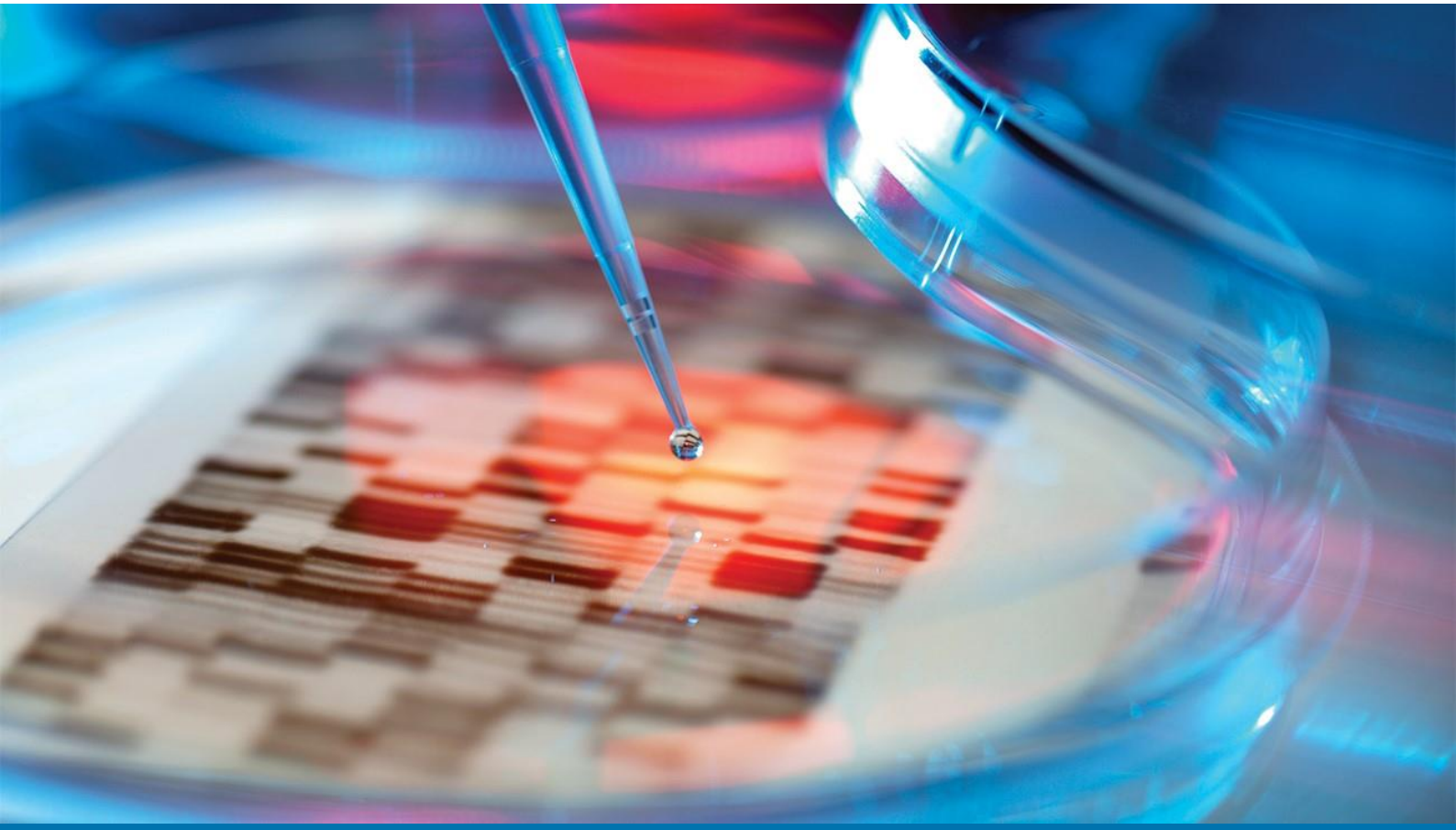
CRA Charles River Associates



The impact of price controls on rare disease medicines access and lessons for the US

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FINAL REPORT

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Executive Summary

Sustaining investment in drug development for rare diseases is inherently challenging due to small patient populations and high fixed costs for drug trials. Certain US policy approaches acknowledge these challenges; this includes the Orphan Drug Act of 1983, which increases the financial incentive for rare disease drug development, and a recent exemption for medicines with multiple orphan disease indications from Medicare drug price negotiations in the One Big Beautiful Bill Act. However, contemplated administrative price setting or "price controls" for medicines, including external reference pricing (where prices in one country are used to inform prices in another country), risk creating a barrier to drug development, particularly for medicines addressing orphan diseases.

In light of the policy debate about drug pricing, Charles River Associates (CRA) was commissioned by the Rare Disease Company Coalition (RDCC) to investigate the effect of international approval and pricing schemes on rare disease medicine access. In this report we evaluate how international pricing frameworks in higher income countries affect access to medicines for rare diseases in those countries.

We studied 142 drugs approved by the US Food and Drug Administration (FDA) from 2022 to 2024, including 74 orphan-designated therapies. We examined approval and reimbursement times for both rare and nonrare disease medicines in six higher income countries: England, France, Germany, Italy, Japan, and Sweden. We considered time to regulatory approval and time to reimbursement in public insurance systems in those countries, finding delays in access relative to the US, particularly for orphan drugs.

Within the six higher income countries we evaluated, we found that drugs with orphan indications were more likely to receive regulatory approval by the European Medicines Agency (EMA), the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), or by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) relative to the drugs without orphan indications (72% vs. 53%). However, once approved by these international regulators, drugs with orphan indications were less likely to receive a reimbursement recommendation (52%) or launch (56%) when compared to drugs without an orphan disease indication (61% recommended for reimbursement; 72% launched). Drugs with orphan indications faced longer delays from regulatory approval to launch (7.0 vs. 5.6 months for nonorphans) despite shorter times from regulatory approval to health technology assessment decisions (7.3 vs. 9.5 months for nonorphans). This means that approved drugs were not becoming available to patients, or access was delayed, due to the time it took to conduct the review and come to an agreement with the payer. These delays could have significant consequences, especially for those rapidly progressive disorders that are fatal or very detrimental to health without therapeutic intervention.

If implemented in the US, MFN would import price levels set by other countries' institutional and regulatory frameworks, along with the potential consequences to access and innovation for orphan drugs. Price controls on orphan drugs, including in an MFN approach, risk dismantling incentives and policies that have enabled the US to lead the world in rare disease treatment, undermining decades of scientific advancement, patient advocacy, and investment.

1. Introduction

1.1 Background

A rare disease is defined as any disease or condition affecting fewer than 200,000 people in the US.[1] Collectively, however, rare diseases affect an estimated 25-30 million Americans across more than 10,000 conditions, of which ~95% lack any US Food and Drug Administration (FDA)-approved therapy.[2] These conditions are often severe, chronic, progressive, and life-threatening, with limited therapeutic options for most patients.[3]

A comprehensive 2019 study by the EveryLife Foundation estimated that across 379 rare diseases, the total burden reached $997 billion, including about $449 billion (45%) in direct medical costs, $437 billion (44%) in indirect costs such as lost productivity, and the remainder in nonmedical and uncovered healthcare expenses.[4] These findings underscore that rare diseases impose not only severe health consequences for patients, but also a substantial economic and societal burden.

Rare disease medicines address high unmet medical needs with a high therapeutic value in small patient populations. Because small patient populations are eligible to receive these therapies, their individual budget impacts are relatively modest.[5,6] Nonetheless, they are typically priced higher than therapies for non-rare conditions, attracting scrutiny and concern about cost management.[7] Payors have historically shown greater pricing tolerance for medicines targeting rare conditions, recognizing their value to patients and their families.

Small patient populations make the drug's development scientifically complex, risky, and commercially challenging. In the US, the Orphan Drug Act of 1983 and subsequent policies over the last four decades have acknowledged this market failure and established incentives and other protections including tax credits, FDA user-fee waivers, seven years of post-approval market exclusivity,

1 Roberts, A. D. (2023). Orphan Drug Approval Laws. In StatPearls. Retrieved from [NCBI Bookshelf]; 21 US Code § 360bb (n.d.); US Food and Drug Administration. (2024, May 21). Orphan Drug Act: Relevant excerpts. US Department of Health and Human Services.

2 Fermaglich, L. J., and Miller, K. L. (2023). A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet journal of rare diseases, 18(1), 163; US Food and Drug Administration. (2024, August 14). 9 Things to Know About CDER's Efforts on Rare Diseases. Retrieved from FDA.gov.

