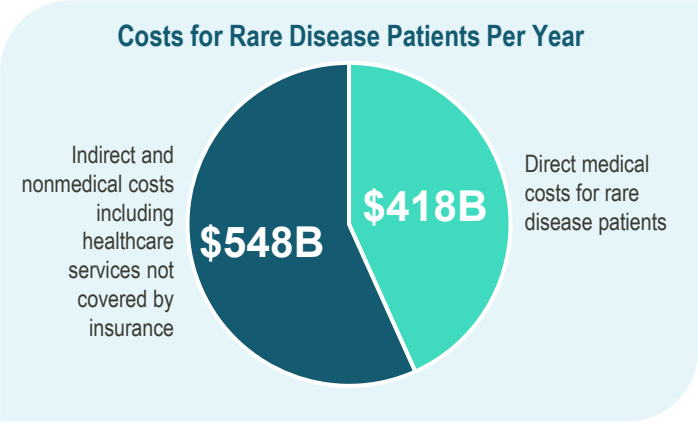
The Unintended Consequences of Drug Pricing Policies on Orphan Drug Development

ADVI

Introduction: Rare Diseases and Orphan Drug Development

In the United States, the human and economic costs of rare diseases remain high as patients have limited treatment options. Despite each rare condition affecting a population of less than 200,000 individuals, there are over 10,000 known rare diseases and they impact nearly 1 in 10 people.[i] About 95 percent of rare diseases in the US do not have an FDA-approved treatment.[ii]

Rare diseases are often chronic, life-threatening, and worsen over time.[iii] Direct medical costs for over 15.5 million rare disease patients in the US reached $418 billion per year.[iv] On average, rare disease patients spend over 6 years searching for an accurate diagnosis and face an average annual medical cost that is $26,887 more compared to a person without a rare disease.[v] Rare diseases also result in immense indirect and non-medical costs, estimated at $548 billion per year, and include absenteeism, presenteeism, forced retirement, and healthcare services not covered by insurance. Taken together, the total annual economic burden of rare diseases in the US is about $966 billion.[vi]



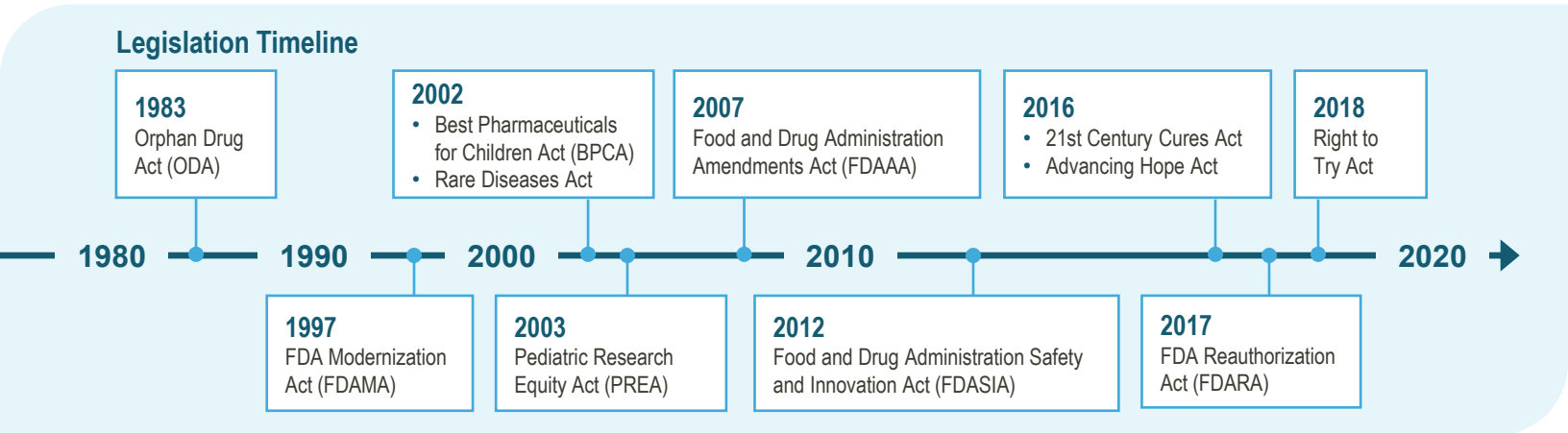
Despite the impacts of rare diseases and advancements in science, orphan drug development continues to be more challenging compared to non-orphan drugs. Small patient populations are a major factor in development, which limits clinical trial recruitment, increases research and development (R&D) costs, and creates greater financial risks. Orphan drug clinical trials are especially difficult because recruiting the right candidates from a smaller patient population is time-consuming and more expensive compared to standard trials.[vii] Rare disease clinical trial failure rates are higher due to these factors.[viii]

