]. Access to protocol assistance is not limited with the possibility of follow-up requests where questions may be posed concerning Quality, Non-Clinical (toxicology) and Clinical development considerations. These requests can be made at any time of development before or after the initial marketing authorization in the case of variations. In addition questions which are specific for orphan medicines such as issues concerning significant benefit and orphan similarity (and clinical superiority within the context of orphan similarity) can be raised at this stage. This process takes a maximum of 70 days following validation. The EMA also offers parallel scientific advice with health-technology-assessment (HTA) bodies. The aim of this is to allow medicine developers to gain feedback from regulators and HTA bodies at the same time, early in the development of a medicine. This helps them to establish the evidence that both parties will need to determine a medicine's benefit–risk balance and value.

The EMA and the FDA also operate a parallel scientific advice service. This can be useful when sponsors have obtained an Orphan Designation in the FDA and EMA by rationalizing the quality, pre-clinical and clinical data needs for both Agencies for a global development plan [5].

Protocol Assistance is also important for sponsors who are developing a product for a condition where the criteria for significant benefit needs to be fulfilled (Art 3(1) (b) Regulation (EC) No 141/2000 of the European Parliament and of the Council). As the COMP reviews the criteria for designation at the time of Marketing Authorisation Application significant benefit assessment is an important step in the establishment of the maintenance of the orphan designation and receiving the 10 years of market exclusivity. Questions raised on significant benefit at the time of Protocol Assistance are reviewed by the SAWP and discussed and endorsed by the COMP. This guidance aims at helping sponsors in their efforts to produce data to support their justification of significant benefit whether it is based on a clinically relevant advantage and/or a major contribution to patient care.

2. Compassionate use programs

Article 83 of Regulation (EC) No 726/2004 offers the possibility of obtaining advice from the CHMP on how to establish a compassionate use cohort for sponsors interested in supporting their development considerations through the use of compassionate use programs, such as generating safety data or making their product available to patients with the condition [6]. This legislation is directed to several areas of interest which are listed in Annex of EC Regulation No 726/2004 "Medicines to be authorized by the community" and which includes products which have obtained Orphan Medicinal Designation. This legislation is aimed at being complementary to Member States national legislation regarding Named Patient Programmes and Compassionate Cohorts.

Sponsors have used data generated under compassionate use programs for the purpose of supporting medical plausibility and significant benefit at the time of submission for Orphan Medicinal Designation. Under certain circumstances the COMP has accepted these data also to support the basis of significant benefit at the time of the review of the orphan medicinal designation. Providing the data is collected in a structured manner and the results generated from it are put within the context of the standard of care making it interpretable the COMP may consider it.

3. Pediatric requirements

In the event that the sponsor intends to submit an application for a marketing authorization they must comply with Articles 7 and 8 of the Paediatric Regulation (Regulation (EC) no. 1901/2006) which state the requirements for a pediatric investigational plan (PIP) at the time of validation of a Marketing Authorisation Application (Regulation (EC) No 1901/2006). In particular Article 7 of the Regulation defines the pediatric regulatory requirements (submission of data, product specific waiver, class-waiver and deferral) needed at the time of validation for the dossier. Article 8 further states "Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration." It should be noted that the procedure for a PIP is free of charge and are evaluated by the Paediatric Committee which after validation follow a maximum 120-day procedure. Applicants should include the results of all studies conducted in compliance with the PIP as referred to in Article 28(3) of Regulation (EC) No 1901/2006). Under Article 37 of this regulation sponsors who have an orphan designation and have submitted results from data generated according to the PIP to CHMP may be eligible to a 2-year extension to their 10-year market. The granting of this extension depends on the CHMP assessment and subsequent recommendation to the European Commission who grants the extension.

4. Fee reductions

Fee reductions are associated with many of these incentives [3]. In specific instances sponsors who are small-to-medium size enterprises (SMEs) can be eligible to free services if they obtain an orphan designation. This is specified under Article 11 of Regulation (EC) No 2049/2005. Companies who qualify need to register with the SME Office at the EMA. Companies which have obtained SME registration are listed on the EMA SME register which is accessible publically on the EMA Website. Fee reductions and waivers are applicable to areas of scientific advice (Protocol Assistance), scientific services and marketing authorization applications. The EMA publishes a letter on these fee reductions each year which is available on the EMA website for consultation.

5. Marketing authorisation issues for orphan designated medicinal products

Once a sponsor with a medicine with orphan designation has generated the data which can be considered adequate for a full submission of a Marketing Authorisation, the sponsor must use the Centralized Procedure to obtain a marketing authorization (Regulation (EC) No 726/2004). The marketing authorization lasts for a maximum of 210 days and is the same as the procedure used for non-orphan products. At the same time of submission of the dossier the sponsors need to consider be aware of specific requirements associated with orphan designation. These are orphan similarity and review of the maintenance of orphan medicinal designation at the time of Marketing Authorisation Application.