3 US Government Accountability Office. (2024). Rare disease drugs: FDA has steps underway to strengthen coordination of activities supporting drug development (GAO-25-106774). US Government Accountability Office. https://www.gao.gov/products/gao-25-106774.

4 Yang, G., Cintina, I., Pariser, A., Oehrlein, E., Sullivan, J., and Kennedy, A. (2022). The national economic burden of rare disease in the United States in 2019. Orphanet journal of rare diseases, 17(1), 163.

5 Schey, C., Milanova, T. and Hutchings, A., 2011. Estimating the budget impact of orphan medicines in Europe: 2010-2020. *Orphanet journal of rare diseases*, *6*(1), p.62.

6 Rollet, P., Lemoine, A. and Dunoyer, M., 2013. Sustainable rare diseases business and drug access: no time for misconceptions. *Orphanet journal of rare diseases*, *8*(1), p.109.

7 Mikami, K. (2019). Orphans in the market: the history of orphan drug policy. Social History of Medicine, 32(3), 609-630.

regulatory support, price control exclusions, priority review vouchers, and grants to stimulate development. [8, 9]

Historically, innovative orphan medicines have launched first in the US after the FDA's evaluation of their safety and efficacy and later pursued regulatory approval and market access in other developed countries. In many countries with universal or publicly funded healthcare systems, drug approval processes incorporate not only clinical assessments but also evaluations of cost-effectiveness and budgetary impact, making access to patients more delayed and difficult compared to in the US. As a result, these countries frequently spend far less on high-cost, innovative medicines relative to their economic capacity. Although it is difficult to compare spending on rare diseases across countries, the US accounts for 60% of total spending on new innovative medicines among high-income Organisation for Economic Co-operation and Development (OECD) countries, despite representing only 38% of their combined gross domestic product (GDP).[10] In contrast, countries such as the United Kingdom (UK) and France spend much less through medicine purchases than their GDP would indicate they have capacity for. Given medicines spending incentives future innovation, this disparity means that the US market disproportionately sustains the development of innovative new therapies, including those for rare diseases.

The data showing that the US bears a disproportionate share of the costs of pharmaceutical innovation, has put global medicine pricing policy under renewed scrutiny.[11] Among approaches under consideration is a most-favored-nation (MFN) model, which would tie US payment rates to prices observed in selected high-income countries. The concept is not without precedent: the Centers for Medicare & Medicaid Services (CMS) finalized an MFN demonstration for Medicare Part B in late 2020 under the previous Trump administration. Within the 2020 MFN demonstration, the Trump administration CMS explicitly sought public comment on excluding drugs for rare diseases and conditions from future MFN Model years.[12] This MFN demonstration was rescinded in 2021 after

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8 *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C.S. §§ 360aa-360ee (LexisNexis 2025); 26 U.S.C.S. § 45C (LexisNexis 2025)).

9 See *21 U.S.C. § 379h(a)(1)(F)* (LexisNexis, 2025) (excludes orphan-designated drugs from certain Prescription Drug User Fee Act fees); *21 U.S.C. § 355c(k)* (LexisNexis, 2025) (exempts orphan-designated drugs from initial pediatric study plan requirements under the Pediatric Research Equity Act); *Medicare Program; Competitive Acquisition of Outpatient Drugs and Biologicals Under Part B,* 70 Fed. Reg. 39022, 39028–29 (July 6, 2005) (CMS exercised discretion to exclude several lifesaving rare disease therapies from CAP due to "severe access issues," including IVIG, alglucerase, alpha1-proteinase inhibitor, blood clotting factors, daclizumab, imiglucerase, and oprelvekin); *Patient Protection and Affordable Care Act,* § 9008(e)(3), 124 Stat. 119, 860 (2010) (codified at *26 U.S.C. § 4001 note prec.*) (LexisNexis, 2025) (excludes orphan drug sales from branded pharmaceutical fee calculation); id. § 2501(a), 124 Stat. at 306–07 (codified at 42 U.S.C. § *1396r-8(c)(1)(B)(iii)(II)(aa)* (LexisNexis, 2025)) (limits Medicaid rebate increase for blood clotting factors); id. § 6301(a), 124 Stat. at 730–31 (codified at 42 U.S.C. § 1320e(d)(2)(B)(ii)(III); *§ 1320e(d)(4)(A)(iii)* (LexisNexis, 2025)) (requires PCORI to convene disease-specific advisory panels for rare disease research); *Health Care and Education Reconciliation Act of 2010*, § 2302, 124 Stat. 1029, 1082–83, amended by *Medicare and Medicaid Extenders Act of 2010*, § 204, Pub. L. No. 111-309, 124 Stat. 3285, 3289–90 (codified at *42 U.S.C. § 256b(e)* (LexisNexis, 2025)) (excludes orphan drugs from 340B pricing for newly eligible hospitals); *Food and Drug Administration Safety and Innovation Act*, § 908, Pub. L. No. 112-144, 126 Stat. 993, 1094–98 (2012) (codified at *21 U.S.C. § 360ff* (LexisNexis, 2025)) (establishes Rare Pediatric Disease Priority Review Voucher Program); *Inflation Reduction Act of 2022*, § 11001, Pub. L. No. 117-169, 136 Stat. 1818, 1840 (2022) (codified at *42 U.S.C. § 1320f–1(e)(3)(A)* (LexisNexis, 2025)) (excludes certain orphan drugs from Medicare price negotiation provisions).

10 EY Quantitative Economics & Statistics. (2025, June 27). High-income country spending on innovative medicines. Prepared for PhRMA. https://cdn.aglty.io/phrma/Attachments/NewItems/Report%20-%20High-Income%20Country%20Spending%20on%20Innovative%20Medicines%20-%20June%202025_20250716125138.pdf.

11 US Department of Health and Human Services. (2025). HHS, CMS set most-favored-nation pricing targets to end global freeloading on American patients [Press release]. Retrieved from https://www.hhs.gov/press-room/cms-mfn-lower-us-drug-prices.html.

12 Centers for Medicare & Medicaid Services. (2020). Most Favored Nation (MFN) Model: Interim Final Rule with Comment Period (42 CFR Part 513). Federal Register, 85(229), 76180–76249.

facing legal challenges on procedural grounds.[13] A new framework was reintroduced by executive order on May 12, 2025, with agencies directed to develop options for incorporating MFN-based pricing into US programs without particular provisions for orphan medicines.[14]

Given the challenges to rare disease medicine development and access, Charles River Associates (CRA) was commissioned by the Rare Disease Company Coalition (RDCC) to investigate the effect of international pricing schemes on rare disease medicine access. Because MFN would reference rare disease medicine prices in key countries outside the US, we sought to understand the rare disease medicine access environment in those countries and what that may signal for people in the US living with rare diseases if these countries are referenced under MFN.

1.2 Methodology

Understanding the potential implications of an MFN-type policy in the U.S. requires situating it within the broader international experience with administrative price setting, including external reference pricing (ERP), of which MFN is a specific form. Our first step was to conduct a targeted literature review of ERP to develop hypotheses on the implications of price controls on rare disease medicines access.[15]

Analysis of access to rare disease medicines in each country

To investigate how these dynamics may manifest under a price control system like MFN, we benchmarked the progression of recently approved US medicines through key access milestones in selected high-income countries. This approach enables like-for-like comparisons across heterogeneous systems; relies on auditable, policy-salient milestones; and highlights where effects differ by therapy type.

We examined six high-income countries: England, France, Germany, Italy, Japan, and Sweden, which reflect diverse pricing systems, health technology assessment (HTA) processes, and ERP tools (See the Appendix for a policy assessment by country).[16] We then identified all drugs approved by the FDA between January 1, 2022, and December 31, 2024. The cohort includes new molecular entities and new biologics approved under original New Drug Applications (NDAs) or Biologics License Applications (BLAs). We excluded supplemental indications, line extensions, vaccine strain updates, diagnostics, generics, and biosimilars to focus on first-time approvals. Rare disease indications were defined by products having an FDA orphan designation at approval and applied consistently across markets.

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13 CMS. (2021). Most-Favored-Nation (MFN) model rescinded. Federal Register. Retrieved from: https://www.cms.gov/priorities/innovation/innovation-models/most-favored-nation-model.

14 The White House. (2025). Delivering most-favored-nation prescription drug pricing to American patients [Executive Order]. Retrieved from https://www.whitehouse.gov/presidential-actions/2025/05/delivering-most-favored-nation-prescription-drug-pricing-to-american-patients/.

