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Review

Orphan drug regulation: a global comparison of the United States Food and Drug Administration, European Medicines Agency, and Japanese pharmaceuticals and medical devices agency approaches

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ABSTRACT

Objective: To perform a comparative review of orphan drug policies and designation criteria implemented by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA), assessing their influence on development, approval, and access.
Method: A targeted review of legislation, guidance documents, and peer-reviewed analyses from each regulatory body was conducted.
Results: The FDA accelerates development via robust tax credits and seven-year market exclusivity, though high pricing remains challenging. The EMA emphasizes unmet medical needs and ten-year exclusivity, ensuring more homogeneous pricing despite slower approvals. Japan's PMDA utilizes specific subsidies and the Sakigake designation to counter "drug loss" and encourage innovation. Despite expedited pathways globally, significant disparities in affordability and patient access persist.
Conclusions: While national incentives successfully boost orphan drug approvals, global access inequities remain unresolved. Harmonizing regulatory criteria and promoting international collaboration on evidence requirements are essential for equitable and sustainable access to rare disease therapies worldwide.
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Regulación de medicamentos huérfanos: una comparación global de los enfoques de la Administración de Alimentos y Medicamentos de los Estados Unidos, la Agencia Europea de Medicamentos y la Agencia Japonesa de Productos Farmacéuticos y Dispositivos Médicos

Palabras clave:
Regulación de medicamentos huérfanos
Enfermedades raras
Aprobación de medicamentos
Administración de Alimentos y Medicamentos de Estados Unidos
Agencia Europea de Medicamentos
Agencia Japonesa de Productos Farmacéuticos y Dispositivos Médicos

RESUMEN

Objetivo: Realizar una revisión comparativa de las políticas de medicamentos huérfanos y criterios de designación implementados por la Administración de Alimentos y Medicamentos de EE. UU. (FDA), la Agencia Europea de Medicamentos (EMA) y la Agencia de Productos Farmacéuticos y Dispositivos Médicos (PMDA) de Japón, evaluando su influencia en el desarrollo, la aprobación y el acceso.
Método: Se llevó a cabo una revisión focalizada de la legislación, documentos de orientación y análisis revisados por pares de cada organismo regulador.
Resultados: La FDA acelera el desarrollo mediante sólidos créditos fiscales y una exclusividad de mercado de siete años, aunque los altos precios siguen siendo un desafío. La EMA enfatiza las necesidades médicas no cubiertas y diez años de exclusividad, garantizando precios más homogéneos a pesar de aprobaciones más lentas. La PMDA de Japón utiliza subsidios específicos y la designación Sakigake para contrarrestar la "pérdida de fármacos" y fomentar la innovación. A pesar de las vías aceleradas a nivel mundial, persisten importantes disparidades en la asequibilidad y el acceso de los pacientes.
Conclusiones: Aunque los incentivos nacionales impulsan las aprobaciones de medicamentos huérfanos, las inequidades globales en el acceso siguen sin resolverse. La armonización de los criterios regulatorios y la

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promoción de la colaboración internacional en los requisitos de evidencia son esenciales para un acceso equitativo y sostenible a las terapias para enfermedades raras en todo el mundo.

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Introduction

An orphan drug is a medicinal product created specifically to treat a rare medical condition, known as an "orphan disease." The pharmaceutical industry often does not pursue these drugs due to economic factors, despite addressing significant public health needs. Additionally, a drug's indications can also be classified as "orphan" if it was used for a common disease, but was subsequently approved for a rare condition.[1]

Orphan drugs are regulated by various countries under different regulations that provide their own definition and information regarding the rare disease, orphan drug development, approval pathway, and other regulatory requirements.

In the United States, the Orphan Drug Act (ODA) of 1983 defines a rare disease as "a disease or condition that affects less than 200,000 people in the United States." According to the Act, "An orphan drug is a drug for a rare disease or condition," noting that some treatments have been 'orphaned' or discontinued because there was not enough financial incentive to continue development or production.[2] The US was the first country to implement separate regulations for orphan drugs through the ODA.

