

## Applying for Orphan Drug Designation:

# Should the USA always be your first regulatory target?

### The myths surrounding EMA vs. FDA for orphan drug designation applications

There are approximately 7000 different rare diseases, and while individually their prevalence is low, collectively they affect between 6-8 % of the EU and US population. This has made the development of orphan medicinal products (OMPs) of vital importance to public health. Many incentives have been introduced by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to incentivize the biopharma industry to meet these unmet needs, under the guise of Orphan Drug Designation.

Securing Orphan Drug status for a product is a key hurdle in any regulatory strategy. For companies based in the USA, it may seem natural to first seek FDA approval before sequentially targeting other markets such as the European Union (EU). However, this assumption could be a missed opportunity for your product.

In this article, we challenge some of the preconceptions commonly surrounding this “USA-first” approach for Orphan Drug Designation.

## ***Myth 1: the application for Orphan Designation is a quicker process in the USA versus the EU***

While the official timelines are similar between the USA's FDA and the EMA (see table 1), the intermediate timelines of the process are less structured for the EMA and more controlled by the applicant. The EMA holds monthly meetings, mid-month, with a calendar visible 2 years in advance.<sup>1</sup> The applicant can align timelines according to their readiness, planning the notification and pre-submission of information around their desired evaluation meeting. Once the submission has been validated, the decision-making sub-committee of the EMA (the Committee for Orphan Medicinal Products: COMP) has a legal requirement to make a decision within 90 days.

Furthermore, the EMA encourages sponsors to request a pre-submission meeting two months (or more) prior to filing an ODD application, and Sponsors who participate significantly increase their chance of a successful designation application. These meetings are free, take place via teleconference, and provide a valuable opportunity for the sponsor and the Agency to discuss any potential difficulties.

The FDA also have a 90-day review timeline for orphan designation requests, however, until recently (when new procedures were implemented to clear the backlog as part of the new Orphan Drug Modernization Plan) many decisions were delayed to well over 120 days, and the FDA website still states that "new <designation> requests typically take 120 to 150 days to review"<sup>2</sup>

An underutilized process is a parallel submission to both the EMA and FDA using the Common EMA/FDA

Application Form for ODDs. This typically yields a quicker approval across EU and USA versus a more sequential approach, streamlining multi-market applications by presenting the same data in region-specific formats. The EMA COMP and FDA's Office of Orphan Product Development (OOPD) have monthly meetings to share information on orphan products and actively encourage Sponsors to submit in parallel by also providing the option for parallel FDA-EMA scientific advice. The benefits of which include getting an early agreement from both territories on your development plan and a scientific consensus on any specific concerns related to the product.

The key goal of these early interactions is to reach agreement on development plans and to highlight any potential challenges in development deriving from the scarcity of data, experts and patients typical of orphan indications.

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## ***Myth 2: the USA requires less information than the EU to decide on Orphan Designation***

The vast majority of required information is similar to both the FDA and EMA, forming the basis for the parallel application process to both bodies. However, there are some key differences – particularly relating to definitions – that can jeopardize submissions if not clearly understood.

For example, the definition of “unmet need”, and the methods of calculating and establishing disease rarity (prevalence vs. incidence), are different between the FDA and the EMA. This means it is possible to submit the same information to both bodies, but have one reject the product due to it not meeting geography specific benchmarks. The key here is to prepare the dossier using definitions and language broad enough to satisfy both boards. For both processes, it is important to ask questions and seek advice from regulatory committee members early on, and throughout the process, to minimize wasted time and effort.

Even if a decision is made to not enter the EU early in development (perhaps to avoid the complications

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of EU clinical trials procedures), it is possible to minimize the submission of information to the EMA by using the joint application process. For example, it is possible to have the drug evaluated simultaneously by both boards at the pre-human trial stage, but then continue trials solely in the USA, submitting only an annual update report to the EMA (and FDA) as the product lifecycle progresses. Such an approach ensures that the EMA are kept abreast of the progress of development and have agreed a clinical development plan, making it much easier to enter the EU market when you are ready to do so.

## ***Myth 3: the USA is more open to discussion, advice and question answering than the EU***

Both FDA and EMA processes pivot on building relationships with advisors and rapporteurs. Such relationships mean advisors will be more amenable to ad-hoc communication if time has been invested in building a solid reputation of collaboration, adherence and understanding. And the most effective way to establish such a reputation is to become known for writing good submissions, and for open and frequent communication with the agencies.

