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Rare Disease Policy in High-Income Countries: An Overview of Achievements, Challenges, and Solutions

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ABSTRACT

Objectives: To provide an overview of policy initiatives in high-income countries aimed at supporting the development and accessibility of treatments for rare diseases.

Methods: We examine how legislative, research, and pricing policies in high-income countries address barriers that have historically hindered innovation and access to rare disease treatments. By analyzing examples from the European Union, United Kingdom, United States, Canada, Japan, and Australia, the article identifies ongoing initiatives, outlines current challenges, and explores proposed solutions to foster a sustainable, innovative, and accessible rare disease treatment ecosystem.

Results: The review highlights policies such as legislative incentives in the European Union, United States, and Japan for orphan drug development, public-private partnerships to boost innovation, and patient registries to support research and clinical trials. Despite these efforts, major challenges persist, including high therapy costs, limited access to innovation for ultrarare diseases, and diagnostic delays, with significant disparities across regions.

Conclusions: Overcoming these challenges will require sustainable pricing and reimbursement frameworks, alongside stronger collaboration between stakeholders, particularly for ultrarare diseases. Advanced technologies, such as artificial intelligence, hold promise for improving diagnostic accuracy and data collection, supported by enhanced coding systems and registries to facilitate more robust research.

Keywords: orphan drugs, pricing and reimbursement, rare disease policy, R&D.

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Highlights

- This commentary examines the legislative, research and development, and reimbursement initiatives across high-income countries to fill the innovation and access gaps in rare disease treatment.
- We discuss the significant advancements in fostering a supportive ecosystem for rare disease treatments but also highlight ongoing challenges such as high therapy costs, unequal innovation distribution, and delayed diagnoses.
- Our findings underscore the need for sustainable pricing models, enhanced global collaboration, and the integration of emerging technologies to improve rare disease diagnosis and treatment access.

Introduction

Rare diseases affect, by definition, small patient numbers. What specifically qualifies as rare differs across jurisdictions: the European Union and the United Kingdom consider diseases with a prevalence of up to 5 cases in 10 000, whereas the United States and Japan include diseases with prevalence figures of up to 200 000 and 50 000 people in the country, respectively.[1-4] It is estimated that >6000 rare diseases exist worldwide, affecting 5% to 8% of the global population, or approximately 400 million people.[5] Further to being rare, most rare diseases are life threatening, chronically debilitating, and genetically acquired.[1,2]

Historically, rare diseases have been characterized by modest therapeutic innovation compared with more prevalent conditions, primarily because of scientific and commercial challenges.[6,7] Scientific challenges, such as poor understanding of disease pathophysiology and heterogeneous manifestation, have translated into different success rates for clinical development programs.[8] Medicines for rare diseases, also referred to as orphan drugs, experience success rates as low as 6.2%, compared with 13.8% for all drugs.[9,10] From a commercial perspective, pharmaceutical firms have often been discouraged from investing in research and development (R&D) by the small number of patients suffering from any individual rare disease because they anticipate that their investment may not be recovered by expected sales, leading to insufficient returns.[11] However, when innovation occurs, it can be transformative.[12] For instance, RNA interference technology, initially developed for rare diseases, such as hereditary transthyretin amyloidosis, has since expanded to treat more common conditions, such as hypercholesterolemia, hypertension, and Alzheimer's disease.[13]

The lack of approved medicinal products for 95% of known rare diseases, combined with their high burden, raises issues of equity.[14,15] Health equity is a complex and multifaceted concept.[16-18] Here, we use the World Health Organization's definition of health equity, which is considered to be "achieved when everyone can attain their full potential for health and well-being."[19] In the case of rare diseases, this de facto translates to rare disease patients having the same opportunity to receive diagnosis, treatment, care, and, more broadly, social opportunities as patients suffering from more common conditions.[20] Because of the challenges discussed above, this generally requires granting these conditions preferential treatment, often in the form of a higher willingness to pay for the same health gains or more flexible evidence requirements

than would be granted to medicines for common diseases.[21] On the other hand, some scholars argue that exceptions for rare diseases on account of fairness and equity considerations are not defensible and that a publicly financed healthcare system should not have a higher willingness to pay for these conditions.[22,23] Instead, they advocate for health maximization, whereby the goal is to obtain as much health benefit as possible for the entire population per dollar spent.[21,24] Despite the tension between equity and health maximization, many countries have implemented policies that provide—to varying extents—special treatment to medicines for rare diseases to advance innovation and access to care, as evidenced in the rest of this piece.