Trial design for orphan drugs is also complex, because there is often a lack of well-established clinical endpoints and limited understanding of a rare disease's natural progression. These complications are compounded by the fact that more than 50 percent of identified rare disease patients are children, and that rare diseases often have diverse manifestations which require tailored clinical approaches for different subgroups.[ix] These additional complexities lengthen the average development lifecycle for orphan drugs to more than 15 years, while non-rare treatments typically take around 10 years.[x]

Market forces also work against the development of orphan drugs, because the inherently smaller market sizes for rare disease therapies limit revenue potential and increase investor risk. New research into the comparative market performance between rare and non-rare innovator companies shows that revenues generated by rare innovator companies lag significantly behind those of non-rare firms. Less than one-third of commercial-stage rare disease companies reported profitability, while over half of their non-rare counterparts reported being profitable.[xi] Furthermore, rare disease innovators have a more difficult time accessing venture capital and IPO funds necessary to support clinical programs due to lower levels of investor confidence.[xii]

To help overcome orphan drug development challenges, policymakers enacted several bipartisan solutions over the past four decades to support treatment options for rare disease patients. Laws enacted by both Democrats and Republicans over the years supported investments in treatments for rare disease patients, providing rare disease innovators and funders additional incentives to advance orphan drug development. While there are several examples, here are four impactful bipartisan laws advancing orphan drug development:[xiii]

- **The Orphan Drug Act of 1983 (ODA)**, spearheaded by Representative Henry Waxman (D-CA) and Senator Orrin Hatch (R-UT) and signed by President Ronald Reagan, is the preeminent example of support for rare treatment development. The law authorized tax credits for qualified clinical testing, established grants for orphan clinical trials, waived the US Food and Drug Administration (FDA) Prescription Drug User Fees, and allowed for seven years of market exclusivity after approval.[xiv, xv]
- **The Rare Diseases Act of 2002**, led by Senators Ted Kennedy (D-MA) and Orrin Hatch (R-UT) and signed by President George W. Bush, established an Office of Rare Diseases at the National Institutes of Health (NIH) and provided for rare disease regional centers of excellence under the agency's umbrella.[xvi] By addressing the need for dedicated research and resources, this act helped advance the understanding and treatment of rare diseases.
- **The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012**, led by Senators Tom Harkin (D-IA) and Michael Enzi (R-WY) and signed by President Barack Obama, led to the FDA's rare pediatric disease (RPD) priority review voucher program (PRV).[xvii]
- **The 21st Century Cures Act of 2016**, led by Representatives Diana DeGette (D-CO) and Fred Upton (R-MI), Senators Patty Murray (D-WA) and Lamar Alexander (R-TN) and implemented by President Donald Trump, streamlined the FDA's review of genetically targeted and protein variant therapies for rare diseases and provided increased funding for FDA to study the Precision Medicine Initiative and Cancer Moonshot program – programs critical for orphan drug development.[xviii]



Unfortunately, recent policy changes are undermining this bipartisan support for rare disease patients, threatening to reverse 40 years of progress and creating additional barriers to orphan drug development. Drug pricing policies like those found in the Inflation Reduction Act (IRA) and state Prescription Drug Affordability Boards (PDABs) negatively impact the rare disease community. Federal and state policymakers need to understand the impact these policies have on patients and should return to the bipartisan support of advancing orphan drug development.

Pricing Policies' Negative Impact on Rare Diseases

New drug pricing policies at the federal and state level will negatively impact rare disease patients by fundamentally changing how orphan drugs are developed. Maximum Fair Prices (MFPs) and Upper Payment Limits (UPLs) set maximum reimbursable amounts for treatments throughout the drug supply chain, and it is well documented that similar pricing policies can limit R&D, negatively impact smaller companies, disrupt patient access, limit quality of life, and delay access to medicines. Policymakers should reconsider these approaches, especially as they may also disproportionately impact rare disease patients and orphan drug development.

