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## Orphan Drug Designation within the Development Strategy

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The value equation for developing a qualifying medicinal product in the orphan drug designation (ODD) category is well known. Be it a start-up or established pharmaceutical company, the associated regulatory and administrative incentives, right from early drug development into life-cycle management, are sufficiently attractive in eliciting proportionate interests from drug developers. From pertinent and extensive EU and US experience base, this article captures the nuances of orphan drug development including regional product designation, applicable regulatory frameworks and incentives, as well as development strategies instructive to achieving successful orphan drug product positioning.

### EU and US Regulatory frameworks and Incentives

Orphan drugs is the term generally used in referring to a set of medicinal products developed to meeting specific standards in the area of rare diseases.

In the EU, the eligibility of a medicinal product for orphan drug designation is determined through careful consideration of a number of criteria and assumptions, all of which must be justified. These are [1] the life-threatening or chronically debilitating nature of the disease condition; a medically plausible orphan indication proposition; the prevalence of the medical condition in EU being not more than 5 in 10,000 individuals; the absence of authorized satisfactory method of diagnosis, prevention or treatment of the medical condition or the evidence that the new medicine promises significant benefit to those affected by the medical condition compared to existing method(s). In some rare cases, the prevalence criterion may be replaced by the anticipated inability for the Sponsor to recover development investments; however, the use of this criterion for orphan designation is anecdotal and not discussed in this article.

Similarly, in the US [2], drugs and biologics qualify for orphan drug designation with prevalence of the disease condition being less than 200,000 persons. In case the prevalence is more than 200,000, the product may still qualify where there is no reasonable expectation that the costs of research and development associated with the drug (for the orphan designated indication) can be recovered from sales of the product in the US.

As of January 2015, over 1,450 orphan drug designations were granted in the EU with more than 80 orphan associated orphan marketing authorizations (MAAs) authorized. In the US, more

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than 3,300 orphan drug designations were granted with about 480 associated orphan new drug applications or biologics license applications (NDAs/BLAs) approved. Figure 1, below, capture the various incentives associated with orphan designation in both the EU and the US. These can be either direct or indirect incentives, and procedural, financial or exclusivity by nature, as accruable to orphan drug development. Principal among these are the financial incentives throughout development, and the 10-year (EU) and 7-year (US) market exclusivity, as well as eligibility to accelerated assessment/approval procedures and parallel scientific advice. In the EU, additional support and financial incentives are available to companies qualifying for micro-, small- and medium-sized-enterprise (SME) status; as there are parallel R&D tax incentives and grants in the US. We have also to admit that the visibility gained by a designated product might also be of interest to sponsors who are interested in fund raising, given that this information is public.

### Application Procedure & Assessment Timelines

The application assessment and orphan designation procedure are managed by regulatory agencies: in the EU, this is carried out

Figure 1: Regulatory frameworks & Incentives

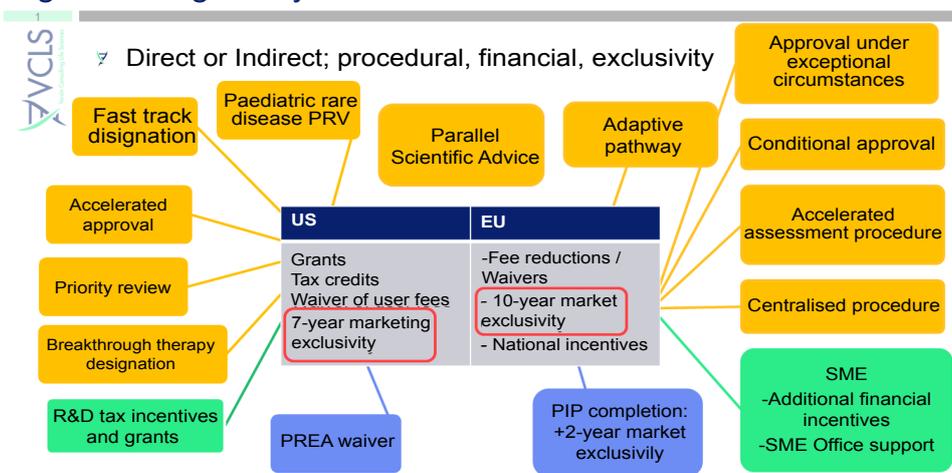


Figure 1 Regulatory frameworks & incentives.

