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FROM RARE TO RECOGNIZED

UNDERSTANDING **ORPHAN DRUG DESIGNATION** IN THE US & EU

Masoud Pourrahmat, BSc - Executive Director and Head of Operations
Ellen Kasireddy, MHsc - Senior Associate Research Scientist
Jean-Paul Collet, MD, PhD - Chief Scientific Officer

Introduction

Rare diseases, though individually uncommon, collectively affect an estimated 6% of the global population, affecting over 470 million people worldwide [1]. Despite this substantial burden, fewer than one in ten patients receive disease-specific treatments [2], primarily due to delayed diagnoses, regulatory inconsistencies, and limited pharmaceutical investment, driven by reduced market potential. Given the small patient populations, the commercial viability of rare disease therapies is often uncertain, leading to fewer incentives for research and development. The absence of a universal definition further complicates drug development and access, as different countries and regulatory bodies use varying criteria to classify rare diseases [3, 4].

To address these challenges, orphan drug designation (ODD) was established as a regulatory framework to incentivize the development of therapies for rare diseases, which may otherwise lack commercial viability. Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) offer financial and regulatory benefits to encourage pharmaceutical companies to invest in these treatments. However, the criteria for designation, prevalence calculations, and submission requirements differ between these agencies [5, 6].

This post provides a comparison of EMA and FDA ODD requirements, including official guidance, prevalence estimation methodologies, regulatory best practices, and common pitfalls, to help sponsors effectively navigate the application process.

Orphan Drug Designation: EMA vs. FDA

Both the EMA and the FDA aim to support drug development for rare diseases, but they have distinct definitions of rarity (**Table 1**).

Table 1. Definitions of a rare disease by the EMA and FDA [3, 4]

Regulatory Agency	Definition of a Rare Disease
EMA	Affects ≤ 5 in 10,000 people in the EU at the time of application
FDA	Affects < 200,000 people in the U.S. at the time of application

Regulatory Benefits: EMA vs. FDA

While both agencies offer financial and regulatory incentives to promote orphan drug development, their approaches and specific benefits differ.

The FDA offers 7 years of market exclusivity, tax credits covering up to 25% of clinical trial costs, and waivers for Prescription Drug User Fee Act (PDUFA) fees, which can save sponsors over $2 million. Additionally, orphan drugs may qualify for FDA grants to support clinical trials.

In contrast, the EMA provides 10 years of market exclusivity (extended to 12 years for pediatric indications) and offers fee reductions for regulatory submissions. The EMA also provides scientific advice and protocol assistance, which can help streamline the development process. Furthermore, the EMA supports orphan drug research through grants and funding opportunities available via EU programs (**Table 2**).

Table 2. Regulatory benefits offered by EMA and FDA

Specific Elements	EMA	FDA
Market Exclusivity	10 years (extended to 12 years for pediatric indications)	7 years upon approval
Financial Incentives	Fee reductions for regulatory submissions	Tax credits covering up to 25% of clinical trial costs
Regulatory Fee Waivers	Fee reductions for regulatory submissions	Waiver of Prescription Drug User Fee Act (PDUFA) fees (~$2 million)
Scientific & Regulatory Support	Scientific advice and protocol assistance from EMA	Eligibility for FDA grants to support orphan drug trials
Research Funding Opportunities	Grants and funding opportunities from EU programs	Eligibility for FDA orphan drug grants

Prevalence Calculation: A Critical Step in Orphan Drug Designation

Accurately demonstrating that a disease meets the rare disease threshold is a central element of ODD applications. Both the EMA and FDA require robust epidemiological data to substantiate the application, with a strong emphasis on prevalence estimation.

Key Epidemiological Definitions

- Prevalence: The proportion of a population affected by a condition at a specific point in time.
  - Point Prevalence: The proportion of affected individuals at the time of application.
  - Period Prevalence: The proportion of individuals affected during a specific timeframe (e.g., 5 years). Sometimes, "partial prevalence" is used to describe cases diagnosed within a limited period, though this is not a standard epidemiological term.
- Incidence: The number of new cases per year. While both EMA and FDA generally prefer prevalence data, they may accept incidence data instead for acute conditions lasting <1 year.

EMA's Guidelines on Prevalence Estimation

The EMA Committee for Orphan Medicinal Products (COMP) has specific guidelines for prevalence estimation:

- Point prevalence is typically required, except when:
  - The disease is acute and has a duration of <1 year, in which case incidence data may be used.
  - The drug is a preventive or diagnostic agent, in which case the number of annual users should be reported instead of disease prevalence.

Key Factors EMA Considers in Prevalence Estimation

- Geographic variation: If EU-wide prevalence data is unavailable, national estimates may be extrapolated.
- Temporal trends: If prevalence changes due to factors like improved diagnostics or treatments, updated data is needed.
- Reliability of data sources: EMA prioritizes peer-reviewed studies, disease registries, and national health databases for prevalence data.