Pricing policies shrink orphan drug R&D budgets and investments

It has long been understood that certain pricing policies undermine R&D investments.[xix, xx, xxi, xxii] Most recently, it is estimated the federal government negotiations and the MFPs will lead to a 12 percent revenue reduction through 2039, and therefore, R&D spending may fall about 18.5 percent in that same period.[xxiii] This impact will be magnified for riskier and longer term orphan drug development, if companies reallocate R&D budgets to prioritize projects with shorter time horizons and treatments with greater demand.[xxiv, xxv] In fact, at least 40 research programs have already been discontinued and 24 companies have made announcements to curtail drug development because of the IRA, including Alnylam's announcement to suspend vutrisiran clinical trials to treat the rare condition Stargardt disease.[xxvi, xxvii]

Rare disease innovator companies have also seen disproportionately less funding from the investor community, which companies rely on to fund R&D. Rare disease companies saw a seven percent decline in market value per year and a 50 percent decline in the cash available to them, as well as a nearly 30 percent decline in total potential deal value, between 2018 and 2023.[xxviii] In 2023, the value of rare disease partnering deals dropped 25 percent in contrast to the 9 percent rise in partnering activity for drug developers overall.[xxix] Additionally, rare disease companies' venture capital funding fell by 2.4 percent and access to other funds through the sale of public and private equity and debt was reduced by 15.5 percent. These stats are particularly concerning as commercial-stage companies focused on rare diseases invest more in R&D relative to revenues, compared to non-rare companies.[xxx]

Funding for rare disease companies

Venture capital funding fell by: **2.4%** ↓

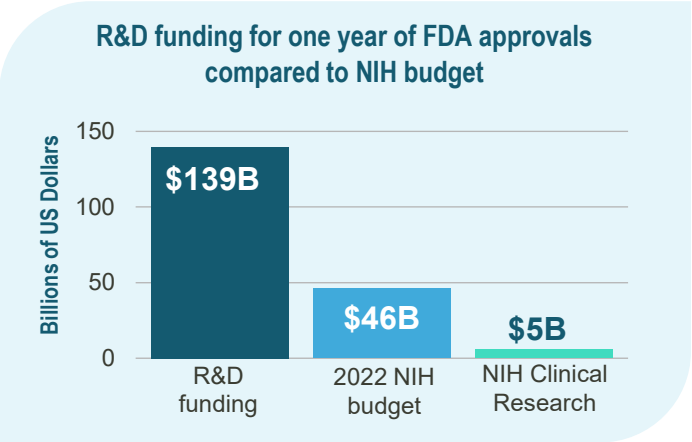
Access to other funds through the sale of public and private equity and debt fell by: **15.5%** ↓

Pricing policies have a greater impact on smaller companies that historically lead orphan drug development

Studies also show pricing policies have a greater impact on smaller companies, which have led on orphan drug development, due to their focused portfolios and limited revenues.[xxxi, xxxii] Small companies account for over 70 percent of the R&D pipeline, and historically were developed out of the need for orphan drugs.[xxxiii, xxxiv, xxxv] These companies often need both larger companies and investors to continue their research; however, these partners pull back in response to government pricing policies. For example, when the European Union (EU) implemented pricing policies, small innovators' fundraising declined and the number of small startups decreased, relative to the US between 2003 and 2020. In fact, the total number of startups in the US, by 2020, was roughly three times greater than the EU.[xxxvi]

ADVI

The federal government plays an important role in orphan drug development; however, these contributions must be placed in context. For example, it is estimated that the cost to replace all private R&D funding for one year of FDA approvals would be $139.6 billion. These total costs are equivalent to 302 percent of the entire NIH 2022 budget of $46.2 billion, and around 25 times the $5.6 billion that NIH dedicates annually to clinical research trials for pharmaceuticals.[xxxvii]



While NIH plays a crucial role in basic science and foundational research for novel therapies, it simply does not have the resources to replace small companies' reduction in R&D spending due to pricing policies.