Figure II: EU OD procedure & timelines

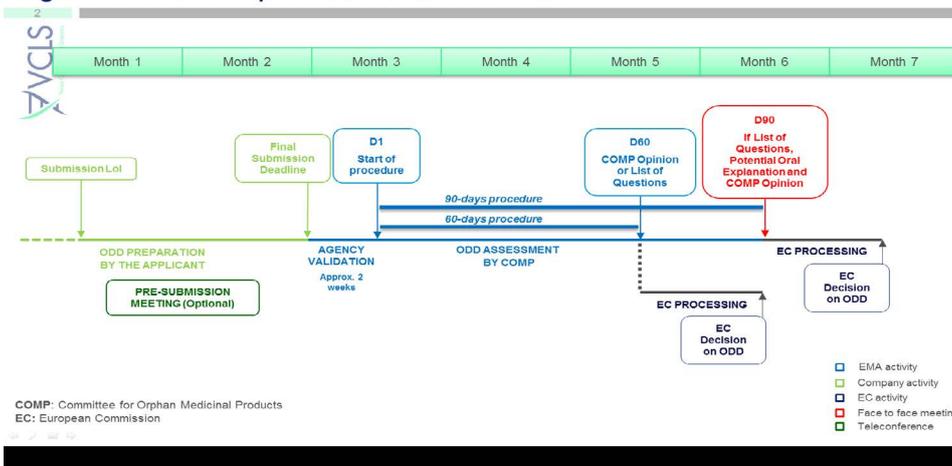


Figure 2 EU OD procedure & timelines.

under the auspices of the European Medicines Agency (EMA)'s Committee of Orphan Medicinal Products (COMP), and in the US by the Food and Drug Administration (FDA)'s Office of Orphan Products Development (OODP).

In the US, the assessment procedure does not follow a pre-set timeline and can typically be concluded within 2 months (Figure 2). Unlike the US, the European Union procedure follows a strict timetable of a 60- or 90-day procedure with an additional 30 days before the decision on the orphan designation is issued by the European Commission (EC). In both regions, pre-submission interactions with regulators are possible, either face-to-face or via teleconferences. These are meant to discuss main challenges identified at the feasibility steps (see Orphan drug designation strategy below).

In both the US and the EU, a structured scientific documentation needs to accompany the application form. This accompanying documentation provides the scientific basis and justification for

the proposed orphan medicinal product meeting the various qualifying criteria.

In the EU, it is mandatory for an EU-based Sponsor (individual or legal entity) to submit the application, whereas the US accepts a foreign Sponsor and US-based permanent resident agents.

## Orphan drug designation strategy

### Data requirements for OD

In the EU, *ENR/6283/00 Rev 3* states that an application for orphan designation can be made "[...] at any stage of the development of the medicinal product before the application for marketing authorization is made". Similarly, in the US, *21 CFR 316, §316.23* indicates that application can be made: "[...] at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the same rare disease or condition".

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In practice, preliminary preclinical and/or clinical data are generally required to support the medical plausibility of the medicinal product. This requirement is further increased when the assumption of significant benefit of the proposed orphan product versus existing therapy is required. Furthermore, as not supported by any form of evidence or results, pharmaceutical concept is not considered sufficient by regulators. For perspective, based on a systematic review of the content of the publically available 'Public Summary of Opinion' released on the European Medicines Agency (EMA) website for each designation, out for the 196 positive opinions issued by the EMA's Committee of Orphan Medicinal Products (COMP) in 2014 (Figure 3), 45% were based on nonclinical data and the rest were based on data from ongoing or completed clinical studies.