15 To inform our analysis of MFN-type policies, we conducted a targeted literature review of ERP and its implications for rare disease medicine access. The review covered English-language publications from January 2010 to August 2025, using key terms such as “external reference pricing,” “rare diseases,” “orphan drugs,” “HTA,” and “international price controls.” Searches were performed in PubMed, Scopus, and Google Scholar. After screening for relevance and quality, 22 publications were included in the final synthesis, comprising 8 peer-reviewed journal articles, 5 policy reports, 4 industry or consulting white papers, and 5 government or intergovernmental analyses.

16 Country selection reflected MFN-application relevance as defined by the US Department of Health and Human Services, which uses a threshold of 60% of US GDP per capita (nominal) to identify comparable economies. England, France, Germany, and Sweden meet the nominal GDP threshold; Italy and Japan fall just below but were retained for their distinctive market features and potential inclusion depending on final criteria, particularly given that they would have qualified under a purchasing power parity–adjusted GDP-per-capita threshold as was proposed in the 2020 model.

To study access outcomes across countries, we mapped each product–country pair onto a four-step access pathway, which captures key milestones in the journey from regulatory approval to patient availability. These steps are as follows:

1. The product has obtained regulatory approval in the US, and also in Europe, the UK, and/or Japan.[17]
2. The product has been submitted for a value assessment in Europe, the UK, and Japan, and has received a positive recommendation for either the full-label population or a defined subset.
3. The product has been granted full or partial reimbursement, indicating that it would be accessible to patients if it launches.
4. The product has launched, with the first sales recorded, confirming that it is accessible to patients.

All access-pathway variables were drawn from NAVLIN Global, with outcomes observed through July 30, 2025. Where available, we also recorded reimbursement restrictions on price and eligibility (e.g., managed-entry terms, indication limits, subgroup criteria). Regulatory approval data was captured for the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

For Japan, HTA submission and recommendation were not consistently observable; accordingly, we reported regulatory approval and downstream reimbursement and launch outcomes but omitted HTA steps. Post-approval steps were not strictly sequential: in several markets, launches occurred before HTA decisions, and reimbursement was sometimes granted prior to a formal HTA conclusion under interim or early-access schemes.

Analysis of pricing and access policies

To contextualize observed access patterns in our data analysis, for each country we conducted a structured review of pricing and access policy environment affecting rare disease medicines access, (as of July 30, 2025), using academic literature, statutes, agency manuals, official guidance, and grey literature. For each country, we evaluated the following:

- Early-access programs and policies: early-access programs, temporary or preapproval reimbursement, and coverage with evidence development or other types of managed-entry arrangements
- Value assessment and pricing policies: HTA frameworks, modified cost-effectiveness thresholds (e.g., severity or rarity modifiers), and orphan-specific pathways
- Price and budget control policies: clawbacks, rebates,[18] premium pricing provisions, and ERP parameters

17 Among the cohort of FDA-approved medicines, we examined regulatory approval by either the European Medicines Agency or Japan's Pharmaceuticals and Medical Devices Agency and examined access among medicines approved by both for comparability.

18 Clawbacks are mandatory repayments imposed on pharmaceutical companies when overall pharmaceutical spending exceeds budget caps, whereas rebates are negotiated, product-specific discounts that reduce the net price of a medicine.

2. MFN and rare disease medicines access

There is a substantial literature showing that countries with price controls or reimbursement hurdles face delayed access.[19] As overall revenue falls for indications with small populations, there is a reduced incentive to invest in and launch new rare disease medicines. If these low international prices were applied to the US, it follows that investment in development for rare disease would decline.[20]

ERP is employed by most high-income countries, typically in combination with other cost-containment instruments.[21] ERP exerts downward pressure on list-price growth and fosters some degree of price convergence across markets, and it results in a price that is not reflective of the value of the treatment.[22] Manufacturers often engage in strategic launch sequencing and selective market entry to avoid low prices in one jurisdiction.[23] Because ERP almost always relies on such public list prices rather than confidential net prices, it also introduces distortions.[24]

A substantial body of prior research confirms that these dynamics translate into slower patient access. Analyses of the EFPIA Patients W.A.I.T. Indicator show that across Europe, patients wait on average 578 days (about 19 months) from regulatory approval to availability (reflecting public reimbursement), with waits ranging from 128 days in Germany to over 800 days in Portugal.[25] Only 46% of centrally approved new medicines were available in the average EU country, and fewer than one-third were reimbursed fully. Launch-sequencing studies similarly demonstrate that manufacturers prioritize the US and Germany, while deferring or forgoing entry in smaller, price-controlled markets.[26] Peer-reviewed econometric studies confirm that expected price and market size are strong predictors of launch timing, with low-price jurisdictions facing systematically longer delays or fewer launches.[27] Taken together, this literature establishes that delayed access linked to pricing and reimbursement policies is not new, but a persistent feature of ex-US markets.

These dynamics are potentially particularly consequential for rare disease medicines, which face inherently small patient populations, high development costs, and low commercial viability, making them especially vulnerable to pricing and reimbursement pressures that can delay access or

19 Post, H. C., Schutte, T., van Oijen, M. G. H., van Laarhoven, H. W. M., and Hollak, C. E. M. (2023). Time to reimbursement of novel anticancer drugs in Europe: a case study of seven European countries. ESMO open, 8(2), p.101208.

20 Seville, T. M. (2025). The unintended consequences of drug pricing policies on orphan drug development. ADVI. Retrieved August 16, 2025, from https://advi.com/wp-content/uploads/2025/06/Report-IRA_Impact_Orphan_Drug_Innovation.pdf

21 Rémuzat, C., Urbinati, D., Mzoughi, O., El Hammi, E., Belgaied, W., and Toumi, M. (2015). Overview of external reference pricing systems in Europe. Journal of market access & health policy, 3(1), p.27675.

22 Rémuzat, C., Urbinati, D., Mzoughi, O., El Hammi, E., Belgaied, W., and Toumi, M. (2015). Overview of external reference pricing systems in Europe. Journal of market access & health policy, 3(1), p.27675; Voehler, D., Koethe, B. C., Synnott, P. G., and Ollendorf, D. A. (2023). The impact of external reference pricing on pharmaceutical costs and market dynamics. Health policy OPEN, 4, 100093.

23 Office of Health Economics. (2025). “The Trump Administration’s US Drug Pricing Proposal – What will happen next?”

24 OECD. (2024). Exploring the feasibility of sharing information on medicine prices across countries. OECD.

25 EFPIA. (2025). “EFPIA Patients W.A.I.T. Indicator 2024 Survey.”

26 IQVIA Institute for Human Data Science. (2024). From orphan to opportunity: Mastering rare disease launch excellence. IQVIA. https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/from-orphan-to-opportunity-mastering-rare-disease-launch-excellence.pdf

27 Danzon, P. M., Wang, Y. R., & Wang, L. (2005). The impact of price regulation on the launch delay of new drugs—Evidence from twenty-five major markets in the 1990s. Health Economics, 14(3), 269–292. https://doi.org/10.1002/hec.931

discourage development altogether.[28] After regulatory market authorization, only 42% of orphan-designated medicines were available on average across EU countries, compared to 49% of non-orphans, and median time to access for orphans stretched up to 32 months in some markets.[29]

Even in the US, patients may still encounter access restrictions through prior authorization requirements, step-therapy protocols, or limited coverage for high-cost medicines.[30] Adopting the MFN pricing policy would further constrain revenues, which are an incentive to drug development. The Congressional Budget Office projects that international price benchmarking would reduce pharmaceutical revenues and incentivize companies to delay or avoid launches in certain markets, leading to less overall medicine development.[31]

Existing research shows that price regulation delays access, but few studies have looked specifically at orphan medicines in countries with price controls. Our analysis aims to fill this gap by considering recent FDA approvals for orphan drugs, and their access relative to real-world access milestones.

3. Access to rare disease medicines outside the US

For each orphan drug, we tracked progression through regulatory approval, HTA review, reimbursement, and launch across the six comparator countries. This approach allows us to quantify relative performance at each stage and compare orphan and nonorphan medicines.

3.1 Greater number of regulatory approvals of novel medicines in the US compared to Europe and Japan

We found 142 new medicines were approved by FDA between 2022 and 2024, including 74 medicines with orphan designations and 68 without. Across all medicines, most (81%) were approved by the FDA before being approved, if at all, by regulators in Europe, Japan, or the UK. For orphan medicines, 78% were FDA-first, compared to 84% for nonorphan medicines.