Most of the existing literature on rare disease policy has focused on specific initiatives and/or jurisdictions.[25,26] This commentary aims to provide a broad overview of initiatives in the rare disease legislative and political environment, R&D, and pricing and reimbursement space in higher-income settings. These 3 clusters were chosen because they were considered by the authors to encompass most policies reviewed in the rare disease literature.[24,25,27-30] The following sections discuss initiatives that authors (subjectively) considered most impactful or innovative, whereas a more comprehensive list can be found in Figure 1. Finally, we reflect on the remaining challenges, explore proposed solutions, and offer concluding thoughts.

Legislation and Political Environment

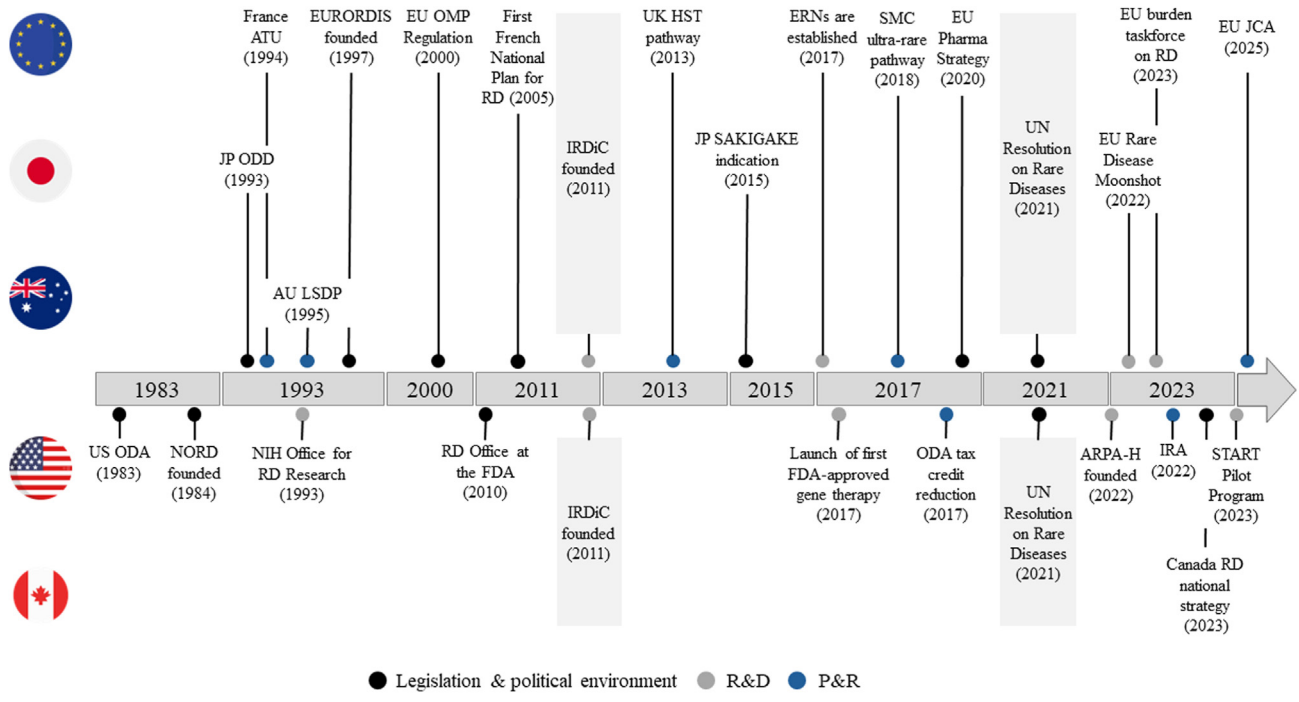
Legislators and regulatory agencies in a number of jurisdictions, such as the European Union, the United Kingdom, the United States, and Japan, have implemented regulations to create a more favorable environment for the development and access of orphan drugs.[1-4]