In essence, orphan designation request is not straightforward. Table 1 describes, based on the experience gained by the authors, what makes an application 'routine' versus 'very challenging'. COMP has been seen as increasingly challenging regarding eligibility to orphan designation over the past few years. The main recurrent questions touch upon 1/ the definition of the orphan indication (which is required to be a well-defined medical condition or a well-defined and justified subset of a well-defined medical condition), 2/ the nature and quantity of data supporting the medical plausibility and 3/ the methodology and sources for prevalence calculations.

Figure 4 and Figure 5 highlight typical situations and potential unforeseen challenges faced by Sponsors.

On one hand, Figure 4 illustrates a case of EU COMP 60-day (short) procedure that resulted in positive outcome; the condition (acute myeloid leukemia) is well-defined and known as rare (with recent epidemiological data; 1/10,000 people in the EU), there is precedence of ODD in the EU (more than 30 designations granted by the EC to date), and a recognized unmet medical need. In addition, clinical data were available and the assumption of significant benefit was supported. On the other hand, while at

first view the designation would have seemed straightforward, a COMP negative opinion was issued as illustrated in Figure 5. In this case, despite precedence of ODD (more than 40 designations granted by the EC), a well-defined medical condition (cystic fibrosis), a well-recognized unmet medical need and a known prevalence of fewer than 5 in 10,000 people, the COMP issued a negative opinion on the orphan designation request mainly based on the fact that the medical plausibility was supported by nonclinical data only (data generated from an animal model not relevant to the target indication) and anecdotal data from one patient only with cystic fibrosis.

Hence, in practice, the success of an orphan designation request is due to a thorough assessment of its feasibility at a given time, taking into consideration both internal factors (such as the medicinal product's mechanism of action and available data), as well as external factors (such as the therapeutic landscape and availability of recent and representative epidemiology data). Altogether, submitting the orphan designation in a timely manner is a key factor towards a positive outcome.

### Orphan designation within the development strategy

The timing of processing an application for orphan designation should be informed by the consideration of the Sponsor's interest and objectives in obtaining the designation. These may include corporate strategy and market access considerations. The orphan designation may also be meant to add value to the product, in view of a promising press release, or simply to increase company visibility in view of fund raising. Seeking orphan drug designation will also allow engaging early with EMA and FDA; this regulatory milestone may be the Sponsor's first step in the maze of these highly regulated markets. Sponsors may also be interested in the use of incentives associated with orphan designation. Nonetheless, it is important to consider the disadvantages of advancing too early request for orphan designation, including