We then consider the median time from FDA approval to approval in the six countries. When the FDA was the first regulator to approve a drug, its approval came a median of 6.1 months earlier than the first approval by the EMA, MHRA, or PMDA, with a lead time of 7.2 months for orphan drugs and 4.2 months for non-orphans. Although orphan drugs were slightly less likely than nonorphans to be approved by the FDA first, possibly due to flexibilities in international regulatory systems, they were still prioritized in the US before European, British, and Japanese regulators.

Further, several FDA-approved medicines were not available abroad at all. Of the 142 FDA-approved medicines, 63% (89) were subsequently approved by the EMA, MHRA, and/or the PMDA, while 37%

28 Post, H.C., Schutte, T., van Oijen, M.G.H., van Laarhoven, H.W.M., and Hollak, C.E.M. (2023). Time to reimbursement of novel anticancer drugs in Europe: a case study of seven European countries. ESMO open, 8(2), p.101208; Brown, F., Vargas, M., Stanisic, S., Fatzinger, G., and Iliach, O. (2025). Impact of changes in regulatory framework on approval of medicines for rare diseases and applicability to market access policies. Frontiers in Medicine, 12, p.1474087.

29 EFPIA. (2025). "EFPIA Patients W.A.I.T. Indicator 2024 Survey."

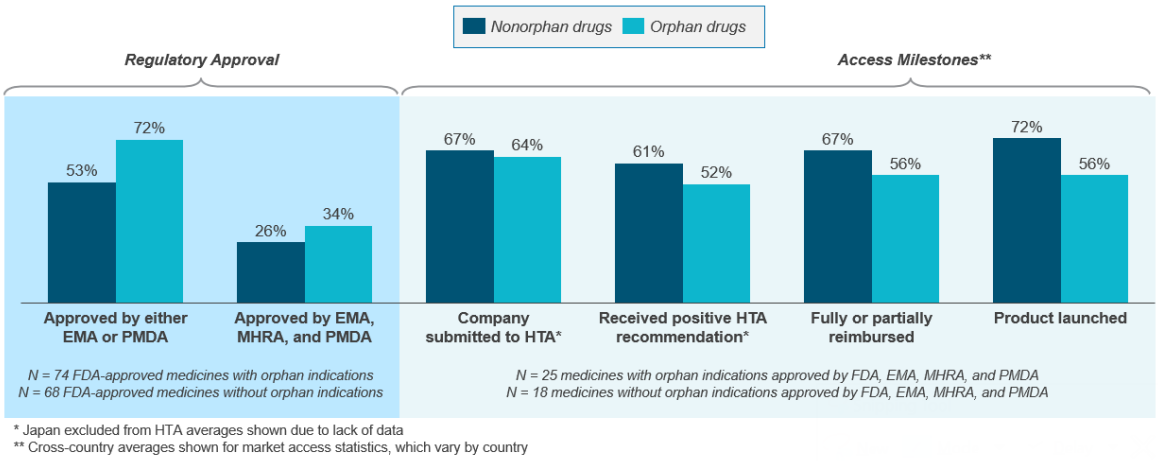
30 UCB. (2025). Taking policy action on rare disease in the United States: Aspire4Rare US report. UCB, Inc. https://www.ucb-usa.com/sites/default/files/2025-02/Aspire4RareUSReport.pdf

31 Center for Strategic & International Studies. (2025). "How Most-Favored Nation Policy Could Undermine US Leadership"; Pharma Manufacturing. (2025). "Roche says Trump's 'most favored nation' executive order jeopardizes its planned $50B US investment."

(53) had not been approved by either agency as of mid-2025.[32] This gap was more pronounced for nonorphan drugs (Figure 1): 53% (36 of 68) were available in at least one other market, compared to 72% (53 of 74) of orphans. Drugs that have not been approved outside the US have been waiting for a median of 20.4 months, with similar delays for orphans and nonorphans. Orphan drugs were more likely than nonorphans to secure at least some international regulatory approval, but a notable share of both groups remained accessible only to US patients.

For medicines approved in the six countries, FDA decisions came earlier by a median of 4.1 months compared to EMA, 5.1 months compared to MHRA, and 4.3 months compared to PMDA. FDA decisions came slightly earlier for orphan drugs (4.3 months before EMA; 5.7 months before MHRA; 4.5 months before PMDA) than non-orphan drugs (3.9 months before EMA; 4.9 months before MHRA; 3.5 months before PMDA).

Figure 1: Percentage of orphan and nonorphan FDA-approved drugs progressing through regulatory approval and access milestones across six high-income countries



* Japan excluded from HTA averages shown due to lack of data
** Cross-country averages shown for market access statistics, which vary by country

We find 43 drugs (30% of the FDA cohort) were authorized by the EMA, MHRA, and PMDA. Within this set, orphans again showed an advantage to approval relative to nonorphan drugs within these countries, with 25 of 74 (34%) securing regulatory alignment across all three agencies, compared to only 18 of 68 (26%) nonorphans. These differences suggest that orphan drugs, were more likely to have regulatory approval across jurisdictions, likely reflecting both patient need and targeted incentives. However, even for these 43 drugs, FDA approval came a median of 2.6, 4.5, and 4.2 months earlier than EMA, MHRA, and PMDA approval, respectively. This lead was longer for orphan drugs in relation to EMA (2.6 months vs. 1.6 months for non-orphans), while the timing advantages over the MHRA and PMDA were similar for both groups.

While our analysis is based on a product's FDA designation, it is worth noting that orphan designation differed across agencies. The FDA designated 74 products as orphans during 2022–2024, whereas

32 Products considered "not approved" by regulatory agencies in this study may still be under review or in pricing and reimbursement negotiations outside the U.S. as of July 30, 2025.

only 51 received orphan status from the EMA and 18 from the PMDA.[33] As a result, some therapies recognized as orphans in the US entered foreign markets without an orphan designation: while 16% of FDA-designated orphan drugs were approved in Europe without receiving orphan status, the figure rose to 42% in the UK and 23% in Japan. This divergence illustrates that different definitions are being applied in different regions and this contributes to differences in subsequent access decisions.

3.2 Persistent access challenges disproportionately affect rare disease medicines

To compare access across countries, we focused on the 43 drugs (30% of the FDA cohort) that secured authorization from the FDA, the EMA, MHRA, and PMDA. This group of products, which includes 25 orphan and 18 nonorphan drugs, provides a harmonized cohort to measure launch, reimbursement, and access between countries.

Of the 43 products in our sample and across the six countries studied (where data were available), on average 28 (65%) products per country were submitted for HTA review, 24 (56%) received a positive recommendation (including those with restrictions), 26 (60%) secured full or partial reimbursement, and 27 (63%) reached launch.

We then considered time from approval to access. Across countries, the median time from regulatory approval to HTA recommendation was 7.3 months, and from regulatory approval to launch was 7.0 months, with some markets (Italy, Sweden) exceeding one year. In several cases, launch preceded HTA recommendation, suggesting use of interim access or managed-entry pathways. Launches before HTA decisions were common in Germany (95% of launched products) and England (58%) but occurred far less often in Sweden (16%), Italy (15%) and France (10%).

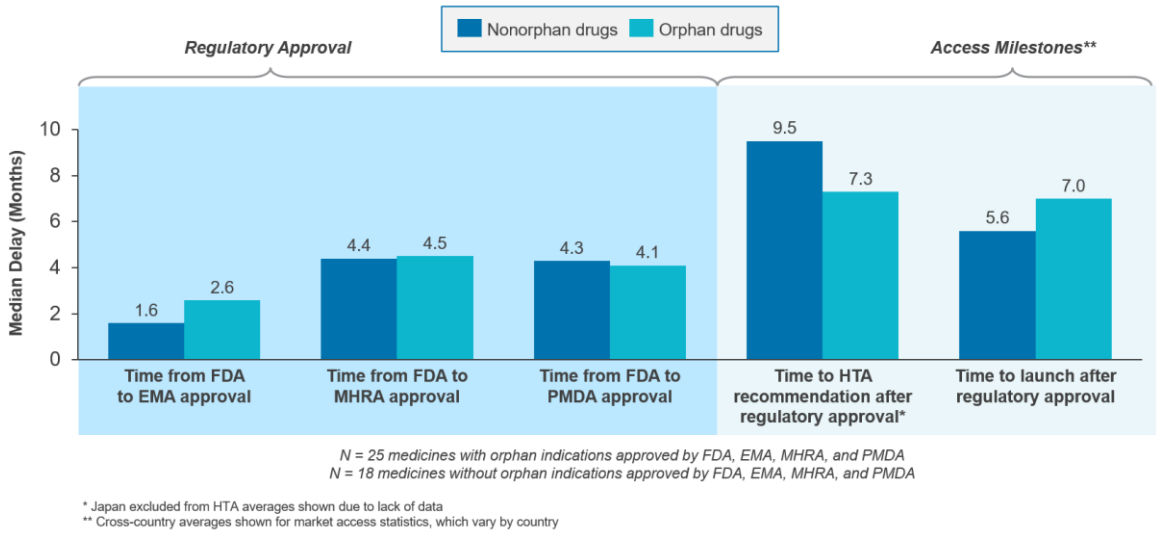
Access to rare disease medicines compared to nonrare medicines