For the European Union (EU), the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) evaluates applications for orphan designation, which is intended for medicines aimed at diagnosing, preventing, or treating rare diseases that are either life-threatening or very serious. In the EU, a disease is considered rare if it affects fewer than 5 in 10,000 individuals across the EU. The European Commission (EC) makes the final decision on granting orphan designation for a medicine based on COMP's recommendations.[3]

According to Japan's Pharmaceuticals and Medical Devices Agency (PMDA), a rare disease affects fewer than 50,000 persons, which is equivalent to 0.04% of the Japanese population.[4]

Orphan Drug Policies (ODPs) refer to the policies that address approximately 300 million people living with rare diseases worldwide. They are developed to optimize orphan drugs' development, licensing, pricing, and reimbursement. Since 2013, the landscape of ODPs has expanded: 92 of 200 countries/areas, or 46.0%, report having documented policies. Another interesting disparity is in the regional establishment of ODPs across different regions and levels of income. The more wealth that a country tends to have, the greater its likelihood of having ODPs, with an associated positive correlation between the scope of a country's ODP and the level of the country's income.[5]

This calls for greater access to orphan drugs across the globe, especially in low-income countries. In summary, though there has been progress in the regulation of orphan drugs across the globe, there is still much to be done. There is a need to bridge policy gaps in price regulation, incentives for market availability, and research and development in order to enhance access to affordable orphan drugs.[5] In addition, international cooperation and a solution to ethical concerns, funding dilemmas, and the formation of a decision-making panel are important to making the strategy more holistic and effective regarding rare diseases globally.[6]

However, there are major differences in orphan drug development and access around the globe. While some countries, such as the United States and EU members, have strong procedures in place, many others fall behind. As a result, orphan medications approved in the US may be unavailable or under development in other countries, such as Japan.[7] The orphan drug market is characterized by high pricing, with an average treatment cost of USD 218,872 for orphan drugs against USD 12,798 for non-orphan drugs.[8]

This narrative review brings forth a holistic comparison of three major regulatory authorities—the US Food and Drug Administration (FDA), the EMA, and the PMDA—regarding orphan drug regulation. Each of these has distinct criteria, incentives, and processes, all with the aim of fostering new developments and access to orphan drugs for patients with rare diseases. In comparing these regulatory strategies, we try to impart the global efforts in addressing the unmet medical needs of rare disease patients and illuminate best practices that could be adopted across different regions.

Methodology

Study design

This study employs a narrative review approach to aggregate and analyze information from a variety of sources, including official websites of the main organizations that regulate drugs (FDA, EMA, and PMDA), the peer-reviewed literature, and gray literature. The primary information regarding regulatory frameworks was retrieved directly from the FDA's Office of Orphan Products Development (OOPD), EMA's COMP, and PMDA's Orphan Drug Working Group. Supporting information for the review was retrieved from the Orphanet Journal of Rare Diseases and leading journals such as Clinical Therapeutics.

Search strategy

A targeted literature review was conducted using databases such as PubMed, ScienceDirect, JSTOR, ProQuest, and Google Scholar. Search terms included "orphan drugs," "orphan drug regulation," "rare disease," "orphan drug policy," "accelerated approval," "market exclusivity," "pricing," "access," "Health Technology Assessment (HTA)," and "regulatory incentives," combined with jurisdictional filters for the United States, European Union, and Japan. The search prioritized English-language publications from 2014 to 2025 to ensure the currency of the regulatory landscape.

Selection and synthesis

Documents were selected based on their relevance to specific regulations or policies on orphan drugs in the US, EU, or Japan. The review included full-text articles, government regulations, and reports. Gray literature, including policy briefs or stakeholder reports, was included where it offered expert views on the regulatory and economic dimensions of the orphan drug industry. Articles that did not pertain to the specific regulatory bodies or lacked full-text access were excluded.

The following information was extracted and synthesized qualitatively: definitions, criteria of designation, incentives, fast-track approaches to approval, HTA procedures, pricing, access, and post-authorization requirements. To assess the broader impacts of regulatory frameworks, qualitative indicators for pricing and access were developed. These were categorized through a semi-quantitative synthesis of median cost data and reported regional disparities in patient availability found in the reviewed legislation and peer-reviewed studies. Tables comparing these elements were developed using official sources of the regulations, official reviews, and official statistics.