Figure III: EC decisions based on positive opinion in 2014

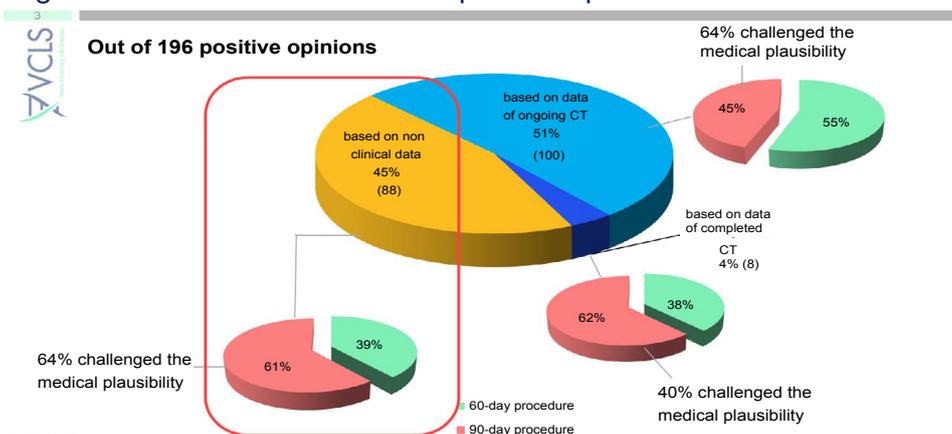


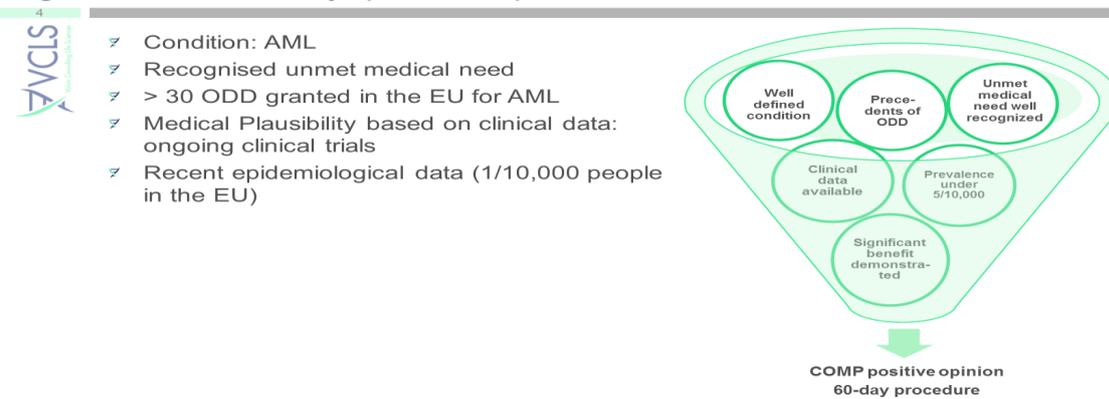
Figure 3 EC decisions based on positive opinion in 2014.

**Table 1:** Dynamics of scientific justification for OD request.

Level of difficulty <sup>†</sup>	Key contributing elements
“Easy”	<ul style="list-style-type: none"> <li>Well known and recognised condition,</li> <li>Existence of ICD code,</li> <li>Existence of designation precedents</li> <li>Absence of therapeutic alternatives</li> <li>PoC in relevant animal models, and/or preliminary clinical data</li> <li>Available (recent) epidemiological data</li> </ul>
“Medium”	<ul style="list-style-type: none"> <li>No (recent) designation precedents, or limited knowledge on condition</li> <li>Borderline prevalence (close to threshold)</li> <li>Assumption of significant benefit based on non-clinical data only, or based on data from other formulation/admin route of the IMP</li> </ul>
“Difficult”	<ul style="list-style-type: none"> <li>Challenging condition definition (e.g. disease manifestation vs. established medical entity)</li> <li>No PoC with product of interest in target condition (models)</li> <li>Scarce prevalence data</li> <li>Assumption of significant benefit based on improved PK profile, or major contribution to patient care (e.g. compliance)</li> </ul>

This table is based on extensive experience of the authors, who have been involved in orphan designations and orphan drug development and registration for more than 15 years, either as Sponsors or as Consultants in the field. Over the past 5 years, authors have been involved in the preparation, submission and management of more than 35 successful orphan designations in the EU.

**Figure IV: Case study: positive opinion**



**Figure 4** Case study: positive opinion.

public disclosure of regulatory strategy and product positioning; as well as the risk of premature application and negative opinion due to insufficient data.

A regulatory strategy is probably not complete without an upfront consideration of the impact of the orphan designation on the whole product development. In particular, it is critical to have a clear understanding of the impact of the orphan designation on clinical development. For example, is it an advantage or a constraint to have an orphan indication, versus the future therapeutic indication? What drives the choice of the comparator for the registration trial(s), taking into consideration the constraints of future demonstration of the product’s significant benefit?

Further, in-depth analysis is necessary in establishing the notion of “(non-) similarity” in the context of the future market exclusivity. Indeed, in the EU, “where a marketing authorization in respect of an orphan medicinal product is granted, the Community and the Member States shall not, for a period of 10 years, accept another application or grant a marketing authorization for the same therapeutic indication, in respect of a similar medicinal product, unless one of the derogations such as clinical superiority applies” [3,4]. Here again the choice of the comparator has direct implication on the demonstration of clinical superiority, in the context where a similar orphan medicinal product would have been authorized previously.