As described above, orphan medicines were more likely than nonorphans to gain EMA, MHRA, or PMDA approval and to reach approval with all three regulators within the six countries evaluated. However, once approved, more orphan drugs never achieved reimbursement or became accessible to patients. 64% of orphans were submitted for HTA review, compared to 67% of nonorphans, but just 52% of orphans received a positive HTA recommendation compared to 61% of nonorphans. Access gaps widened at later stages in the six countries: 56% of orphans received reimbursement compared to 67% of nonorphans, and only 56% of orphans ultimately launched compared to 72% of nonorphans.

Of those orphan drugs submitted, they moved somewhat faster through HTA review relative to nonorphans, with a median time of 7.3 months compared to 9.5 months for nonorphans (Figure 2). However of those receiving a favorable HTA review, launch timing was 7.0 months after regulatory approval for orphan drugs versus 5.6 months for nonorphans. This pattern highlights how HTA and subsequent payor negotiations together often create a binding constraint on access for rare disease therapies. This is consistent with high evidentiary uncertainty and high up-front prices make orphans more vulnerable to restrictive reimbursement thresholds established by HTA (see Appendix).

33 The U.S. Orphan Drug Act defines a rare disease as one affecting fewer than 200,000 people in the United States, or where development costs are unlikely to be recovered from sales (Orphan Drug Act of 1983, 21 U.S.C. § 360bb). In the European Union, an orphan condition is one affecting no more than 5 in 10,000 people, with no satisfactory treatment available or where the new medicine would provide significant benefit (Regulation (EC) No 141/2000 of the European Parliament and of the Council, 1999). In Japan, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) designate orphan drugs for conditions affecting fewer than 50,000 patients nationwide, provided the condition is serious, there is a high medical need, and the development plan is scientifically feasible (MHLW Notification No. 4, 1993; PMDA Orphan Drug Designation Guidelines, 2015).

Figure 2: Regulatory, HTA, and launch delays for orphan and nonorphan FDA-approved drugs across six high-income countries[34]



Country variation in access to rare disease medicines

Country-level results show sharp variation in access. For HTA recommendations, on average, 57% of regulatory approved drugs received positive recommendations across the four European countries and England, but country-specific rates varied widely: Germany (86%) and France (74%) were far higher than Italy (44%) or Sweden (19%). Orphans were especially disadvantaged in England and Sweden, where they received far fewer positive HTA recommendations as nonorphans (52% vs. 72% in England; 8% vs. 33% in Sweden). Germany was the one market where positive HTA recommendations were greater for orphans relative to nonorphans (92% vs. 78%). Average delays from regulatory approval to HTA recommendation were around eight months across all six countries but stretched to 14.9 months for orphans vs. 13.1 for nonorphans in Italy. The variation is likely to reflect different willingness to pay for health outcomes in each country and distinct, often time consuming, approaches to evaluate value. (as discussed in the Appendix).

Reimbursement decisions also differed significantly, with lower rates of reimbursement for drugs for orphan conditions. On average across the six markets, 63% of reviewed drugs were reimbursed, with rates ranging from 86% in Germany to just 19% in Sweden.[35] England, Italy, and Sweden were the markets for orphans, where orphans were reimbursed at much lower rates than nonorphans: 72% vs. 94% in England; 36% vs 56% in Italy; and 8% vs 33% in Sweden. By contrast, Germany and Japan orphans reimbursed more often than nonorphans (92% vs. 78% in Germany; 76% vs. 72% in Japan). Restrictions were also common: Of products with reimbursement, Germany imposed price ceilings on

34 In some countries, medicines may launch with interim pricing or under early-access schemes before HTA decisions are finalized.

35 Our dataset includes products reimbursed through hospital-level negotiations, which follow a separate pathway from the TLV process. These products are often labeled as not reimbursed, likely because they fall outside the national, systematic reimbursement framework. While this distinction is noted, the Swedish statistics remain relevant, particularly as the small share of drugs with positive HTA recommendations and reimbursement is contextualized by a slightly larger group of launched products, which are likely covered through hospital-level arrangements.

39% of orphans and 71% of nonorphans,[36] while England and Sweden applied reimbursement restrictions on half of orphans (56% and 50%, respectively).

Ultimately, differences in pricing and reimbursement structures were reflected in launches of orphan medicines between countries. Overall, 66% of medicines with regulatory approval launched across the six countries, after an average delay of seven months from regulatory approval. England, France, and Sweden stood out as markets where orphan medicines were much less likely to launch than nonorphans: 84% vs. 94% in England, 40% vs. 56% in France, and 32% vs. 67% in Sweden. In Germany orphan launch rates slightly higher than nonorphans (88% vs. 83%). Germany allows drugs to launch prior to HTA assessment and price negotiation, which may explain some of this difference. However, under the 2023 GKV-FinStG reform, this "free pricing" period was shortened from 12 months to six months, after which a negotiated reimbursement price applies. This reduction may reduce the number of timely launches in Germany over time.[37] In France, orphans took nearly four months longer to reach market than nonorphans (14.6 vs. 11.1 months), while in Italy and Sweden, orphans faced delays of 13.2 vs. 12.1 months and 11.7 vs. 8.1 months relative to nonorphans, respectively. In France, orphan medicines launched an average of 10.2 months after value assessments were completed compared to 4.4 months for nonorphans, suggesting that a delayed launch due to price negotiations or strategic considerations like market attractiveness.

4. Implications of pricing and access policies for US rare disease drug access

Our analysis showed that these six high income countries with complex processes that implement price controls, have lower rates of availability for medicines and delayed launches relative to the US, with an even larger gap in access for orphan drugs. As US policymakers consider referencing other countries' pricing schemes, they should consider the implications particularly on incentives to develop and provide access to medicines for rare diseases.

Other countries' pricing models hinder patient access to rare disease medicines

After regulatory approval, orphan drugs outside the US experienced longer delays to HTA decisions and launch compared to nonorphans. Timelines are longer where the assessment and pricing steps are strictly sequential; they are shorter where initial listing or freer entry pricing is allowed with later adjustments (e.g., Germany). Early-access routes (e.g., England's Early Access to Medicines Scheme (EAMS), France's Early Access Program (AAP) and Compassionate Use Program (AAC), Italy's Law 648/96) can bring earlier, conditional availability, but participation is limited and does not guarantee routine reimbursement, especially for rare diseases that continue to generate evidence postlaunch. The limited and conditional nature of early access programs is particularly relevant for rare disease therapies, where postlaunch evidence generation may be required and price-control mechanisms can further restrict access by lowering net prices or narrowing the eligible patient population.

In such environments, price and access control mechanisms, including budget caps, ERP, and managed-entry agreements, can further restrict access by lowering prices or narrowing the eligible

36 Price ceilings in Germany refer to G-BA determinations that a product price cannot be higher than the cost of a comparator therapy due to insufficient clinical benefit.

37 Laube, Y., Serra-Burriel, M., Glaus, C. C., & Vokinger, K. N. (2024). Launch and postlaunch price developments of new drugs in the US, Germany, and Switzerland. JAMA Health Forum, 5(11), e244461. American Medical Association. https://doi.org/10.1001/jamahealthforum.2024.4461

patient population. These constraints can delay access and discourage manufacturers from launching in certain markets, exacerbating disparities in availability.[38,39]

Orphan medicines are even more negatively affected by restrictive pricing schemes compared to nonorphan medicines

There are rules that attempt to streamline process for rare disease medicines but these to do overcome challenges. Orphan drugs received positive HTA recommendations less frequently than nonorphans. In settings driven by cost-effectiveness thresholds (e.g., England's NICE single technology appraisals (STA), Sweden's Dental and Pharmaceutical Benefits Agency (TLV), and Japan when cost-effective analysis applies), rare disease therapies are less likely to receive a positive recommendation even with severity or rarity modifiers. In comparative clinical benefit assessment frameworks (e.g., France, Germany, Italy), initial decisions can be more accommodating. Differences in orphan status across regulators also affect whether a therapy can use orphan-specific HTA pathways.