In the European Union, incentives for developing orphan drugs include fee reduction, regulatory support granting, and, most importantly, a 10-year period of market exclusivity (ME). During this time, approved orphan drugs are protected from competition by generic or similar drugs. In this context, the term similar refers to drugs intended for the same indication that, despite having different active ingredients, share the same principal molecular structure and mechanism of action with the originator.[1] In the United States, the Orphan Drug Act awards a 7-year ME period and fee waivers, as well as a 25% tax credit for expenditures incurred during the clinical testing phase.[2] Similarly, in Japan, orphan drugs are granted a 10-year ME, ad hoc scientific advice, as well as a 12% tax exemption from R&D related expenses.[31]

Unlike these jurisdictions, Canada and Australia do not have specific incentives for the development of rare disease therapies.[32] These countries launched their first national plan for rare diseases in 2023 and 2020, respectively.[33,34] In its national strategy, Canada pledged to invest up to $1.5 billion over 3 years to increase access to and affordability of drugs for rare diseases in the country, indicating a renewed commitment to the rare disease patient community.[34] Australia's National Strategic Action Plan for Rare Diseases, prioritized prelaunch efforts, with an investment of $3.3 million in rare disease awareness and education, and committing to expand newborn screening and genetic testing.[33]

Political progress has also been achieved at the international level with the adoption of the first-ever United Nations Resolution on Addressing the Challenges of Persons Living with a Rare Disease and Their Families in December 2021.[20] The resolution urges Member States to enhance healthcare systems and promote equal opportunities for individuals with rare diseases, supporting their full development and meaningful participation in society.[20] A

Figure 1. Timeline of key rare-disease-related initiatives and milestones in Europe, Japan, US, Canada, Australia, and internationally.



ARPA-H indicates Advanced Research Projects Agency for Health; ATU, Autorisation temporaire d'utilisation; ERNs, European Reference Networks; EU, Europe; FDA, Food and Drugs Administration; FR, France; HST, highly Specialised technologies; IRA, Inflation Reduction Act; IRDiRC, International Rare Diseases Research Consortium; JCA, Joint Clinical Assessment; JP, Japan; LSDP, Life Saving Drugs Program; NIH, National Institutes of Health; ODA, Orphan Drug Act; ODD, orphan drug designation; OMP, orphan medicinal products; RD, rare diseases; SMC, Scottish Medicines Consortium; START, Support for clinical Trials Advancing Rare disease Therapeutics; UN, United Nations.

similar commitment to tackling rare diseases was demonstrated by the creation of the International Rare Diseases Research Consortium (IRDiRC) in 2011 by the European Commission and the US National Institutes of Health. Since its establishment, the IRDiRC has nearly tripled in size, now comprising 60 member organizations worldwide.[27]

R&D

Political will and suitable legislative frameworks are in themselves insufficient if not coupled with promising science. Accordingly, a number of initiatives have been put forward to derisk the clinical development of rare diseases and advance basic science to promote innovation.

Public-led initiatives have emerged across various regions. In the European Union, the creation of European Reference Networks in 2017 facilitated knowledge exchange and coordination between leading research centers.[35] The United States established the National Institute of Health Office for Rare Disease Research, now called the National Center for Advancing Translational Sciences, in 1993 to serve as the federal focal point for rare disease biomedical research. More recently, the Food and Drugs Administration launched the Support for Clinical Trials Advancing Rare Disease Therapeutics Pilot Program to accelerate the development of novel drugs and biological products for rare diseases.[36,37] Canada committed $32 million over the next 5 years to the Canadian Institutes of Health Research for better diagnostics and establishing a robust Canadian rare disease clinical trials network, whereas Japan introduced an accelerated regulatory pathway in 2015 to promote the development of innovative drugs with the potential to address serious and life-threatening conditions, including rare diseases.[34,38]

Public-private partnerships are also viewed as an alternative to the traditional model in which academia leads the early stages of R&D, whereas pharmaceutical companies focus on the translational stage. These initiatives are seen as having the potential to overcome challenges across the development stages of R&D by pooling resources and expertise.[39] Examples of public-private partnerships in the rare disease field include the Innovative Health Initiative and the Accelerating Medicines Partnership, coordinated by the European Commission and the National Institutes of Health, respectively, which aim to speed up R&D and involve numerous representatives from the biopharmaceutical industry.[40,41]

