



**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

HARMONIZATION OF ORPHAN DRUG REGULATIONS ACROSS EU MEMBER STATES: IMPACT ON APPROVAL TIMELINES AND PROCESSES

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Received 26th April 2024; Revised 29th Aug. 2024; Accepted 21st Oct. 2024; Available online 1st Oct. 2025

<https://doi.org/10.31032/IJBPAS/2025/14.10.9541>

ABSTRACT

In 2000, the European Union introduced orphan medicine legislation to support individuals with serious, rare diseases that currently lack effective treatments. As a result of the European Commission designating numerous medications as orphans based on favourable recommendations, several orphan medications have since been licensed for the European market. This study examined whether the market exclusivity incentive under the European Orphan Drug Regulation creates a monopoly or if other factors, such as market size or time, influence the difficulty of finding treatments for the same rare ailment. Further investigation is needed to understand the influence of market exclusivity on the development of follow-on OMPs, benefiting patients with rare diseases. The research indicates that factors like time and market size are more significant in explaining the lack of additional OMPs than the market exclusivity incentive's potential to create a monopoly. With public funding, the current system should be restructured to find more effective ways of encouraging the development of durable and effective medicines for those with orphan diseases.

Keywords: European Orphan Drug Regulation, European Orphan Drug Regulation, Licensed medications, Serious, rare diseases, Market exclusivity incentive, Orphan medicine legislation

INTRODUCTION

In the European Union (EU), around 30-40 million people are impacted by approximately 7,000 rare diseases. "Orphan drugs" are pharmaceuticals specifically designed for these uncommon conditions, and EU legislation actively promotes their development. Since the European Commission (EC) implemented Regulations 141/2000 and 847/2000 in 2000, significant progress has been made in treatments for rare diseases, bolstered by various incentives [1].

The task with reviewing applications for orphan drug designation, intended for products that diagnose, prevent, or treat serious or life-threatening conditions affecting no more than 5 out of 10,000 EU citizens. Following COMP's assessment, the EMA forwards its final recommendation to the EC, which makes the ultimate decision. Additionally, COMP advises the EC on policies and guidelines related to orphan drugs within the EU and facilitates international collaboration on these issues. Notably, COMP was the first EMA committee to include patient advocates as full members, supported by a specialist EMA expert network of 3,000-4,000 members [2].

However, there is debate over the effectiveness of these regulations Joppi et al. argue that the high number of designated orphan drugs may give patients with rare

diseases false hope, as only a small fraction of these drugs receive market approval in the EU. Additionally, there is a notable concentration of orphan drug designations and approvals in specific disease areas, particularly oncology, in the EU. Overall, the development of orphan drugs is driven by numerous legislative and financial incentives, with the most significant being market exclusivity periods of seven years in the US and ten years in the EU [3].

Partners of the European Union

“As a networking organization, the European Medicines Agency (EMA) collaborates closely with Member States and institutions of the European Union (EU)”.

The “European Medicines Agency (EMA)”, the European Commission, and more than fifty national human and veterinary medication regulatory authorities work together to create the European Pharmaceuticals Regulatory Network, a unique network that is vital to the EMA's operations inside the European Economic Area.

The scientific assessments provided by the “European Medicines Agency (EMA)” are crucial for the EU's centralized process of medicine authorization. These evaluations also contribute significantly to national and EU discussions on key public health issues and pharmaceutical regulations.

In addition, the EMA participates in EU initiatives meant to improve ties with EU enlargement nations and assist them in being ready to join the EMA in the future [4].

HISTORICAL OVERVIEW OF ORPHAN DRUG REGULATIONS IN THE EU

On December 20, 1995, the European Council published a resolution (95/C 350/03) that examined several key aspects as an initial step towards addressing the issue of orphan pharmaceuticals on a Europe-wide scale. These aspects included defining "orphan" drugs and "rare" diseases, establishing criteria for obtaining "orphan" drug status, providing financial incentives and regulatory measures to support the development and marketing of orphan drugs, and assessing the health impacts of a European policy on orphan drugs in Member States. In December 1999 The Orphan Medicinal Product Regulation was enacted by the European Parliament and Council and was later implemented by the European Commission in April 2000 [5].