Importantly, positive HTA recommendations do not necessarily translate into broad coverage. Orphan drugs were reimbursed less frequently than nonorphans across the six benchmark markets. This is consistent with budget tools, such as expenditure caps and clawbacks (France), statutory rebates and revenue-triggered reassessment (Germany), and finance-based managed-entry agreements (Italy, Sweden), pushing realized prices down and often restrict eligible use through indication limits or strict criteria. Sweden frequently denies reimbursement for orphan products; where coverage is granted there (and often in England), it typically requires confidential discounts and tight eligibility. In Japan, national listing generally enables reimbursement, but market-expansion repricing and meaningful patient coinsurance can reduce effective access.

Taken together, orphan drugs were launched less frequently and with longer delays than nonorphans, even after achieving regulatory and HTA milestones in the six countries we evaluated. Whether a medicine reaches the patient depends on expectations about sustainable net prices and international price referencing. Where ERP, midcycle repricing, or purchasing frameworks imply low list prices or deep discounts, biopharmaceutical companies are more likely to delay or forgo launch. Where initial pricing has more flexibility (with later review), first availability tends to be faster even if prices are reduced later. For rare disease therapies, where revenues must be made over small populations, these dynamics appear to weigh heavily, contributing to lower launch rates and longer waits even after positive clinical and regulatory milestones.

By benchmarking to international prices, MFN could compress margins in small-population therapies, weaken free-market launch incentives. It could also import foreign valuations of human life via cost-per-QALY (quality-adjusted life year) thresholds used in countries like England, Sweden, and Japan, despite the absence of such metrics in US policy. Moreover, unlike the single-payer systems used as benchmarks, the US has a fragmented multi-payer structure, and applying MFN across Medicare, Medicaid, and commercial insurers would affect payer-specific pricing and reduce the ability to negotiate differentiated access terms for rare disease populations.

38 Eichler, H. G., Kossmeier, M., Zeitlinger, M., & Schwarzer-Daum, B. (2023). Orphan drugs' clinical uncertainty and prices: Addressing allocative and technical inefficiencies in orphan drug reimbursement. Frontiers in Pharmacology, 14, 1074512. https://doi.org/10.3389/fphar.2023.1074512

39 Nuijten, M., & Van Wilder, P. (2021). The impact of early phase price agreements on prices of orphan drugs. BMC Health Services Research, 21(1), 222. https://doi.org/10.1186/s12913-021-06206-3.

There will be less investment in their development in rare disease medicines if external reference-based pricing models were adopted

Currently, the US policy environment encourages manufacturers to launch many rare disease therapies there first relative to other countries. This reflects strong incentives and prioritization, but also the receptiveness of the environment in Europe and Japan, indeed a sizable share of FDA-approved rare disease medicines never obtain EMA, MHRA, or PMDA approval. If the US imports price levels from other countries reflecting their price control frameworks, this will significantly reduce revenues in the US. For rare diseases, small patient numbers and price uncertainty may reinforce this drop-off in launches.[40] Moreover, evidence suggests that if the US were to adopt an ERP model such as an MFN policy, manufacturers might not develop these drugs for any market.[41,42]

4.1 Conclusions

Given the size of the US market, the impact of a price control policy like MFN in the US could be particularly damaging; therefore there is a strong argument orphan drugs should not be included in any contemplated price controls. US policy has long recognized the unique challenges of rare diseases and has implemented targeted protections to support innovation and access. This precedent should be continued building on the 40 years of policy grounded in a strong public health rationale: The Orphan Drug Act provides market exclusivity and tax incentives to encourage development.[43] More recently, the Inflation Reduction Act introduced an exemption from Medicare price negotiation for drugs approved solely to treat a single rare disease.[44] This exemption was designed to preserve incentives for therapies with limited commercial viability. The One Big Beautiful Bill Act expanded this protection by exempting drugs approved only for rare indications, including those treating more than one rare disease, but not drugs that also carry a non-rare indication.[45] These measures reflect a bipartisan understanding that rare disease therapies require tailored policy treatment – not blunt cost-containment tools. An MFN framework applied to orphan drugs in the US risks directly undermining this consensus by importing foreign price levels determined by countries' respective institutional and regulatory frameworks, and accompanying access and innovation challenges. By benchmarking US prices to those in countries with centralized price controls and restrictive HTA thresholds, MFN could override the very exemptions and incentives US policymakers have put in place to protect vulnerable patient populations affected by rare disease.

Appendix: The impact of the policy environment on access

40 Mikami, K. (2019). Orphans in the market: the history of orphan drug policy. Social History of Medicine, 32(3), 609-630.

41 Center for Strategic & International Studies. (2025). "How Most-Favored Nation Policy Could Undermine US Leadership." Accessible at: https://www.csis.org/blogs/perspectives-innovation/how-most-favored-nation-policy-could-undermine-us-leadership. Accessed: September 1, 2025.

42 USC Schaeffer Center. (2025). "'Most-Favored Nation' Drug Pricing Has Three Significant Problems." Accessible at: https://schaeffer.usc.edu/research/most-favored-nation-drug-pricing-has-three-significant-problems. Accessed: September 1, 2025.

43 US Food and Drug Administration. (n.d.). Designating an orphan product: Drugs and biological products. Retrieved from https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products. Accessed: September 1, 2025.

44 Medicare. (2022). Inflation Reduction Act: Implementation of the Medicare Drug Price Negotiation Program (CMS Publication No. 12124). Centers for Medicare & Medicaid Services. https://www.cms.gov/inflation-reduction-act

45 US Congress. (2025). H.R.1 - One Big Beautiful Bill Act, 119th Congress (2025–2026). Retrieved from https://www.congress.gov/bill/119th-congress/house-bill/1. Accessed: September 1, 2025.

Our review of the policy environment in the markets of focus revealed that three broad policy areas are especially important for rare disease medicines: early-access programs and policies, which seek to accelerate availability but often with conditional or temporary arrangements; value assessment and pricing policies, which determine how clinical and economic evidence is interpreted and price and budget control policies, which control spending and revenue.

Early-access programs and policies

To address access challenges for orphan drugs, several countries have implemented early-access programs that combine provisional patient access with evidence generation. While these programs can provide timely availability of treatments, participation does not guarantee subsequent reimbursement. They vary by country in scope, eligibility, and funding mechanisms, and uptake is often limited, meaning only a small proportion of rare disease patients benefit (Table 1).

Table 1: An overview of the early access programs and policies

Framework & Challenges	Corrective Measures & Limitations
Early-access programs: Designed to provide provisional access to orphan drugs while generating real-world evidence. Challenges include conditional eligibility, limited scope, inconsistent uptake, and no guarantee of subsequent reimbursement.	**France:** Early access is provided through the Early Access Authorization (AAP) and Compassionate Access Framework (AAC), granting early availability while collecting real-world data. In some cases, retroactive rebates apply if the drug is later fully reimbursed, partially offsetting payor costs.[46] **Italy:** Multiple early-access routes exist, including Balduzzi's Law for filing pricing and reimbursement before EMA approval, Law 648/96 for off-label or unapproved rare disease medicines, the Nonrepetitive Use of Advanced Therapies for patient-specific ultra-rare treatments, and the Compassionate Use program for investigational drugs.[47,48,49,50] **England:** The Innovative Medicines Fund (IMF) can provide interim funding while further evidence is collected. However, only two rare disease drugs have received interim IMF funding to date, reflecting the program's limited reach.[51]

Value assessment and pricing policies

46 ANSM. (2024). "Early access to health products." Accessible at: https://ansm.sante.fr/uploads/2024/09/06/1-l-acces-precoce-2.pdf. Accessed: August 15, 2025.

47 AIFA. (2025). "Orphan medicinal products." Accessible at: https://www.aifa.gov.it/en/farmaci-orfani. Accessed: August 15, 2025.

48 AIFA. "Legge 648/1996." Accessible at: https://www.aifa.gov.it/en/legge-648-96. Accessed: August 15, 2025.

49 AIFA. "Nonrepetitive use of advanced therapies" https://www.aifa.gov.it/en/uso-non-ripetitivo-di-terapie-avanzate. Accessed: August 15, 2025.