Patient registries collecting real-world evidence of disease progression are also pivotal to enabling innovation and epidemiological research. Over the years, Western countries have set up many registries, which have helped improve knowledge about natural history, map heterogeneous disease courses, and identify meaningful endpoints for clinical trials.[42-44]

Patients and patient organizations are increasingly involved in rare disease research efforts.[45,46] As the primary users of medicines, patients and their families have organized to advance research in rare diseases. One of the most notable success stories is the one of the Cystic Fibrosis Foundation, which at the beginning of the 90s invested approximately $150 million of their donations in Vertex Pharmaceuticals, leading to the development of ivacaftor (Kalydeco), a transformative treatment for cystic fibrosis patients.[47]

Pricing and Reimbursement

Beyond incentives and support for research, some countries have introduced, explicitly or implicitly, different reimbursement pathways and/or higher willingness to pay for orphan drugs.

In Europe, the National Institute for Health and Care Excellence, the UK health technology assessment body, has established a distinct pathway for ultrarare medicines, with a cost-effectiveness threshold of up to £300 000 per quality-adjusted life-year—10 times higher than standard appraisals.[48] Scotland has a separate pathway for ultrarare diseases, which includes a Patient and Clinician Engagement meeting that a company can request in the event of a reassessment.[49] This process grants patient groups and clinicians a stronger voice in the Scottish Medicines Consortium decision making. Germany uses a different assessment process for orphan drugs with annual revenues under €30 million, characterized by more flexible evidence requirements (eg, no requirement for comparative data) and the assumption of added clinical benefit already proven by the marketing authorization.[30]

In the United States, the Inflation Reduction Act was passed in 2022, establishing the ability of the Center for Medicare and Medicaid Services to negotiate the price of the 10 drugs with the highest budget impact on Medicare Part D.[50] The first round of negotiations happened earlier this year and will be effective starting in 2026.[51] However, medicines with only orphan indications are excluded from the price negotiation to retain the existing incentives for the development of treatments for rare diseases.[52] To help pay for medicines for Australian patients affected by ultrarare and life-threatening diseases, Australia set up the Life Saving Drugs Program in 1995.[53] This program covers medicines that have not proven to be cost-effective but can give patients longer survival expectations.[54]

Turning to Canada, no separate pricing and reimbursement approach is adopted for rare diseases. This may partially explain why only 60% of orphan medicines authorized in the United States and/or the European Union between 2015 and 2022 were approved in Canada, with many of them not reimbursed by government drug plans or only reimbursed for a subgroup of patients.[32]

Current Challenges and Proposed Solutions

The initiatives discussed above have undoubtedly contributed to the development of and access to more treatments, as well as fostering a supportive ecosystem, ultimately leading to improved quality of life and life expectancy for patients with rare diseases.[8,55-57] Nonetheless, challenges persist, and a few of the most salient ones are discussed below along with solutions that have been proposed in the literature.

First, technological advances of the last decades have led to the development of new promising therapies, such as gene and CAR T-cell therapies, which offer significant potential benefits for the rare disease community but are at risk of straining government budgets within the current payment paradigm.[58,59] For example, onasemnogene abeparvovec (Zolgensma) is the first gene therapy for spinal muscular atrophy and is priced at up to $2.1 million per one-off injection.[60] Although the budget impact for a single rare disease might be limited, the cumulative effect of multiple gene therapies entering the market can be problematic because payers must consider not only current costs but also the future financial burden of therapies not yet approved, compounded by the unpredictability of long-term outcomes.[61,62] As science evolves, so should pricing and reimbursement frameworks. For example, flexible payment models, such as annuity payments or pay-for-performance models, can ensure that access to expensive but potentially life-saving drugs is not delayed or forgone.[63] These models work by spreading the cost of treatments over time or tying payment to how well the treatment works, ensuring that payers only fund therapies that deliver the expected clinical outcomes.[64,65] This approach can help make budgeting of high-cost therapies more predictable by aligning incentives for both manufacturers and payers. However, further work is needed to find