COMMITTEES' WORKSIGHT

Through seven scientific committees, multiple working parties, and affiliated groups, the "European Medicines Agency (EMA)" conducts its scientific operations. Evaluations of applications for marketing authorization submitted through the centralized method serve as the basis for the approval of medications in Europe.

Boards and task force contribute to the advancement of medications and their regulation by:

- Offering companies engaged in research and development of new drugs scientific guidance.
- Creating regulatory suggestions and scientific guidelines to assist pharmaceutical businesses in preparing applications for marketing authorization.
- Supporting the international and EU-wide harmonization of regulatory standards.

"EMA'S COMMITTEES"

- "Committee For Medical Product For Human Use (CHMP)"
- "Pharmacovigilance Risk Assessment Committee (PRAC)"
- "Committee For Medical Product For Veterinary Use (CVMP)"
- "Committee For Orphan Medicinal Product (COMPP)"
- "Committee For Herbal Medicinal Product (HMPC)"
- "Committee For Advance Therapies (CAT)"
- "Paediatric Committee (PDCO)"

"COMPOSITION OF COMMITTEES AND WORKING PARTIES"

National authorities or academic institutions from EU and EEA Member States provide

European experts to EMA's committees, working parties, and related groups. For a list of these EEA national competent authorities, refer to "National competent authorities (human)." There is also a list of national veterinary authorities. Experts listed publicly by the Agency are eligible to participate in EMA activities, but only after their statement of interests has been reviewed and approved by the Agency.

“ADOPTING A COMMITTEE OPINION OR RECOMMENDATION”

Procedures within EMA committees can differ. Typically, a scientific evaluation is conducted by a rapporteur assigned by a committee and then reviewed and approved as a scientific opinion or recommendation. In certain cases, a "co-rapporteur" may also provide a separate evaluation.

The rapporteur and co-rapporteur are supported by an evaluation team that supplies essential information and resources. The EMA secretariat offers administrative, scientific, and technological assistance for every evaluation.

Rapporteurs and co-rapporteurs can create international evaluation teams by including experts from both their own and other Member States. This approach ensures the highest quality expertise is utilized in drug assessments, regardless of the experts' locations. More details are available through the European Medicines Regulatory Network.

Peer review acts as an additional quality assurance step for some scientific evaluations. EMA committees aim for consensus, but if consensus is not reached, a vote is taken. Refer to the "Guidance document on voting in the context of CHMP opinion adoption and discussion" for more details.

EMA can prevent committee members from voting on specific issues by implementing its conflict-of-interest policy. All EMA committee communications, working papers, and plenary sessions are conducted in English, with no translation or interpreting services provided.

Through "Fees Payable to EMA," the agency compensates national authorities for certain services performed by their employees on behalf of EMA committees, including expert or rapporteur work [6].

MARKET ACCESS ROADBLOCK

A novel therapy might receive conditional approval from federal regulatory agencies, but this does not guarantee patient access. According to a Tufts Centre for Drug Development report, patients still struggle to obtain orphan drugs, even though the EU has been approving them more rapidly. One major issue is determining who will pay for the treatment, whether it be the patient, private insurance, or public funding, with the high cost of many orphan drugs being a significant concern. The study suggests that the extensive time and effort required for

each new market filing could lead to significant delays in drug availability. Additionally, many countries in the Asia-Pacific region may not be a priority for smaller pharmaceutical companies due to their smaller markets and diverse regulatory requirements [7].

EMA'S ROLE IN ORPHAN DESIGNATION

The evaluation of sponsor applications for designation as an orphan fall under the purview of the EMA. A medicine needs to fulfil a number of requirements in order to be designated as an orphan drug:

- The drug must aim to treat, prevent, or diagnose a life-threatening or chronically debilitating disease.
- The disease's prevalence in the EU must not exceed 5 in 10,000 people.
- It is unlikely that the drug would generate sufficient revenue to cover development costs.
- There must be no existing approved method for diagnosing, preventing, or treating the condition, or if one does exist, the new drug must provide significant benefits to those affected.

The EMA's Committee for Orphan Medicinal Products (COMP) uses its expert network to review these applications, a process that takes up to ninety days after validation.

The "COMP's" recommendation is then forwarded to the "European Commission", which grants the orphan status.

Details about every orphan drug designation and any modifications adopted by the COMP are available in the List of Opinions on "Orphan Medicinal Product Designation".