While this is not very common the CHMP has accepted under certain circumstances full submissions for Marketing Authorisation based on bibliographic data for the clinical section for an orphan designated product that has been used for greater than 10 years in the condition and has been subject to a prior license in Europe or a Member State.

6. Orphan similarity

Orphan similarity is a specific assessment that is conducted for any application for marketing authorization if a similar orphan medicinal product has been authorized for the same condition (Article 8 of Regulation [EC] No 141/2000) [7]. If any of the designated orphan medicinal products have been granted a marketing authorization in the Union, and a period of market exclusivity is in force, the sponsor will have to provide in Module 1.7.1 a similarity report addressing the possible similarity between their medicinal products and the orphan medicinal product(s) which have received a marketing authorization.

The assessment of similarity and, where applicable, of the derogation report vis-à-vis authorized orphan medicinal products will be conducted by the CHMP Rapporteur and Co-Rapporteur in charge of assessing the quality, safety and efficacy of the sponsor's medicinal product. This is a two-step procedure with the first step being a quality assessment which follows a 60-day procedure that can occur at any time during the 210-day procedure. This assessment includes the consultation of the Quality Working Party or the Biologicals Working Party, as appropriate, for the aspects concerning the similarity of the molecular structures of the products. Where necessary, a list of questions will be adopted by the CHMP on day 60 and a timetable of 30 days applies, normally, for assessment of the responses to the questions raised.

Where the outcome of the CHMP assessment is that the medicinal products are considered similar, the applicant will be requested to provide a justification that one of the derogations in Article 8(3) is fulfilled. These derogations are establishing either clinical superiority, and/or supply problems in Europe and/or permission from the holder of the market exclusivity. This assessment will follow also a 60-day timetable with a possibility for raising questions to the applicant with a timetable of 30 days. Should the CHMP conclude that the product which is the subject of the application for marketing authorization is considered similar to an authorized orphan medicinal product and none of the derogations provided for in Article 8(3) of the Orphan Regulation applies, the CHMP will adopt an opinion recommending the refusal of the granting of the marketing authorization/extension to the marketing authorization, irrespective of the demonstration of the quality, safety or efficacy of the medicinal product. The European Commission has a publically accessible guideline on how orphan similarity is assessed (Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorized orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity).

Similarity is not limited to the centralized procedure but also applicable to decentralized procedures managed by Member States and can block certain generic product submissions where an orphan indication is part of the wider therapeutic indication of an off-patent product.

7. Maintenance of the orphan medicinal designation and eligibility for 10-year market exclusivity

Assessment of the "Maintenance of the Orphan Medicinal Designation" is conducted by the COMP who reviews the Orphan Medicinal Designation Criteria at the time of the evaluation of the Marketing Authorisation Application. The authorized therapeutic indication has to fall under the designated orphan condition.

The sponsor needs to re-establish the key criteria associated with the Orphan Medicinal Designation. These are the condition, seriousness of the condition, prevalence and significant benefit. Advances in science may affect the definition of the orphan condition which in turn would affect the prevalence calculation. Prevalence may also be affected by better survival of patients following the introduction of new therapies before the review of orphan medicinal designation pushing the prevalence above 5 in 10,000. This would make the designation no longer valid and disqualify the sponsor for the 10-year market exclusivity.

Significant benefit needs to be established using clinical data generated with the product in the orphan condition. Ideally this data should be generated from clinical trials designed within the context of the clinical development of the product as parameters regarding either a clinically relevant advantage or a major contribution to patient care can be built into the trial designs. Questions on how to establish significant benefit can be raised during the Protocol

Assistance procedure (70 days) through the SAWP. These are reviewed and/or amended as well as endorsed by the COMP. This generally should meet the assumptions made at the time of the original designation (a clinically relevant advantage or major contribution to patient care) however may be different if new authorized products have been introduced in the time changing treatment algorithms in Europe between the original designation and the time of review. Sponsors should keep a watch for these changes and how this could affect the establishment of significant benefit and thus obtaining the granting of the 10-year marketing exclusivity.

The COMP generally initiates review of the maintenance after day 150 of the centralized procedure and makes every attempt to ensure that a recommendation can be made in the event of a positive CHMP opinion at day 210. Sponsors should be aware that during this evaluation they may be sent a list of questions and invited to an oral explanation at the following COMP 30 days later. The criteria for establishing significant benefit are the same whether there is a conditional or full license application. Following their deliberation the COMP makes a recommendation to the European Commission on maintaining the orphan designation and therefore being eligible for the market exclusivity incentive. The Commission has 30 days to process the recommendation before making it official unless it does not agree with the recommendation in which case it can request an independent consultation.

There have been 93 submissions to date for Market Authorisation under the orphan medicinal designation system in Europe. The COMP has refused renewal of an Orphan Medicinal Designation at the time of Market Authorisation for products indicated for renal cell carcinoma where the prevalence rose above the threshold of 5 in 10,000 following the introduction of new therapies since the original designations of this condition were given. The COMP has also refused to renew Orphan Medicinal Designation due to sponsors not establishing significant benefit because they have not generated data which could be assessed.