50 AIFA. "Medicines for compassionate use" https://www.aifa.gov.it/en/farmaci-a-uso-compassionevole Accessed: August 15, 2025.

51 Department of Health & Social Care. (2024). "England Rare Diseases Action Plan 2024: Main Report." Accessible at: https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2024/england-rare-diseases-action-plan-2024-main-report. Accessed: August 15, 2025.

HTA bodies evaluate the clinical and economic value of new medicines to guide coverage and reimbursement decisions. Broadly, there are two types of HTA frameworks: cost-effectiveness analysis (CEA) frameworks, which use explicit cost-per-QALY thresholds to determine value, and comparative clinical benefit assessment frameworks, which assess added clinical benefit, therapeutic impact, or broader societal value through structured benefit ratings or multicriteria assessments.[52] CEA frameworks are used in England, Sweden, and Japan, while comparative clinical benefit assessment frameworks primarily being applied in France, Germany, and Italy (Table 2). The table provides an overview of the existing framework, highlights the key associated challenges, and summarizes the corrective measures introduced by HTA bodies to address them, although some limitations persist. It is worth noting that the US does not have a centralized HTA body that determines drug prices; instead, pricing is typically negotiated between manufacturers and private or public insurers, resulting in a more decentralized and market-driven approach to drug access and reimbursement.

Starting with regulatory process, the FDA, EMA, MHRA, and PMDA assess safety, efficacy and quality. The approach is tailored for rare disease medicines. FDA orphan designation and status does not always translate into equivalent recognition from other regulatory agencies. In fact, only 41% of cancer drugs designated as orphan by the FDA received the same status from the EMA, as the EMA applies stricter criteria to subgroups of more prevalent cancers, granting orphan designation only if the subgroup is considered a distinct condition with prevalence below the threshold.[53] Across all therapeutic areas, only about one-third of FDA orphan drugs are designated by the EMA.[54] Given the orphan status affects eligibility for different HTA pathways, certain FDA-designated orphan drugs may not benefit from the tailored HTA processes or pricing provisions available for orphan medicines outside the US.

Table 2: An overview of the different value assessment and pricing frameworks

Framework & Challenges	Corrective Measures & Limitations
Cost-effectiveness analysis (CEA): Relies on explicit or informal cost-per-QALY thresholds, which are often too restrictive for orphan drugs since small patient	**England (NICE):** Introduced the Highly Specialised Technology (HST) pathway with a £100k–£300k/QALY threshold and modifiers, but it applies only to very rare conditions. Most orphan drugs instead undergo Single Technology Appraisal (STA) at the stricter £20k–£30k/QALY threshold, limiting access.[55,56]

52 Fontrier, A. M., Visintin, E., & Kanavos, P. (2022). Similarities and differences in health technology assessment systems and implications for coverage decisions: Evidence from 32 countries. PharmacoEconomics – Open, 6(3), 315–328. https://doi.org/10.1007/s41669-021-00315-2.

53 Vokinger, K. N., & Kesselheim, A. S. (2019). Application of orphan drug designation to cancer treatments (2008–2017): A comprehensive and comparative analysis of the USA and EU. BMJ Open, 9(10), e028634. https://doi.org/10.1136/bmjopen-2018-028634.

54 Kamerikar, V., Dheer, P., & Seoane-Vazquez, E. (2023). HPR78 A comparison of orphan drugs approved by the FDA and EMA, 1995–2022. Value in Health, 26(6), S225. https://doi.org/10.1016/j.jval.2023.04.820.

55 NICE. (2025). "About highly specialised technologies guidance." Available at: https://www.nice.org.uk/what-nice-does/our-guidance/about-highly-specialised-technologies-guidance. Accessed: August 15, 2025.

56 NICE. (2025). "Technology appraisal processes and timelines." Available at: https://www.nice.org.uk/what-nice-does/our-guidance/about-technology-appraisal-guidance/our-methods-and-processes-health-technology-evaluation-manual/technology-appraisal-processes-and-timelines. Accessed: August 15, 2025.

populations require higher prices to recover R&D costs.	**Sweden (TLV):** Uses informal willingness-to-pay bands that rise with disease severity (250k–1m SEK/QALY).[57] A 2025 "staircase model" was added to progressively increase acceptable cost-effectiveness ratios for rarer conditions, improving but not guaranteeing access.[58] **Japan (Chuikyo):** Applies a 5m yen/QALY threshold for most drugs, and a higher 7.5m yen/QALY for orphan, pediatric, and cancer therapies.[59,60] Some drugs for "intractable diseases" can be exempt from cost-effectiveness analysis, but this designation is discretionary, creating ambiguity and inconsistent access.[61]
Comparative clinical benefit assessment frameworks: Assess added clinical benefit, therapeutic impact, and societal value rather than QALY thresholds. While this approach is **more flexible, practical and financial controls still constrain orphan drug access.**	**Germany (G-BA):** Orphan drugs automatically receive a positive "added benefit" rating unless annual revenue exceeds €30m (recently reduced from €50m). Crossing the threshold triggers a reassessment of added benefit and price renegotiation, removing orphan privileges.[62] **France (HAS) & Italy (AIFA):** No dedicated orphan pathways exist, though accelerated reviews are sometimes available.[63,64] Additionally, France has expanded cost controls on orphan drugs through ERP and revenue caps.[65]

57 Viollet, J., O'Leary, E., Gonzalez, C. C., Lauppe, R., & Oldsberg, L. (2022). HTA228 Willingness to pay for different severity levels in Sweden: An analysis of TLV decisions (2014–2022). Value in Health, 25(12), S341. https://doi.org/10.1016/j.jval.2022.09.918

58 TLV (2025). "TLV introduces new working methods to increase access to medicines for patients with rare health conditions" Accessible at: https://www.tlv.se/press/nyheter/arkiv/2025-01-02-tlv-infor-nya-arbetssatt-for-att-oka-tillgangen-till-lakemedel-for-patienter-med-sallsynta-halsotillstand.html. Accessed: August 15, 2025..

59 Hasegawa, M., Komoto, S., Shiroiwa, T., & Fukuda, T. (2020). Formal implementation of cost-effectiveness evaluations in Japan: A unique health technology assessment system. Value in Health, 23(1), 43–51. https://doi.org/10.1016/j.jval.2019.07.002

60 Inizio Advisory. (2023). Comparisons of economic evaluation guidelines between Japan and 6 other countries (England, France, Germany, Sweden, Canada, and Australia). Retrieved August 15, 2025, from https://www.ispor.org/docs/default-source/euro2023/michael-lees2023comparisons-of-economic-evaluation-guidelines-between-japan-and-six-countries-england-france-germany-sweden-canada-and-australia132424-pdf.pdf.

61 Uchida, T., Takahashi, Y., Yamashita, H., Nakaoku, Y., Ohura, T., Okura, T., Masuzawa, Y., Hosaka, M., Kobayashi, H., Sengoku, T., & Nakayama, T. (2022). Evaluation of clinical practice guidelines for rare diseases in Japan. JMA Journal, 5(4), 460–470. https://doi.org/10.31662/jmaj.2022-0033.

62 Federal Ministry of Health. (2022). "Statutory Health Insurance Financial Stabilization Act (GKV-FinStG)" Accessible at: https://www.bundesgesundheitsministerium.de/service/gesetze-und-verordnungen/detail/gkv-finanzstabilisierungsgesetz-gkv-finstg.html. Accessed: August 15, 2025.

63 CEPS. (2022). "Annual activity report 2022." Accessible at: https://sante.gouv.fr/IMG/pdf/ra_ceps_2022.pdf Accessed: August 15, 2025.

64 AIFA. (2025). "Orphan medicinal products." Accessible at: https://www.aifa.gov.it/en/farmaci-orfani Accessed: August 15, 2025.

65 CEPS. (2022). "Annual activity report 2022." Accessible at: https://sante.gouv.fr/IMG/pdf/ra_ceps_2022.pdf Accessed: August 15, 2025.

Price and budget control policies

Payors are increasingly relying on financial and budget control mechanisms to manage the costs of orphan drugs and limit fiscal risk. These include financial-based agreements (such as budget caps, price-volume deals, and confidential rebates), which are now widely used in Germany, Italy, and Sweden to constrain expenditure and provide predictable spending levels, though at the cost of limiting revenue potential for manufacturers. In Japan, market expansion repricing systematically reduces drug prices as sales volumes grow or indications expand, further restricting long-term revenue prospects. In parallel, several countries apply clawback mechanisms that require manufacturers to return funds if spending exceeds defined thresholds, as seen in France, Germany, Italy, and England (Table 3). While these approaches help control healthcare budgets, they also reduce incentives for orphan drug development by capping revenues and increasing financial uncertainty for manufacturers.