Results

FDA regulatory approach

In 1983, the United States enacted the ODA with the intention of providing financial motivation to drug manufacturers to develop drugs for rare diseases.[9] Since coming into force, the Act has been instrumental in drug development, with 6340 orphan drug designations granted and 882 FDA approvals for 392 rare diseases between 1983 and 2022.[10] Interestingly, while the Act has succeeded in stimulating drug development for rare diseases, it has raised concerns. Approximately 20% of orphan drugs have been approved for both rare and common diseases, with some having reached the top-selling drugs around the world.[9] This naturally raised questions about whether the purpose of the Act has been served, particularly regarding “partial orphan drugs", which are applicable to both rare and common diseases.[11] The ODA has tremendously affected drug development for rare diseases, with a proposal where most approvals have increased by four times in the last 40 years.[12] However, concern regarding orphan drug development exists, on the one hand, whereas it is further buttressed by the high costs of orphan drugs and the possible abuse of the Act's incentives for drugs that are widely more applicable. Even so, debates continue about the adequacy of the Act and whether it would need modifications.[13,14] Regardless of the concerns, the Act continues to perform an indispensable role in offering one of the limited options available to bring treatments to rare disease patients.

A significant feature of the ODA is the provision that extends market exclusivity by seven years for each approved rare disease treatment, which enables manufacturers to postpone the entry of generic competitors. Consequently, some medications have enjoyed exclusivity periods that surpass ten years, with those having five approvals averaging an additional 13.4 years of exclusivity.[14] Nonetheless, this prolonged exclusivity has sparked concerns regarding the affordability of orphan drugs, as the median price for these drugs is markedly higher than that of non-orphan drugs (USD 218,872 compared to USD 12,798).[8] The ODA has effectively promoted the development of drugs for rare diseases, with 220 out of 497 novel drugs approved from 2010 to June 2022 receiving orphan designation.[14] However, it is crucial to recognize that only approximately 5% of rare diseases have an FDA-approved treatment, while up to 15% have at least one drug currently in development.[10]

The approval pathway for orphan drugs by the FDA involves several key steps:

1. Pre-Submission Phase:

- Identify the Rare Disease: Ensure the drug is intended to treat a disease affecting fewer than 200,000 people in the US.[15]
- Preliminary Research: Conduct initial research and gather data to support the drug's potential efficacy and safety.

2. Orphan Drug Designation (ODD):

- Submit ODD Request: Submit a request for orphan drug designation to the FDA with Form FDA 4035. This can be done through the Center for Drug Evaluation and Research (CDER) NextGen portal, email, or mail.[15]
- FDA Review: The FDA reviews the request to determine whether the drug meets the requirements for orphan status.[15]

3. Incentives and Benefits:

- Tax Credits: Eligible for tax credits for qualified clinical trials.[15]
- Fee Waivers: Exemption from certain user fees.[15]
- Market Exclusivity: Seven years of market exclusivity upon approval.[15]

4. Clinical Trials:

- Phase 1: Evaluate safety and dosage in a few healthy volunteers or patients.[16]
- Phase 2: Assess efficacy and adverse effects in a larger patient group.[16]
- Phase 3: Confirm efficacy, monitor adverse effects, and compare with existing treatments in a larger patient population.[16]

5. New Drug Application (NDA) or Biologics License Application (BLA):

- Prepare Application: Compile all data from preclinical and clinical trials, manufacturing information, and proposed labeling.[15]
- Submit Application: Submit the NDA or BLA to the FDA for review – Form FDA 356h.[15]

6. FDA Review:

1. Initial Review: The FDA conducts an initial review to ensure the application is complete.[15]
2. Advisory Committee: An advisory committee may be convened to provide recommendations.[16]
3. Final Decision: The FDA makes a final decision on approval based on the review of all submitted data.[16]

7. Post-Approval Phase:

- Post-Marketing Studies: Conduct additional studies to monitor long-term effects and ensure continued safety and efficacy.[16]
- Risk Evaluation and Mitigation Strategies (REMS): Implement REMS if necessary to manage any identified risks.[16]

