Orphan Medicinal Products in the EU:

Integrated Available Tools for Their Development

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SCOPE

This paper captures the key aspects that Orphan Medicinal Products (OMP)s sponsors should consider when applying for the Orphan Drug Designation (ODD) in Europe, analyses their proclivity to make use of available interactions and regulatory tools provided by the European Medicines Agency (EMA), and identifies the most common causes of OMP development failure.

Introduction

Rare diseases are chronically debilitating or life-threatening conditions with low prevalence. The European Union (EU) contemplates those that affect less than 5 in 10,000 citizens.[1] Currently, there are about 6,000 recognised rare conditions and around 224 OMPs marketed in the EU.[2] These data reveal that an enormous unmet medical need for the affected population exists, which constitutes a major challenge for public health.[3]

Regulatory Framework and EMA Incentives

The European Regulation (EC) No 141/2000 of the European Parliament and of the Council, known as EU Orphan Regulation, was adopted in 1999 to encourage the development of quality treatments and accurate diagnosis for rare diseases through economic and regulatory incentives.[1,4] This Regulation establishes scientific and regulatory assessment provided by the EMA (i.e. protocol assistance), access to the centralised authorisation procedure and the advantageous 10-year market exclusivity period (extendible to 12 years if the paediatric investigational plan (Regulation (EC) No 1901/2006) is completed), which prevents that a similar medicine for the treatment of the same indication is placed on the market.

Additionally, the EU allocates annually a specific budget to the Agency to financially support OMPs development. This special contribution covers the cost of certain incentives offered by the EMA to OMPs sponsors: as an example, in 2020, a total of 11,374,395€ was dedicated to fee reductions for designated OMPs.[5]

On the other hand, because of the nature of rare diseases, OMPs sponsors are also eligible for other regulatory tools provided by the Agency, such as Priority Medicines (PRIME), accelerated assessment and conditional marketing authorisation.[4]

To be eligible for EU Orphan incentives, the medicinal product has to be designated as orphan by the EC after the Committee for Orphan Medicinal Products (COMP) has reviewed the fulfilment of the ODD criteria:

- The condition to be treated is life-threatening or has a chronically debilitating nature,
- The proposed orphan indication is medically plausible,
- The prevalence of the condition in the EU is not more than 5 in 10,000, or it is unlikely that marketing the medicinal product in the EU without incentives would generate sufficient return to justify the necessary investment,
- No satisfactory methods of diagnosis, prevention or treatment exist, or if such methods exist, the medicinal product is of Significant Benefit (SB) to those affected by the condition.

The SB should be supported by nonclinical and/or preliminary clinical data relying on clinically relevant advantage or major contribution to patient care at the time of orphan designation, and with comparative clinical data at the time of Marketing Authorisation Application (MAA). Moreover, whether any of the designated OMP has been granted an EU marketing authorisation for the same therapeutic indication and a period of marketing exclusivity is in force, a similarity report addressing the possible similarities between the new medicinal product and the marketed OMPs should be provided to benefit from the orphan incentives.[4]

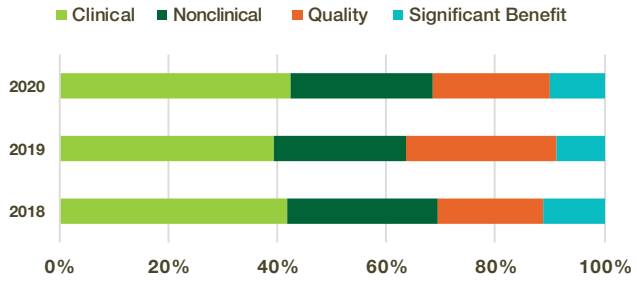
Analysis – Use of the available tools by sponsors

Interactions with the Agency

Marketing authorisation is given by EC to medicinal products, including OMPs, that fulfil the quality, safety and efficacy criteria. Compliance can be challenging for companies developing OMPs due to the heterogenicity and size of the population intended to treat, in addition to the poor knowledge about the natural history of the condition and disease biological mechanism.[6] To address these issues, which have led to about 40% of ODD granted during development to fail between years 2000-2020*, Protocol Assistance (PA) assesses questions regarding quality, SB, nonclinical and clinical development.[2,4] Unlike scientific advice, PA is only offered to OMPs sponsors. Even if the number of PAs received by the EMA varies over the years, the percentage of each type of questions has remained stable. As depicted in Figure 1, the majority of the questions raised during PA are related to clinical development, and are directly linked to the difficulties companies face during OMPs development (i.e. clinical protocol design, population to include, standard of care, etc.).