FDA's Approach to Population Estimates

The FDA's Office of Orphan Products Development (OOPD) has strict guidelines for estimating U.S. patient populations:

- Use the highest available prevalence estimate for a conservative approach.
- Avoid averaging multiple prevalence rates. Instead, justify the selection of the most reliable estimate.
- Provide detailed methodology and conduct sensitivity analyses when dealing with incomplete data.

Key FDA Recommendations for Population Estimates

- Use the National Cancer Institute (NCI) SEER Program for cancer statistics.
- For chronic diseases, use prevalence over incidence unless the incidence × disease duration approach is justified.
- For preventive or diagnostic uses, report the estimated number of individuals receiving the intervention annually.
- Address the generalizability of foreign or regional U.S. data when used in prevalence estimates.

Common Pitfalls in Orphan Drug Applications

Even promising orphan drug candidates may face rejection if the prevalence calculation is flawed or the scientific rationale is insufficient. Below are common mistakes and practical solutions to address them:

1. Incomplete or Poorly Justified Prevalence Estimates

❌ Mistake: Stating that a disease is rare without providing sufficient epidemiological evidence.

✅ Solution: Provide comprehensive prevalence data, including multiple reliable data sources, and clearly outline the methodology used in the calculation.

2. Incorrect Use of Incidence Instead of Prevalence

❌ Mistake: Submitting incidence data for a chronic disease.

✅ Solution: Justify the use of incidence only if the disease is acute and its duration is less than 1 year. For chronic diseases, prevalence data should generally be used.

3. Defining the Disease Too Narrowly

❌ Mistake: Applying for ODD based solely on a specific stage of a disease (e.g., only metastatic cases of cancer).

✅ Solution: Provide a clear scientific rationale explaining why the disease subset in question cannot be treated the same way as the broader condition. Consider broader disease classifications that may meet the orphan criteria.

4. Failure to Address Evolving Disease Classifications

❌ Mistake: Assuming that a previously designated condition still qualifies without considering updated disease classifications or guidelines.

✅ Solution: Regularly review the most current disease definitions and classifications of the disease under international standards (e.g., WHO, EMA, or FDA) to ensure that the disease still qualifies under the orphan drug criteria.

5. Not Accounting for Disease Subtypes with Varying Life Expectancy

❌ Mistake: Treating all forms of a disease as a single entity without adjusting for different disease expressions (e.g., neonatal, infant, young adult, older adult forms), which may have varying life expectancy and impact overall prevalence estimates.

✅ Solution: Calculate the prevalence of each subtype individually and compute a weighted prevalence estimate to accurately represent the overall disease burden, accounting for variations in disease expression and life expectancy.

Accurately calculating the prevalence rate at the EU or US level can be particularly challenging due to multiple sources of bias, such as underreporting, diagnostic variability, and geographic disparities in healthcare access and infrastructure. These factors can significantly impact the estimated disease burden, potentially affecting ODD eligibility. ***For a more in-depth exploration of the complexities of prevalence estimation and common biases, check out our related blog post.***

Best Practices for a Successful Orphan Drug Designation Application

Step 1: Clearly Define the Disease

- Align with WHO classifications or other recognized medical definitions to ensure consistency and regulatory acceptance.
- If requesting designation for a specific disease subset, provide clear scientific justification explaining why this subset meets the orphan criteria distinct from the broader disease.

Step 2: Establish a Strong Scientific Rationale

- Present a comprehensive mechanism of action and any available clinical and preclinical data supporting the therapeutic potential of the drug.
- If clinical data is lacking, justify the application using biomarker or surrogate endpoints as valid evidence for the drug's efficacy and safety profile.

Step 3: Provide Robust Prevalence Data

- Use point prevalence for chronic diseases, as this provides a reliable snapshot of the affected population.
- Where appropriate, justify the use of incidence-based estimates, especially for diseases with a duration of less than one year.
- Cross-check estimates across multiple sources (e.g., disease registries, peer-reviewed studies) and conduct sensitivity analyses to address uncertainties or incomplete data.

Step 4: Follow a Structured Application Format

- Follow the application templates provided by the FDA or EMA to ensure consistency and compliance with their formatting requirements.
- Cite all data sources and methodologies thoroughly to substantiate your application and ensure transparency.

Step 5: Pre-Submit for Regulatory Advice

- EMA offers protocol assistance to guide ODD applications, providing expert guidance on the application process to ensure alignment with regulatory expectations.
- FDA allows for pre-submission meetings with the OOPD to clarify requirements and receive feedback on your application.

Conclusion

ODD offers valuable regulatory and financial incentives for the development of therapies targeting rare diseases. However, a successful application requires careful and comprehensive preparation. In addition to robust prevalence estimates, applicants must present a strong scientific rationale that clearly demonstrates the severity of the disease, its unmet medical need, and its impact on both patients and healthcare systems. The FDA, in particular, expects detailed evidence on the disease burden, including its progression, morbidity, mortality, and healthcare costs.

By leveraging robust epidemiological data, clear disease definitions, and regulatory best practices, sponsors can strengthen their application and maximize their chances of obtaining ODD from both the EMA and FDA.

References

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