Key features and incentives of the Act include:

1. To qualify for the financial incentives outlined in the Act, drug developers must secure ODD.[12]
2. Following approval, drugs receive a market exclusivity period of seven years, which hinders the entry of generic alternatives.[13] Certain drugs have received multiple orphan designations, extending their exclusivity beyond the initial seven years.
3. Developers can benefit from tax credits (25%) related to clinical research expenditures.[15,17]
4. Waiver for FDA user fees.[14]
5. Eligibility for FDA research grants is available.[15]

These incentives have significantly boosted the development of orphan drugs. From 1983 to 2019, a total of 5099 drugs achieved orphan status. The number of designations increased more than fourfold from the 1990s to the 2010s.[12]

FDA accelerated approval

The FDA's Accelerated Approval Program allows the approval of drugs based on surrogate or intermediate clinical endpoints that are “reasonably likely” to predict clinical benefit. An accelerated approval pathway is especially useful in diseases that are considered rare, where traditional endpoints may be infeasible or require a very long follow-up. This program is usually used in conjunction with other expedited programs: Fast Track, Breakthrough Therapy, and Priority Review. After approval, sponsors must conduct confirmatory trials to demonstrate clinical benefit. Delays in completing these trials can result in the withdrawal of approval, a process recently enhanced through the Consolidated Appropriations Act, 2023, which gives the FDA authority to require the start of confirmatory trials before approval and to accelerate procedures for withdrawal in case of failure to fulfill obligations.[18–20]

Randomized controlled trials are favored over single-arm trials, especially in cancer trials, but with an element of flexibility in the case of rare disorders, in which performing an RCT may not be feasible.

EMA regulatory approach

Efforts in the development of drugs to treat rare diseases were made legal in the US through the introduction of the ODA of 1983, establishing financial incentives coupled with regulatory backing for orphan drugs in developing medicine.[10] This became an example that also inspired other global regions, such as the EU. As in the case with the FDA counterpart in the U.S., the EMA plays an imperative role in governing orphan drugs across Europe. Since 2000, orphan pharmaceutical legislation in Europe was created for the sake of creating incentives that were necessary to begin developing medicinal products for rare diseases.[21,22] This law created the COMP within the EMA, responsible for assessing applications for ODD.[21] The process involves assessing medical plausibility and significant benefit over the available therapies. Importantly, 80% of the applications for orphan designation were based on preliminary clinical data indicating a potential efficacy and an added clinical benefit.[23]

The EU Orphan Regulation significantly supports the advancement of medicines for rare diseases.[23] Ironically, although the legislation on orphan drugs has led to more applications in gene therapy for rare diseases, sponsors have not often availed themselves of incentives available, such as protocol assistance and Priority Medicines (PRIME), for reasons that are not fully clear.[21] In conclusion, there has been an upward trend in the designation and authorization of orphan drugs in recent years due to the EU orphan medicinal product regulation. In a nutshell, Orphan Medicinal Product Regulation (EC) No 141/2000 is being reviewed. The European Commission adopted a proposal to amend the EU pharmaceutical legislation on 26 April 2023. This proposal modifies the Orphan Drug Regulation and seeks to rebalance the incentives with an increase in focus on areas with substantial unmet medical needs.[24]

The approval process for orphan medicinal products at the EMA involves several key steps:

1. **Orphan designation:** Sponsors may apply for orphan status prior to submitting a marketing permission application. The COMP reviews orphan designation petitions based on the condition's rarity, severity, and possible benefit.[21] This categorization creates incentives for development.
2. **Scientific advice and protocol aid:** To enhance their development plans, sponsors can seek counsel from the EMA through protocol assistance tailored to orphan pharmaceuticals.[21] This stage is optional but can be advantageous to sponsors.
3. **Marketing Authorization Application:** The marketing authorization applicant will submit an application to the EMA together with clinical trial data, among other relevant information concerning the safety and efficacy of the product.[22,25]
4. **Scientific evaluation:** The COMP conducts a comprehensive scientific evaluation of the submitted application. For orphan drugs, this usually entails reviewing evidence from nonrandomized, open-label studies conducted on a few patients because such conditions rarely manifest.[25]
5. **Opinion and Decision:** It is the EC that finally decides on whether to approve marketing authorization based on the recommendation of the Committee for Medicinal Products for Human Use (CHMP).[22]
6. **Post-marketing requirements:** The EMA may impose post-marketing requirements (PMRs) to monitor long-term safety and efficacy. For orphan drugs, these often focus on both efficacy and safety (47.1% of cases).[22]
7. **Maintenance of orphan status:** Continued eligibility for the criteria at the marketing authorization stage; at marketing approval time, the marketing applicant must prove the existence of a product with meaningful advantages over any available therapy.[23]