A good way to foster these relationships in the EU is to engage first with a country level scientific board who, will have members who sit on the COMP at the EMA. Country level boards are often more accessible than approaching the centralized EMA board in the first instance. These boards encourage informal communication, questions and advice seeking, with the added benefit of ensuring early familiarity with your product before it reaches the formal EMA process as previously discussed.

## Myth 4: the process for securing Orphan Designation is cheaper in the USA versus the EU

In both regions, application for Orphan Drug Designation is free, and the cost of meetings with the FDA and EMA are comparable, if not free of charge. The costs and incentives awarded by each are summarised in Table 1 below:

**Table 1: Incentives of orphan legislation in the US<sup>2</sup> and EU<sup>3</sup>**

Incentives	In US	In EU
<b>Marketing exclusivity</b>	7 years	10 years+12 more for paediatric indications
<b>Orphan designation</b>	No fees Parallel submission to the EMA and FDA, using the Common EMA/FDA Application Form for ODDs encouraged	No fees Parallel submission to the EMA and FDA, using the Common EMA/FDA Application Form for ODDs encouraged
<b>Support from agency during the development process</b>	Free scientific advice meetings with FDA OOPD (Office of Orphan Product Development) <b>Free Joint Advice COMP and OOPD</b>	Free or reduced fee protocol assistance and scientific advice from the EMA COMP (Committee for Orphan Medicinal Products); discounts available are reviewed annually, and levels depend on Sponsor status and product/indication type (SME, ATMP, paediatric, etc.) <b>Free/reduced fee Joint Advice COMP and OOPD</b> Free and reduced fee scientific advice and regulatory support available from some Member State Agencies for OMPs
<b>Clinical development costs</b>	Tax credits (up 50% of clinical development costs)	EC funding is available through schemes such as Horizon 2020, and previously FP7. EC discounts and funding available for SME's, ATMPs, and other product classes Member State's offer a variety of tax reductions or waivers, public funding/grants for research and SME's
<b>MAA</b>	Fee reduction	Fee reduction; free of charge for SME's and for paediatric products
<b>Reimbursement</b>	No formal HTA process US payers have previously reimbursed for high-value orphan drugs in most approved indications. But the inclusion of Payers Rebates, risk sharing agreements and the tried-and-true payer policies of prior authorization and patient case management are likely to be utilized more heavily in future, in response to Payer budget pressures and the creeping prices of orphan drugs, reimbursement and healthcare.	EMA is working to harmonize reimbursement decisions for OMPs. Decisions made locally by each Member State, although some have introduced joint assessment procedures for OMPs (e.g. BE, NL & LX) Almost all Member States allow pre-authorization access to OMPs through compassionate use/Early Access/named patient supply procedures. Some Member States waive administration fees for reimbursement applications or the annual fees. Some Member States allow exemption of the OMP from the cost/benefit analysis.

## Myth 5: the USA is more likely to award Orphan Drug Designation than the EU

A recent study<sup>2</sup> highlighted significant differences in orphan drug designations between the US and the EU. Differences of between 2.5 & 3 times exist across both the number of ODD granted and approved products, as well as the number of rare conditions addressed with therapies.

However, while this myth may, on the surface, appear true, a misunderstanding of differing qualifying definitions (e.g. unmet need and rarity) can result in rejection from one board and recommendation by the other, despite submission of almost identical information, highlighting the need for good, experience-driven regulatory writing. The status of orphan drugs designated that have not yet received a marketing authorization or are already marketed for patients affected by rare diseases in the EU and US up to December 2015.

**Table 2: ODD summary**

	US	EU
<i>Granted ODD</i>	3082	1264
<i>Products approved</i>	415	133
<i>Indications</i>	521	179
<i>Rare conditions addressed</i>	300	122
<i>Mean of designations per year</i>	93.4	79
<i>Mean of approval indications per year</i>	15.8	8.5

### Conclusion

The key to a successful and efficient regulatory strategy is avoiding inaccurate preconceptions. Ideally submissions would be written by (or under the advice of) someone with good market specific knowledge of processes and requirements; an ability to use language that is appropriate and understood correctly by the board in question and proactive

fostering of relationships with regulatory board members for advice and mutual understanding. These factors, plus an understanding of the nuances of regulatory strategy design for each member state, will maximize the use of available incentives, and ensure a fit-for-purpose submission without unnecessary wasted time, effort, or cost.

### About the author:

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<sup>1</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500003985.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003985.pdf)

<sup>2</sup> <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

<sup>3</sup> <https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0617-1>