ways to make them less burdensome for payers, thus ensuring the sustainability and adoption of these payment schemes. Value frameworks that guide price negotiations based on value delivered, such as those implemented by many European health technology assessment bodies, can help ensure that budgets are allocated to drugs that provide the greatest benefit to patients.[66,67] Although necessary, these approaches have shortcomings. For example, cost-effectiveness analyses should not assume that the incremental value of health remains constant regardless of illness severity because this has been found to undervalue treatments for disabling conditions, including many rare diseases.[68] Generic and biosimilar substitution is also an effective strategy to create financial headroom for funding new and costly therapies.[69] However, the production of generics after orphan drug patents expire is limited, often focusing on more prevalent conditions such as cancer or cystic fibrosis.[70] This may be partially due to weaker market incentives in rare diseases, for which small patient populations and high development costs diminish the financial viability of producing generics.[71]

Further access-related challenges are likely to be posed by the EU Joint Clinical Assessment, which is to be applied to advanced therapy medicinal products and orphan drugs starting in January 2025 and 2028, respectively.[72] Although the Joint Clinical Assessment aims to standardize the clinical assessment of medicines across the European Union and avoid duplication of work, concerns have been raised as to whether this new system is fit for purpose for some orphan drugs for which randomized clinical trials are unfeasible or unethical. Although the regulation acknowledged these challenges, the current methodological guideline is unclear on the degree to which real-world evidence and single-arm trials would be considered in future appraisals.[73,74]

Second, innovation has not been equally distributed among all rare diseases. Although the majority of rare disease patients are affected by the approximately 150 diseases with the highest prevalence (1-5 in 10 000), >80% of rare diseases are extremely rare, affecting <1 in 1 000 000 people.[75] All of these extremely rare diseases currently lack treatment, and the path to innovation remains unclear.[14] There appears to be a consensus that the pharmaceutical industry alone is unable to drive innovation in such rare conditions; an alternative model may be necessary.[76] Such a model could involve collaboration across private, public, and nonprofit entities, leveraging novel technologies, such as artificial intelligence, platform technologies, and drug repurposing to optimize and speed up drug discovery and development processes.[37,77-79] Additionally, public-private collaborative initiatives, such as the IRDiRC, are essential to facilitate resource sharing across borders, especially in the case of extremely rare diseases.[80]

Finally, even where drugs are available and reimbursed, patients with rare diseases often remain undiagnosed for years, with an average delay of 4.8 years from symptom onset to correct diagnosis.[14,81] Delayed or missed diagnoses have detrimental effects on health outcomes because treatments are usually most effective when started early. Although some countries have made efforts to implement routine newborn screening and include rare diseases in mainstream medical education, significant regional disparities persist.[82,83] Technology, such as artificial intelligence and machine learning, show promise in accelerating and improving diagnosis while reducing costs.[84-86] Furthermore, advancements in understanding the burden of rare diseases are pivotal to justify broader diagnosis and access programs. In 2023, the European Burden of Disease Network launched the Task Force on Rare Diseases to address this gap by researching the health impact of rare conditions in Europe.[87] However, good-quality patient-level data to inform research can only be collected if coding barriers are overcome. Currently, the availability of specific International Classification of Diseases codes for only 8% of rare diseases in electronic health records creates significant gaps in data collection, which hampers the ability to conduct comprehensive research on these conditions.[88] Although an increasing number of hospitals are adopting more accurate coding systems, such as the Orphanet nomenclature, projects such as RD-CODE, which aim to improve the identification and coding of rare disease patients within health information systems, are fundamental to ensuring that rare disease data are collected correctly and uniformly across countries.[89,90]

Conclusions

This article provides an overview of key initiatives used by several high-income countries to create a supportive legislative and political environment, boost R&D efforts, and introduce greater flexibility in their pricing and reimbursement systems to better address the needs of rare disease patients. Although major steps have been taken with regard to the development of and access to treatments, several challenges remain. These include the high costs of new therapies, uneven distribution of innovation among rare diseases, and persistent diagnostic delays. To move forward, it is crucial to develop sustainable pricing and reimbursement models, enhance global collaboration across public and private sectors, and leverage emerging technologies to improve diagnosis, data collection, and medicine development. Addressing these challenges will enable a more equitable and effective ecosystem that ensures all rare disease patients have access to the treatments they need and deserve.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

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