"Community Database of Orphan Medicinal Products for Human Use" has the entire list of designations.

In February 2018, the EMA released a Q&A document to clarify common misconceptions about orphan designation and related aspects of orphan drugs.

AFTER ORPHAN DESIGNATION

In a typical market, there is little commercial incentive to develop drugs for small patient populations. The EU provides various incentives in an effort to promote the creation of authorized orphan medications.

Achieving orphan status grants sponsors benefits such as market exclusivity post-launch and protocol assistance, which is scientific guidance specifically for orphan drugs. Additionally, sponsors can receive fee reductions based on their status and the type of service required.

Starting June 19, 2020, academic applicants are eligible for free protocol assistance for orphan drug development. For more information, refer to "Academia and Costs Associated with Paying the European Medicines Agency."

Sponsors intending to create a medicinal product should review pertinent scientific guidelines.

Sponsors are required to provide the Agency with a report every year that summarizes the development of the medicine [8].

ORPHAN DESIGNATION: MARKETING AUTHORISATION

All orphan drugs in the European Economic Area (EEA) that must follow the mandatory centralized procedure are required to undergo a scientific evaluation by the European Medicines Agency (EMA) before receiving marketing authorization.

“ORPHAN MEDICINES'S APPLICATION FOR MARKETING AUTHORISATION”

The European Medicines Agency (EMA) not only evaluates applications for marketing authorization but also checks if a medicine continues to fulfill the criteria for orphan status. Sponsors may be required to provide an orphan similarity assessment, allowing the EMA to decide if the drug can retain its orphan designation and market exclusivity.

Since September 19, 2018, all post-designation activities must be submitted through the EMA's IRIS system; submissions outside of IRIS will not be accepted. For guidance on using IRIS, refer to "The application for Orphan Designation."

ORPHAN LIKENESS

Applicants must verify if any comparable medications with exclusive market access exist in the Community list of orphan medical products before submitting an application for marketing permission. A similarity report must be included in the application if a designated orphan medication with an EU marketing license enjoys market exclusivity. Any parallels between the novel product and the current orphan medication should be described in this report.

The following “Article 8(1) of the Orphan Regulation (EC)No 141/2000”, no similar product can be authorized for the same therapeutic indication within ten years of an orphan product’s marketing authorization, unless specific exceptions apply.

Article 8(3) permits marketing authorization for a similar product if:

- The original orphan product’s holder grants permission to the new applicant.
- The original product’s holder cannot supply adequate quantities.
- The new product demonstrates clinical superiority, such as being safer or more effective.

"Commission Regulation (EC) No 847/2000" provides a definition of comparable and clinically superior products. A comparable drug is one that shares the same chemical compound and medicinal indication as an orphan medicine that has

received approval. Active ingredients that are similar share the same or similar processes and basic molecular structures.

When assessing similarity, factors considered include:

- Mechanism of action
- Major structural characteristics
- Therapeutic indication

Marketing authorization may be granted if the product is shown to be safe, effective, and of high quality, and if it does not infringe upon existing orphan drug exclusivities, or if applicable exceptions are met.

If the CHMP finds that the new product is similar to an approved orphan drug and no exceptions apply, it will recommend refusing the marketing authorization, regardless of the new product's proven efficacy, safety, or quality [9].

EVALUATION OF ORPHAN STATUS DURING MARKETING AUTHORIZATION

A report on preserving the orphan designation must be submitted by the sponsor of a pharmaceutical that has been designated for orphans when they apply for marketing authorization or to extend an already-existing authorization. If the application is accepted for expedited review, it must be submitted within 150 days, or approximately on day 121 of the regular 210-day process. It is the sponsor's responsibility to make sure the application for marketing authorization is approved

before sending the maintenance report via the IRIS system.

The report should include details on:

- The current prevalence about condition.
- The condition's potentially fatal or severely crippling effects.
- The availability of alternative treatments.
- A basis of the medication's major advantage, if applicable.

This report allows the organization to ascertain if the drug capable of retain the orphan stage and market exclusivity. If granted, the orphan drug remains exclusively available for the approved indication.

“The Committee for Orphan Medicinal Products (COMP)” reviews maintenance report alongside available data to decide if the orphan designation should continue. During this time, the “Committee for Medicinal Products for Human Use (CHMP)” reviews the “Marketing Authorization Application (MAA)”. Once CHMP gives favorable opinion, the COMP provides its stance on the orphan designation, which is then sent to the European Commission by the EMA.