Though rare diseases are difficult to investigate, the EMA displayed flexibility in reviewing orphan medications, frequently accepting surrogate endpoints and sparse clinical evidence.[25] Regulatory decision-making for orphan medicinal products is also increasingly considering the use of real-world data, which may supplement or even replace traditional clinical trial data in certain situations.[26,27]

Analysis of regulatory decisions shows that while randomized clinical studies are ideal, non-randomized data are often accepted for rare diseases, provided the quality of the methodology is supportive of the positive assessment of benefit–risk. Moreover, the use of protocol assistance during the development stage has been statistically demonstrated to result in more approvals and less dropouts during the assessment stage.[28,29]

The EMA offers several key features and incentives to encourage the development of orphan medicinal products for rare diseases.[30] Which includes:

1. Orphan Designation: A medicine shall have received orphan designation from the EC after a favorable opinion from EMA's COMP. The designation is given to medicines intended for the treatment, prevention, or diagnosis of a life-threatening or chronically debilitating condition that affects fewer than 5 in 10,000 people in the EU.[31]
2. Scientific Advice and Protocol Assistance: Orphan-designated medicine sponsors get scientific advice and protocol assistance from the EMA regarding the development of their medicinal products.[30]
3. Market Exclusivity: A ten-year market exclusivity is provided once orphan medicines receive marketing authorization in the EU. In other words, similar medicines with a similar indication cannot be marketed during that period.[32]
4. Fee reductions: Fees charged for regulatory activities like marketing authorization applications and inspections are reduced.[30]
5. Extension of market exclusivity: The product can be granted an extra two years of market exclusivity if the sponsor completes a Pediatric Investigation Plan (PIP) and reflects it in the summary of its product characteristics.[32]
6. Access to the PRIME: PRIME scheme that gives early as well as enhanced support to promising treatments.[21]

EMA conditional marketing authorisation and accelerated assessment

The EMA offers two principal expedited pathways for orphan drugs:

- Conditional Marketing Authorisation (CMA): This is a temporary marketing authorisation that is granted on the basis of incomplete clinical trial data, if the balance is positive and the medicinal product is able to meet a medical need. It is valid for one year and can be extended on the basis that the sponsor submits extensive data after the marketing authorisation.[33]
- Accelerated Assessment: Shortens the evaluation period from 210 days to 150 days for drugs of major public health interest, many of which are also orphan drugs. The Chairperson of the CHMP can use Accelerated Assessment for those drugs that satisfy an important medical need or offer a therapeutic innovation. Not all orphan drugs are assessed via Accelerated Assessment, but only on a case-by-case basis.[33]

The EMA also operates the PRIME scheme, which provides early and enhanced scientific and regulatory support for promising medicines, often in the rare disease space.

PMDA regulatory approach

The Japanese regulatory approach to orphan drugs involves both the PMDA and the Ministry of Health, Labour, and Welfare (MHLW). Japan, along with the United States, is one of the few countries with specific orphan device regulations in addition to orphan drug regulations.[34] However, Japan faces significant challenges in the development and approval of orphan drugs compared to other regions, particularly the United States. The Japanese pharmaceutical industry has been struggling with a large trade deficit and a need to improve its new drug discovery

and development capabilities. Unlike other regions, especially the United States, where biotech startups established in the 1990s and 2000s have significantly contributed to drug development, Japan's approved drugs are primarily created by established pharmaceutical companies.[35] This lack of startup involvement has led to a growing gap in orphan drug availability between Japan and other countries, particularly the United States. To address these issues, Japan needs to foster partnerships with international startups and cultivate an ecosystem that nurtures local startups to ensure access to promising orphan drugs.[7] Additionally, focused investment in modality technology development, strengthening collaboration with academia in biology, and reutilizing small-molecule drug discovery capabilities are important strategies for improving drug discovery productivity in Japan.[35] These efforts are crucial for Japan to keep pace with global trends in orphan drug development and ensure that patients with rare diseases have access to innovative treatments.