Table 3: An overview of the different price and budget control policies

Framework & Challenges	Corrective Measures & Limitations
Financial-based agreements: Increasingly used to control spending on orphan drugs and reduce payor **risk. These include budget caps, price-volume arrangements, and confidential rebates. While they expand access in some cases, they also restrict revenue potential and reduce incentives for orphan drug development**	**Germany (GKV):** The GKV Financial Stabilization Act has expanded the use of financial-based agreements across therapy areas, including orphan drugs.[66] **Italy (AIFA):** Italy is moving away from outcome-based agreements toward financial-based agreements to reduce economic uncertainty for payors, but this increases revenue constraints for manufacturers.[67] **Sweden (TLV):** Sweden has adopted financial-based agreements with confidential rebates, lowering payor risk and enabling faster/broader reimbursement for orphan drugs despite limited clinical evidence.[68]
Market expansion repricing (MER): A mechanism that reduces drug prices as sales increase, discouraging revenue growth for orphan drugs when indications expand, or sales exceed forecast thresholds.	**Japan (Chuikyo):** MER systematically lowers prices based on sales growth, indication expansion, or availability of similar products. While this mechanism ensures payer savings, orphan drugs may be partially protected by exemptions, although they

66 Federal Ministry of Health. (2022). "Statutory Health Insurance Financial Stabilization Act (GKV-FinStG)" Accessible at: https://www.bundesgesundheitsministerium.de/service/gesetze-und-verordnungen/detail/gkv-finanzstabilisierungsgesetz-gkv-finstg.html Accessed: August 15, 2025.

67 Xoxi, E., Facey, K. M., & Cicchetti, A. (2021). The evolution of AIFA registries to support managed entry agreements for orphan medicinal products in Italy. Frontiers in Pharmacology, 12, 699466. https://doi.org/10.3389/fphar.2021.699466.

68 Abacus Medicine. (2025). "Navigating market access in Sweden." Accessible at: https://www.abacusmedicinepharmaservices.com/market-access-in-sweden/. Accessed: August 15, 2025.

	remain at risk of repricing if sales grow significantly or if they move beyond their orphan indication.[69,70]
Clawback mechanisms: Manufacturers are required to return revenue if drug spending exceeds national caps or thresholds. This provides payors **with budgetary control but creates uncertainty for manufacturers.**	**France (HAS/LFSS):** Industry-wide clawbacks apply when national drug expenditure surpasses limits. For 2025, the total health insurance budget is €265.9bn; €1bn in savings is targeted for medicines, and clawbacks are triggered if drug spending exceeds €27.25bn.[71] **Germany (GKV):** Biopharma companies contribute rebates tied to their share of Statutory Health Insurance expenditure. The mandatory manufacturer rebate was raised from seven percent to 12% in 2023, reverting to seven percent in 2024.[72] **Italy (AIFA):** Public spending on medicines is capped at 15.3% of the national healthcare fund (2024). This cap is divided into two categories: 6.8% for medicines distributed through the retail channel and 8.5% for medicines purchased by hospitals. Exceeding this cap triggers clawback payments by companies to reimburse the government.[73] **England (NICE/VPAG):** The 2024 VPAG requires rebates from manufacturers but exempts orphan drugs designated as New Active Substances (NAS) for the first 36 months after UK marketing authorization. After this period, rebates apply.[74]

69 Ministry of Health, Labour and Welfare. (2022). “Japan’s NHI drug price system.” Accessible at: https://www.pmda.go.jp/files/000248690.pdf. Accessed: August 15, 2025.

70 Shibata, S., Uemura, R., & Suzuki, T. (2016). Evaluating the effectiveness of repricing for market expansion in the Japanese drug pricing system. Therapeutic Innovation & Regulatory Science, 50(6), 751–758. https://doi.org/10.1177/2168479016632274.

71 Simon Kucher. (2025). “P&R brief France: What the latest updates mean for pharma pricing and market access.” Accessible at: https://www.simon-kucher.com/en/insights/pr-brief-france-what-latest-updates-mean-pharma-pricing-and-market-access. Accessed: August 15, 2025.

72 Simon Kucher. (2023). “Germany: How the GKV-FinStG law is transforming the pharma P&R landscape.” Accessible at: https://www.simon-kucher.com/en/insights/germany-how-gkv-finstg-law-transforming-pharma-pr-landscape. Accessed: August 15, 2025.

73 GLI. (2024). “Pricing & Reimbursement Laws and Regulations 2024 – Italy.” Accessible at: https://www.globallegalinsights.com/practice-areas/pricing-reimbursement-laws-and-regulations/italy. Accessed: August 15, 2025.

74 Department of Health & Social Care. (2024). “The 2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth: Payment percentage for 2025.” Accessible at: https://www.gov.uk/government/publications/the-2024-voluntary-scheme-for-branded-medicines-pricing-access-and-growth-payment-percentage-for-2025/the-2024-voluntary-scheme-for-branded-medicines-pricing-access-and-growth-payment-percentage-for-2025. Accessed: August 15, 2025.

Acronyms and key terms

- **AAC** – France's Accès Compassionnel compassionate use program
- **AAP** – France's Accès Précoce early-access program
- **AIFA** – Agenzia Italiana del Farmaco, Italian HTA body
- **BLA** – Biologics License Application submitted to the FDA
- **CEA** – Cost-effectiveness analysis used to assess value based on cost per QALY
- **CEPS** – France's pricing committee for health products
- **Clawback** – Policy requiring manufacturers to return funds if spending exceeds limits
- **CMS** – Centers for Medicare & Medicaid Services in the US
- **Early-Access Program** – Allows patient access before full approval or reimbursement
- **EMA** – European Medicines Agency
- **ERP** – External reference pricing, where countries set prices based on those of other countries
- **FDA** – US Food and Drug Administration
- **GKV** – Germany's statutory health insurance system
- **GKV-FinStG** – German law to stabilize health insurance finances
- **HAS** – Haute Autorité de Santé, France's HTA body
- **HST** – Highly Specialised Technology pathway in England
- **HTA** – Health technology assessment evaluates clinical and economic value
- **HTA Delay** – Time between regulatory approval by the EMA, MHRA, or PMDA and HTA recommendation
- **IMF** – Innovative Medicines Fund in England
- **Launch** – When a drug becomes commercially available in a market
- **Launch Delay** – Time between regulatory approval by the EMA, MHRA, or PMDA and commercial availability in a country
- **Launch Sequencing** – Strategic timing of drug launches across countries
- **Managed-Entry Agreement** – Conditional access to a drug while collecting more data
- **MER** – Market expansion repricing in Japan lowers prices as sales grow
- **MFN** – Most-favored-nation pricing model ties US drug prices to those of other countries
- **MHRA** – UK's Medicines and Healthcare products Regulatory Agency
- **NAS** – New Active Substance designation for newly developed drugs in the UK
- **NDA** – New Drug Application submitted to the FDA
- **NICE** – National Institute for Health and Care Excellence in England
- **OECD** – Organisation for Economic Co-operation and Development
- **Orphan Drug** – Drug for a rare disease affecting fewer than 200,000 people in the US
- **PMDA** – Japan's Pharmaceuticals and Medical Devices Agency

- **Price Ceiling** – Maximum price allowed for a drug
- **QALY** – Quality-adjusted life year is used in measuring health outcomes
- **Rare Disease** – Condition with low prevalence, often severe and lacking treatments
- **Reimbursement** – Approval for a drug to be paid for by insurers
- **Regulatory Delay** – Time between FDA approval and approval by the EMA, MHRA, or PMDA
- **STA** – Single Technology Appraisal, NICE's standard HTA process
- **TLV** – Sweden's HTA and pricing authority
- **Value Assessment** – Evaluation of a drug's benefit and cost-effectiveness
- **VPAG** – England's Voluntary Scheme for Branded Medicines Pricing, Access, and Growth

About Charles River Associates

Charles River Associates is an economic and strategy consultancy with offices in North America, Europe, Latin America, and Australia. CRA offers services to all the key functions of the life sciences industry and specializes in public policy issues. CRA focuses on delivering high-quality, robust analysis in a compelling fashion that is accessible to the target audience and has worked for the industry, national trade associations, and individual companies on a wide range of issues over the last 20 years.

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