“The European Public Assessment Report (EPAR)” for all recently granted drugs includes the orphan maintenance assessment report, containing both beneficial and

adverse COMP comments and any discontinuations, as of January 17, 2018.

“PENDING ORPHAN DESIGNATION APPLICATIONS”

A medication that is authorized as an “orphan drug” even if its orphan designation application is pending when the marketing authorization application is submitted. This is possible if the “Committee for Orphan Medicinal Products (COMP) approves orphan designation and the European Commission (EC)” validates it before the marketing authorization is granted.

However, under certain conditions, the application for marketing authorization may not qualify for the centralized procedure according to “Point 4 and Article 3(1) of the Annex of Regulation (EC) No 726/2004”. Additionally, There won't be any payment reductions if the marketing authorization application is submitted before the orphan designation is officially approved [10].

MARKET EXCLUSIVITY: ORPHAN MEDICINES

In the EU, 10 years of market exclusivity are awarded to orphan drugs upon receiving marketing permission. By prohibiting the marketing of comparable medications with the identical indications throughout this time, exclusivity is intended to safeguard the advancement of medicines for uncommon diseases.

Market exclusivity is a benefit associated with orphan designation granted by the

European Commission. It applies for ten years to the specific clinical indication for which the orphan designation was given.

If a drug has orphan status for multiple conditions, each designation receives its own distinct period of market exclusivity. In order to be eligible for exclusive market access, the medication must still hold orphan designation during receiving “marketing authorization”.

EXPIRY OF MARKET EXCLUSIVITY

Once the “Market Exclusivity” period outdated, the “European Commission” takeout the notification from the public list of “orphan medicinal products”, and it ceases to be classified as an orphan.

A medication loses its orphan drug status and becomes ineligible for orphan incentives once all its related orphan designations have expired or been withdrawn by the sponsor [11].

“ORPHAN INCENTIVES”

NORM SUPPORT

An agency’s protocol assistance is a specific type of expert guidance. “exclusively for orphan medicines”. It helps supporter understand the research needed to demonstrate the drug's effectiveness, safety, and benefits, as well as its notable advantages.

This support is available at a reduced fee for certain orphan drugs, with discounts based on the sponsor’s status. Sponsors can

request protocol assistance multiple times as needed. For more information, visit:

- Scientific guidance and protocol support

ACCESS TO THE CENTRALISED AUTHORISATION PROCEDURE

In the EU, all orphan medicines undergo a centralized evaluation for marketing authorization. This enables businesses to apply to the European Medicines Agency only once, resulting in one view and ruling from the European Commission that is valid for all EU member states. Supporters might also qualify for conditional approval under orphan designation, which follows a centralized procedure. For more information, refer to Central Authorization of Medicines.

TEN YEARS OF MARKET EXCLUSIVITY

Once approved, orphan medicines are protected from competition with similar drugs for ten years. If the drug has also met the requirements of an approved pediatric investigation plan during the orphan designation review, this exclusivity is extended by an additional two years. For more information, refer to market exclusivity and the European Medicines Agency's guidelines on verifying pediatric investigation plan compliance and incentives.

Micro, small, and medium-sized enterprises (SMEs) receive additional benefits when developing "orphan drugs", charge savings

and assistance with procedures from the "Agency's SME office". For more details, consult the SME office and the User Handbook for micro, small, and medium-sized enterprises.

FEE REDUCTIONS

Businesses applying for orphan-designated drugs benefit from reduced regulatory fees. This includes discounts on protocol support, marketing authorization applications, pre-authorization inspections, post-approval modification requests, and annual fees. Fee reductions are adjusted annually based on available funds.

GRANTS

Although sponsors of orphan drugs cannot obtain research grants from the Agency, they can explore other funding options such as those provided by the European Commission:

- "E-Rare ERA-NET": A transnational initiative for the uncommon ailments investigation.
- Horizon Europe: The EU Framework Programme for Research and Innovation, which includes funding for new medicines for rare diseases.

For research in Japan or the United States, sponsors can apply for grants from:

- FDA (United States): Orphan product awards program.
- Japan: Orphan Products Development Support Program,

National Institute of Biomedical Innovation.