The approval process for orphan drugs in Japan:

While the provided context does not offer a detailed step-by-step process, it does give some insights into the approval of orphan drugs in Japan:

1. **Orphan drug designation:** The Japanese MHLW grants orphan drug designation to drugs targeting rare diseases.[35] This designation is an important first step in the approval process, providing incentives for drug development.
2. **Regulatory review:** The PMDA is responsible for reviewing and approving new drugs, including orphan drugs.[37] The agency conducts a thorough evaluation of the drug's safety and efficacy data.
3. **Approval decision:** Based on the PMDA's review, the MHLW makes the final decision on drug approval.[36,37]
4. **Post-marketing surveillance:** After approval, orphan drugs are subject to ongoing monitoring for safety and efficacy.[22] While this information is based on FDA and EMA practices, it is likely that similar post-marketing requirements exist in Japan.

In conclusion, the exact step-by-step process for orphan drug approval in Japan is not fully provided in detail.

In Japan, the regulatory approval pathway for orphan drugs is designed to promote research and development for treatments of rare diseases.[38] Which includes:

1. Orphan Drug Designation: The PMDA grants orphan drug designation to drugs intended for the treatment of diseases affecting fewer than 50,000 patients in Japan or diseases designated as intractable by the MHLW.
2. Incentives: Orphan drug designation comes with several incentives, including:
   - Grant-in-Aid for R&D: Financial support for research and development.
   - Tax Deduction: Deductions for R&D expenses.
   - Priority Review: Expedited review process by the PMDA.
   - Market Exclusivity: Extended exclusivity period to encourage investment.
3. Application Process: The application for orphan drug designation includes providing detailed information about the drug, its intended use, and the applicant.
4. Regulatory Support: The PMDA offers priority scientific consultation and other supportive measures to facilitate the development and approval of orphan drugs.

PMDA accelerated approval mechanisms

Japan's PMDA offers several expedited pathways for orphan drugs:

- Priority Review: The median approval times for orphan medicinal products are nine months, while non-orphan products are twelve months.
- Sakigake Designation: The Sakigake designation was launched in 2015 and targets innovative therapies that are expected to be first approved in Japan. The SAC provides priority consultations, a review period of six months, and a longer period of exclusivity. Sakigake would only work for therapies that showcase strong early clinical data targeting serious and life-threatening diseases with a high level of unmet medical need, followed by post-approval monitoring and potential additional studies.[39,40]

Table 1 highlights the key similarities and differences between the FDA, EMA & PMDA in their approach to orphan drug regulation. All provide robust frameworks and incentives to encourage the development of treatments for rare diseases, but there are some differences in criteria, incentives, and specific processes.

Comparative synthesis: similarities, differences, strengths, and weaknesses

Similarities.

- Incentive Structures: Each of the three entities provides a reward of exclusivity, financial incentives, and support to encourage the development of orphan drugs.
- Expedited Pathways: Each region has its own fast-track mechanisms based on the disease type, considering it is rare.
- Post-Marketing Obligations: Clinical trials, such as confirmatory and post-marketing studies, are mandatory for drugs approved through expedited procedures.
- HTA Engagement: Improved engagement with HTA agencies to ensure alignment in evidence requirements for access.

Differences.