Figure 1

Percentage of types of questions answered by the CHMP as a response to the submitted PA by companies during 2018, 2019 and 2020. Source: European Medicines Agency (http://www.ema.europa.eu)



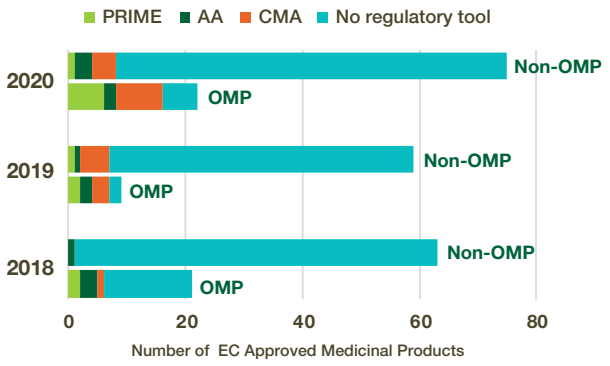
Use of regulatory tools from EMA

An analysis of the EMA's Committee for Medicinal Products for Human Use (CHMP) recommendations for the authorisation of new medicines, either OMPs or non-OMPs, has been carried out over 2018, 2019 and 2020 to evaluate the use of available regulatory tools at the time of the MAA. The results are shown in Figure 2. Note that more than one regulatory tool can be requested for the same medicinal product at the time of MAA or during its development.

*Estimation made by the author for the purpose of this article.

Figure 2

Number of EC Approved medicinal products which have used regulatory tools between 2018 and 2020. AA: Accelerated Assessment; CMA: Conditional Marketing Authorisation; OMP: Orphan Medicinal Product; PRIME: Priority Medicines. Source: European Medicines Agency (http://www.ema.europa.eu).



Although the number of OMPs approved in the EU has been increasing since the establishment of the EU Orphan Regulation, it remains low compared to the non-OMPs available on the market.[2] However, OMPs sponsors are more likely to use the tools provided by the EMA during the development process and at the time of MAA than non-OMPs sponsors, as displayed in Figure 2. This trend is believed to come from the very nature of OMPs, intended to cover unmet medical needs, one criterion to fulfil to be eligible for the EMA's regulatory tools.

Conclusion

It is of the utmost importance for the OMPs sponsors to understand the rare disease intended to be treated, the product characteristics and the presence of competitors to successfully receive market approval from EC as OMP and benefit from EU Orphan incentives. To overcome these challenges, companies should find strategic, scientific and patient support through early and continuous interactions with the EMA along their product development, jointly with guidance and operational assistance from regulators and experts in the field.

Future perspectives

It is expected that the economic and regulatory incentives from the EU Orphan Regulation will improve the number of available orphan treatments, which will lead to the progress of survival rates, life expectancy, therapeutic opportunities and quality of life of European patients. Nevertheless, these changes in the EU orphan landscape might come gradually over time, taking into account the time medicinal products take to reach the market since their discovery (i.e. 10-15 years).[7]

Veristat experience

Veristat has successfully conducted challenging ODD processes for companies worldwide and has extensive experience in ODD singularities in Europe. In-deep understanding of the key ODD criteria, such as medical plausibility, prevalence and SB, and regulatory support throughout the whole designation procedure, including the submission of orphan annual reports once ODD is obtained, is provided by Veristat. We can elaborate robust arguments to successfully substantiate the ODD criteria and provide support at the time of COMP's interactions, such as pre-submission meetings and oral explanations, if any. Veristat can also assist in the management activities via EMA IRIS portal, the EMA's online portal through which OMP procedures should be submitted for review.

About the author

Laura Pintado Batlle is a Biotechnologist (2019, University of Barcelona, Faculty of Biology, Spain) and holds a MSc in Pharmaceutical and Biotechnology Industry (2020-2021, Pompeu Fabra University, Spain). She currently serves as Regulatory Officer at Veristat with offices in Barcelona and Amsterdam.

ABOUT VERISTAT

Veristat, a scientific-minded global clinical research organization (CRO), acquired Drug Development & Regulation (DDR) in November 2021. With more than 27 years' experience in clinical trial planning and execution, Veristat is equipped to support any development program. To date, our team has supported more than 140 marketing applications which have led to more than 75 regulatory approvals from regulatory agencies around the world.

Veristat's focus on novel drug development has led to success when handling the unknowns that arise across complicated therapeutic areas, such as rare/ultra-rare disease, advanced therapies, oncology, and infectious disease trials. We apply this knowledge base every day to solve any clinical program's challenges, from the simplest to the most complex.

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