INCENTIVES IN MEMBER STATES

EU Member States provide additional incentives for orphan drugs. Applicants should contact their national medicine regulatory authority for more details:

- National Competent Authorities for Human Medicines [12]

REMOVING AN ORPHAN DESIGNATION

Supporters reporting post-designation actions and filings made external of the IRIS system must utilise EMA'S IRIS SYSTEM will not be processed by EMA. For guidance on using IRIS, visit the relevant section.

To request the removal of orphan designation, sponsors need to:

- Draft a letter requesting the removal, signed by an authorized representative.
- Submit the request through the IRIS portal, selecting "Removal of an orphan designation from the EU register" and attaching the electronic version of the letter.

Sponsors must ensure they have all necessary IRIS access credentials before submitting their request.

Upon receiving the submission, EMA will forward it to the European Commission, which will inform the sponsor once the removal is confirmed.

Once removed from the Community register, an orphan designation cannot be reinstated. As stated in Article 5(12) of the Orphan Regulation, an orphan designation may be removed. A medication will no longer be considered an orphan drug or receive related incentives once all associated designations have expired or been withdrawn.

PUBLICATION OF REMOVAL

The Agency will update the Public - List of Opinions on Orphan Medicinal Product Designation to indicate The Public list of orphan designation was eliminated once it has been officially removed [13].

CONCLUSION

Harmonized orphan drug regulations across the EU have sped up approvals and increased rare disease treatments. Regulation 141/2000 incentivized pharma companies, boosting recognized orphan products. However, the gap between designations and market approvals raises accessibility concerns. The EMA and COMP facilitate orphan drug designation and approval, with programs to expedite patient access. Despite progress, high therapy costs remain a barrier. More efforts are needed to address market access and ensure timely, effective care. Collaboration and innovative approaches are essential for improving orphan drug regulations' impact.

REFERENCES

- [1] Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU Roberta Joppi & Vittorio Bertele' & Silvio Garattini
DOI:<http://dx.doi.org/10.1007/s00228-012-1423-2>
- [2] European Regulation on Orphan Medicinal Products: 10 Years of Experience and Future Perspectives. Kerstin Westermark, Birthe Byskov Holm, Mirjam Söderholm, Jordi Linares DOI:
<https://doi.org/10.1038/nrd3445>
- [3] Delayed access to treatments for rare diseases: Who's to blame?_Karen Feltmate, Peter M. Janiszewski, Sheena Gingerich and Michael Cloutier.
DOI:<https://doi.org/10.1111/resp.12498>
- [4] EU partners -
<https://www.ema.europa.eu/en/partners-networks/eu-partners>
- [5] **Historical Overview Of Orphan Drug Regulations In The Eu.** Ref - [Legal Background of Orphan Medicine] Regulatory Issues for Orphan Medicines: a review. Luísa Bouwman, João José Sousa, Eugénia Pina.
DOI: <https://doi.org/10.1016/j.hlpt.2019.11.008>
- [6] **How the committees work.**
<https://www.ema.europa.eu/en/committees/how-committees-work>
- [7] **The Regulatory Process: Drug Approval In Jurisdictions Around The World**
<https://onlinelibrary.wiley.com/doi/epdf/10.1111/resp.12498>
- [8] **Ema's Role In Orphan Designation** -
<https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview>
- [9] **Orphan Designation: Marketing Authorisation.** The European Medicines Agency (EMA) is responsible for the scientific evaluation of marketing authorisation applications for all orphan medicines in the European Economic Area (EEA), as they fall under the mandatory scope of the centralised procedure.
<https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/orphan-designation-marketing-authorisation>
- [10] **Applying For Marketing Authorisation: Orphan Medicines.**
<https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/orphan-designation-marketing-authorisation/applying->

[marketing-authorisation-orphan-medicines](#)

- [11] Market exclusivity: orphan medicines.

<https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/orphan-designation-post-authorisation/market-exclusivity-orphan-medicines>

- [12] Orphan incentives.

<https://www.ema.europa.eu/en/human-regulatory-overview/research-development/orphan-designation-research-development/orphan-incentives>

- [13] Removing an orphan designation.

<https://www.ema.europa.eu/en/human-regulatory-overview/research-development/orphan-designation-research-development/removing-orphan-designation>