- Exclusivity Periods: Ten years (with extensions in the EMA) in both EMA & PMDA; while in the FDA, it is seven years.
- Tax Credits: The FDA has the most generous tax credits; second comes the EMA, with incentives offered by member countries; third comes PMDA, with moderate tax credits along with direct subsidies.
- Approval Timelines: FDA and PMDA tend to be faster than the EMA, and the expedited tracks are the shortest.
- HTA Role: Unlike the US, which depends on private payer evaluation as well as the work of a third-party organization known as the Institute for Clinical and Economic Review (ICER), the European Union's HTA is well organized under the Health Technology Assessment Regulation (HTAR), with Japan's still undergoing changes to focus on real-world studies and managed entrance agreements.
- Price and Access: Prices in the US are higher and faster access with wider variations. The EU charges more similar prices with varying access. In Japan, extensive coverage with some delays due to some evaluations.

Strengths.

- FDA: Flexibility in the evidentiary requirement, strong incentives, rapid access, and high engagement with patient advocacy.
- EMA: Robust benefit–risk analysis, integrated regulatory approach, excellent HTA cooperation, as well as cooperation on post-marketing
- PMDA: Efficient review procedures, generous subsidies, integration of innovative routes (Sakigake), and increased international cooperation.

Weaknesses.

- FDA: High prices, possible abuse of exclusivity, and inconsistent insurance coverage.
- EMA: Slower timelines for approval, heterogeneous availability based on country-wide reimbursement decisions, and complex post-commercialization processes.

Table 1
Comparison of Orphan drug regulations in the US, EU and Japan.

Aspect	US	EU	Japan
Orphan drug designation criteria	The disease affects fewer than 200,000 people in the US[15]	The disease affects no more than 5 in 10,000 people in the EU[31]	The disease affects fewer than 50,000 people in Japan[41]
Regulatory framework	The ODA 1983, 21 CFR 316	Orphan Medicinal Products Regulation (EC) No 141/2000	Pharmaceuticals and Medical Devices Act (PMD Act), specifically Article 77–2
Key committees and working groups	Office of Orphan Products Development (OOPD), various FDA advisory committees	COMP	Pharmaceutical Affairs and Food Sanitation Council (PAFSC), Orphan Drugs Working Group (WG)
Incentives	Tax credits for certain clinical studies, exemption from user fees[15]	Fee reductions, protocol assistance, and access to the centralized authorization procedure[31]	Tax deductions for R&D expenses, priority scientific consultation, priority review, premium at drug pricing, and extension of re-examination period[42]
Market exclusivity	7 years	10 years	10 years, extensions are possible
Application process	Submission of a request for ODD, including data supporting the rarity and need for the drug[15]	Submission of an application to the EMA's COMP, including data on disease prevalence and lack of satisfactory treatment[31]	Submission of an application to the MHLW, including data on the number of patients and medical needs[41]
Review time	90 days for orphan drug designation[15]	90 days for orphan medicinal designation[31]	Review time varies, but priority review is available[41]
Median approval time	~10 months (expedited pathways)[43,44]	~12–14 months[43]	~9–10 months[43]
Post-approval requirements	Ongoing post-market surveillance and compliance with FDA regulations[15]	Annual reports on the development of the orphan medicinal product, and compliance with EMA regulations[31]	Annual reports on the development of the orphan drug, and compliance with MHLW and PMDA regulations[41]
Expedited pathways	Priority review and accelerated approval pathways for drugs that address unmet medical needs[15]	Similar expedited pathways, including conditional marketing authorization and accelerated assessment[31]	Priority review and other supportive measures to facilitate orphan drug development[42]
*Pricing[45]	Highest	Moderate, homogeneous	Moderate
*Access inequality[46]	High	Moderate, GDP-linked	Moderate
% Rare diseases with approved treatment	~5%[47]	<10%[48]	~7% (as of 2022)[49,50]

* Note on Indicators: Pricing levels and access inequality are presented as qualitative/semi-quantitative indicators synthesized from the literature.

- PMDA: Lack of international recognition of designations, possible delays in obtaining access, and ongoing integration with HTA.

Discussion

The comparative analysis of the FDA, EMA, and PMDA frameworks reveals a complex landscape where regulatory speed often conflicts with economic accessibility and evidentiary depth. While all three regions have successfully increased orphan drug approvals through robust incentives, the data in Table 1 highlight significant trade-offs that directly affect global health systems and hospital pharmacy practice.