These discussions must take place with regulators ahead of time,

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Figure IV: Case study: positive opinion



- ✔ Condition: AML
- ✔ Recognised unmet medical need
- ✔ >30 ODD granted in the EU for AML
- ✔ Medical Plausibility based on clinical data: ongoing clinical trials
- ✔ Recent epidemiological data (1/10,000 people in the EU)

Figure 5 Case study: negative opinion

Figure VI: Orphan similarity: decision tree at time of MAA

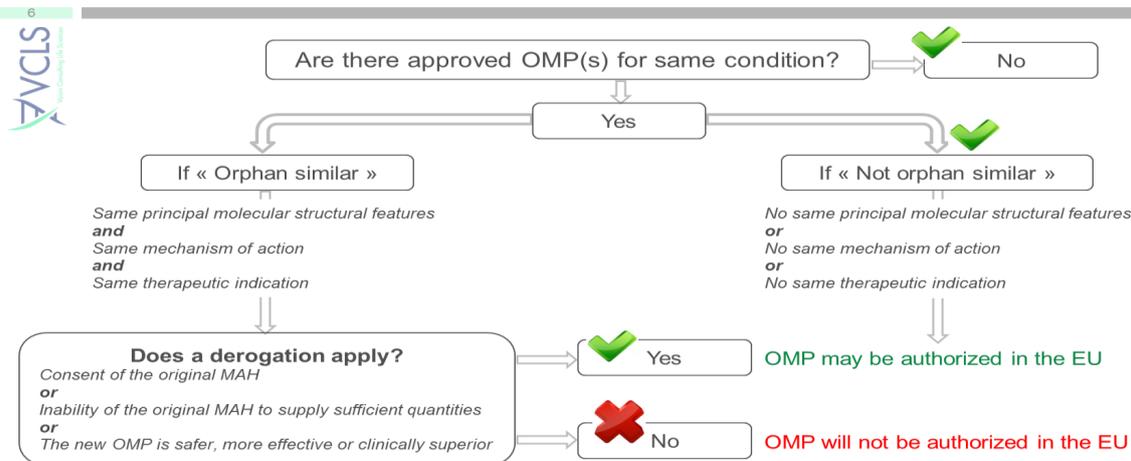


Figure 6 Orphan similarity: decision tree at time of MAA

e.g. through EMA Protocol Assistance or dedicated meetings with FDA, in order to establish a clear path forward in a context where patient resources are scarce.

### Market Authorization Application of a designated orphan drug

At time of product registration, both acceptability of the marketing authorization application and maintenance of orphan designation are key components of a successful regulatory strategy. This implies in particular a continuous and thorough surveillance of competition.

In the EU, the request for maintenance of the orphan designation is reviewed by the COMP based on data available at time of filing the marketing authorization application. The objective is to

enable regulators to determine whether the medicinal product can maintain its orphan status and therefore benefit from associated incentives.

In parallel, the formal assessment of orphan similarity is conducted by the regulators, leading to the acceptability of the application and its eligibility to registration, assuming the benefit to risk profile is assessed as positive by the EMA's Committee of Human Medicinal Products (CHMP). Figure 6 illustrates the associated decision tree.

### Summary and Conclusions

In summary, the orphan designation criteria are the following:

- Current prevalence of the medical condition, or the

potential return on investment

- Current life-threatening or debilitating nature of the medical condition
- Current existence of other methods for the diagnosis, prevention or treatment of the condition
- Justification of the medicine's significant benefit (when developed at the time of ODD request and over new methods approved since the designation was granted)

Obtaining orphan designation is not a straightforward regulatory procedure; however, based on discussions with companies developing orphan medicinal products, gaining orphan status has proven worth the effort in terms of benefiting from direct or

indirect incentives linked to this status. The timing to the request for orphan designation is variable, and dependent on the overall corporate and regulatory strategies as well as available data.

In the EU, it takes approximately 6 months to obtain orphan drug designation status while it is usually much quicker in the US. Orphan designation is one important milestone, and maintenance of the status throughout the life of the product is also of key importance for Sponsors.

Early and frequent interactions with regulators allow streamlining the development of the orphan drug and in most cases lead to a positive outcome, provided the data generated meet expectations.

## References

- 1 The european parliament and the council of the european union (2000) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Off journal of eu communities.
- 2 21 CFR Part 316 - Orphan Drugs
- 3 Article 8(1) of Regulation (EC) No 141/2000
- 4 Article 3 of Regulation (EC) No 847/2000