8. Eligibility for additional 2-year market exclusivity

Orphan medicinal designated products are eligible for a 2-year market exclusivity extension which is dependent on the results from the trials recommended in the PIP which falls under the orphan condition. The valid PIP results can be submitted to the CHMP for evaluation at any time during or after the applicant has obtained an initial market authorization for the orphan product. The application to the CHMP needs to be done during the 10-year market exclusivity period. Final approval for the 2-year extension is given by the European Commission based on the recommendation of the CHMP.

9. Additional considerations regarding marketing authorization submissions

There is flexibility regarding the route of submission for an MAA regarding products which have an Orphan Medicinal Designation.

10. Conditional licensing

Indeed legislation exists which provides access to conditional licensing submissions which falls under the Regulation (EC) No 507/2006 and is based on a less complete data set. Sponsors interested in a potential conditional marketing authorization may request CHMP scientific advice or protocol assistance. The basis for submission is subject to specific criteria obligations such as a positive benefit/risk balance and the benefits of immediate availability outweigh the risks of incomplete data. Only the clinical part of the application can be less complete (incomplete pre-clinical or pharmaceutical data are accepted only in the case of emergency situations). There are specific obligations to initiate or complete certain clinical studies. The conditional marketing authorization is valid for 1 year and may be used only for an initial authorization (submission under Article 8(3) of Regulation (EC) 726/2004) [8]. The granting of a conditional marketing authorization will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and will ensure that additional data on a product are generated, submitted, assessed and acted upon. It is important to note that in case the designation is for a condition with the requirement for the significant benefit, the COMP will review the clinical data available for the fulfillment of the significant benefit, among other orphan criteria at the time of the initial submission of the conditional marketing. Conditional licensing has been used for indications in oncology which are difficult to treat as well as multi-drug resistant tuberculosis and Duchene's Muscular Dystrophy. To date the CHMP has given eight conditional licenses.

11. Exceptional circumstances

Orphan conditions may present special challenges regarding developmental considerations as the condition may be very rare or little know about the disease so sponsors maybe unable to provide comprehensive data on the efficacy and safety for their products under the current normal conditions of use. The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information, may be eligible for marketing authorization under exceptional circumstances. Indications where products were

submitted using this route were primarily rare diseases where patient recruitment is difficult and mortality high such as inborn errors in primary bile acid synthesis, severe veno-occlusive disease and lipoprotein lipase deficiency. To date the CHMP has given 16 exceptional circumstances licenses.

12. Accelerated review process

Sponsors who have a product which could be considered of therapeutic innovation which is expected to be of major public health interest may consider the accelerated review process [9]. According to Recital 33 and Article 14 [10] of Regulation (EC) No 726/2004, the applicant may request an accelerated assessment procedure in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and in particular from the view point of therapeutic innovation. Based on the request, the justifications presented, and the recommendations of the Rapporteurs, the CHMP will formulate a decision. Such a decision will be taken without prejudice to the CHMP opinion (positive or negative) on the granting of a marketing authorization. If the CHMP accepts the request, the timeframe for the evaluation will be reduced to 150 days.

13. Conclusion

Europe has implemented legislation and services in an effort to promote development of medicinal products in rare diseases. These services include incentives which become available after a sponsor obtains Orphan Medicinal Designation. The aim of the incentives is to facilitate the development and access of these products in the target patient population and practicing physicians identified in the orphan condition. It is hoped that access will be enhanced through better trial designs and where possible compassionate use programs. Recognition of difficulty in developing products and making them accessible has led to the use and introduction of legislation aimed at rendering the licensing process more flexible. Orphan designated products have obtained licenses under different regulatory mechanisms such as bibliographical submissions, exceptional circumstances and conditional licensing. These have made products available across Europe in a uniform manner with standardized formulations and treatment regimes. This will potentially translate it is hoped in improved standard of care. As licenses for orphan designated products obtain a centralized license this should make products available in all 28 member states.

Products in the treatment of multi-drug resistant tuberculosis have benefited from the incentives of the orphan designation system by obtaining a conditional license through the incentives. Patients with mucopolyssacharidosis have had access for treatments through the market exclusivity incentive. Rare diseases like Laron syndrome where previously there were no therapies and the condition has a prevalence of 2 in 10,000 have benefited also from the 10-year market exclusivity.

Incentives in place for small to medium enterprises are designed to help and facilitate these resource restricted companies to develop their products more effectively thereby improving the changes of improving access to medicines to patients with rare diseases. Enhancement of the awareness of the different considerations available is hoped to help these companies bring their products to licensing in a shorter period of time.

In conclusion, sponsors who wish to obtain an orphan designation should carefully consider how to integrate the various incentives [11] they are entitled to once they have the European Commission decision on the designation following a positive opinion from the COMP.

Through the use of these incentives it is envisioned that orphan developments will be successful in obtaining the marketing authorization and increasing effective therapies for patients with rare diseases.

Declaration of interest

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