Interpretative analysis of regulatory trade-offs

The results demonstrate a clear “speed-versus-cost” tension. The United States (FDA) model, characterized by the shortest median approval times (~10 months) and robust incentives like the seven-year market exclusivity, has successfully fostered a deep innovation pipeline. However, this comes with the highest global pricing, averaging $218,872 per treatment and significant access inequality.[51]

In contrast, the EMA's ten-year exclusivity and focus on “significant benefit” lead to more moderate, homogeneous pricing across Europe, but with a slower approval trajectory (~12–14 months). Japan's PMDA has recently outperformed in median approval speed for orphan products (~9 months) through the Sakigake designation, specifically targeting “drug loss” to ensure local patients do not lag behind international birth dates.

Evidentiary requirements and hospital pharmacy implications

For hospital pharmacists and clinicians, the use of expedited pathways across all three regions, such as the FDA's Accelerated Approval and the EMA's Conditional Marketing Authorisation, creates a unique challenge.

- Reliance on Surrogate Endpoints: As noted in the results, many orphan drugs are approved based on surrogate or intermediate clinical endpoints rather than long-term survival data.[52]
- Post-Marketing Burdens: The high percentage of post-marketing requirements (PMRs) (47.1% in the EU) means hospital pharmacies are often dispensing “living” products where long-term safety and efficacy are still being monitored.[53]
- Inventory and Budgeting: The vast price disparity between orphan and non-orphan drugs (USD $218,872 vs. $13,000) necessitates that hospital systems implement highly specialized value-based procurement strategies to manage the financial risk of these essential therapies.[51]

Addressing global inequities and evidence harmonization

Despite the success of national incentives, the fact that only 5% to 10% of rare diseases have an approved treatment across these major regions suggests that current frameworks are insufficient for the rarest conditions. The disparity in access remains a “critical challenge,” particularly where pricing prevents the realization of a drug's clinical potential.[54,55]

The findings suggest that the next phase of orphan drug regulation must move beyond competition between agencies toward harmonized evidence requirements. Collaboration on international clinical trial data and HTA evaluations could reduce the “drug loss” phenomenon and facilitate more equitable access in lower-income regions that currently fall outside these three primary regulatory spheres.[4,54]

Conclusion

This review highlights both progress and persistent challenges in ensuring equitable access to rare disease therapies. Each framework has successfully stimulated innovation through tailored incentives, tax credits and seven-year exclusivity in the United States, ten-year

exclusivity with protocol assistance in Europe, and subsidies with Sakigake designation in Japan. Yet, disparities remain in affordability, patient access, and the balance between incentivizing industry and safeguarding public health.

For hospital pharmacists, these insights are particularly relevant. Pharmacists play a critical role in evaluating orphan medications for formulary inclusion, assessing therapeutic value against high costs, and guiding clinicians and patients through complex access pathways. Understanding the nuances of exclusivity periods, conditional approvals, and expedited reviews enables pharmacists to anticipate availability timelines and budgetary impacts. Moreover, awareness of international differences in designation criteria and incentives informs cross-border procurement strategies and collaborative financing models.

Ultimately, while regulatory frameworks have expanded treatment options for rare diseases, pharmacists remain at the frontline of translating policy into practice. Their expertise in medication evaluation, cost-effectiveness, and ethical stewardship is essential to bridge the gap between regulatory approval and real-world patient access. Strengthening collaboration among regulators, healthcare providers, and pharmacists will be vital to ensure that the promise of orphan drug innovation translates into sustainable, equitable care for patients worldwide.

Declaration of the use of generative artificial intelligence

The authors declare that generative artificial intelligence tools were not used in the preparation of this manuscript, except for language editing and grammar improvement, for which the authors took full responsibility for the content.

Declaration of ethical responsibilities

The authors affirm that this work complies with ethical standards of scholarly publishing. No data involving human participants or animals were collected, and all sources have been properly acknowledged.

Contribution to the scientific literature

This review article contributes to the scientific literature by synthesizing current knowledge, highlighting regulatory and policy perspectives, and providing a structured framework for future research and practice in the field of orphan medications.

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Robinraja Elango: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Russell Martin:** Writing – review & editing, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Shivanand K. Mutta:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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