The IRA disincentivizes pursuing orphan indications first and additional orphan indications

In some cases, companies could start drug development with rare disease populations, representing a win-win scenario for both patients and the company. Rare patients would receive access to treatments first and companies can refine their drug's efficacy profiles before moving on to larger patient populations and diseases.[xxxviii, xxxix]

While well intentioned, the Orphan Drug Exclusion (ODE) within the IRA creates several perverse incentives for orphan drug development. Under the ODE, rare disease drugs are only excluded from price negotiation when they are designated for a single rare disease or condition, and when FDA approvals are solely within that designation. Additionally, the date used to begin a drug's count toward negotiation eligibility begins on the date of its first approval, even if that approval is for a rare disease.[xl]

Because eligibility for IRA negotiations is based on its initial approval, rare disease innovators have a limited amount of time to recoup their R&D investments before potentially facing an MFP. This dynamic encourages companies to target larger disease populations first, instead of pursuing orphan drugs that have limited patient populations. The IRA also discourages investments in additional indications because the law eliminates the incentives to conduct this work. At the recent 2025 JP Morgan (JPM) conference, survey data showed 56 percent of venture capital firms are less interested in supporting future rare disease development due to the IRA, and 87 percent are less interested in small molecule development.[xli]

The IRA also penalizes rare disease innovators who seek additional orphan designations and discourages the exploration of more orphan drug approvals for the same drug. Limiting the ODE to a single orphan designation discourages companies from further investing in an existing orphan drug that may meet the needs of other rare disease patients. Even if the drug is solely indicated to help rare disease patients and then receives a second orphan indication, the drug becomes eligible for price negotiations. In fact, there are over 100 orphan drugs with two or more orphan indications that could be impacted due to this provision.[xlii, xliii]

Pricing policies that impact R&D lead to fewer orphan drugs and could increase off-label use

Ultimately, the tightening of R&D activities will lead to fewer therapies for rare patients.

The Orphan Drug Exclusion, while well intentioned, changes the calculus for orphan drug development, excluding those drugs with only a single orphan designation.[xl]

In fact, a recent orphan drug-specific analysis predicts a 40 percent reduction in orphan FDA approvals from 2026 to 2035 due to the IRA, as companies begin to shift their pipeline priorities toward non-rare drugs.[xliv] However, these estimates could increase if additional government pricing policies are implemented.[xlv]

A recent orphan drug-specific analysis predicts a 40 percent reduction in orphan FDA approvals from 2026 to 2035.

Limited treatment options for rare disease patients may also lead to further off-label use, which is when a physician prescribes a product that the FDA has deemed to be safe and effective for a condition other than the one it is being prescribed to treat. The practice of prescribing off-label drugs is estimated between 20 percent to 30 percent and is common for rare disease patients, who typically lack treatment opinions.[xlvi, xlvii]

However, off-label use is not a panacea for rare disease patients. First, off-label uses of FDA-approved drugs are made without the benefit of an FDA-reviewed analysis of safety and effectiveness data, and this lack of scrutiny has been proven to put patients at higher risk for medication errors, side effects, and unwanted drug reactions.[xlviii, xlix] Similarly, if physicians are unaware of the potential uses or possible side effects of medications, they may not be able to properly recommend medicines to their patients and jeopardize the important patient-physician relationship.

Off-label prescribing puts rare disease patients in a precarious financial situation. Insurers and pharmacy benefit managers typically do not reimburse off-label use of drugs on the basis the treatment is “experimental” or “investigational.” Consequently, patients are often required to pay out-of-pocket for these therapies, leading to substantial financial strain.[l]

Not only is this bad for patients, but if left unchecked, it could threaten the FDA gold standard of drug approval. Treatment options may not be further explored or invested in if off-label use for a particular drug becomes common practice.[li] Innovator companies should be encouraged to generate the necessary research to support label expansion for prescribers to reference, which off-label prescribing disincentivizes.

Pricing policies shorten life expectancies, which also disproportionately impact rare disease patients

Pricing policies lead to significant reductions in life expectancy by delaying research and limiting treatment options for both current and future patients.[lii] A recent IRA analysis projects there is a loss of 116 million life years over the next two decades.[liii] Rare disease patients are likely to be disproportionately affected, as this vulnerable population already faces limited treatment options and shorter life expectancies.[liv, lv]

With 95 percent of rare diseases currently lacking any approved treatment, policies that hinder orphan drug development risk exacerbating these disparities.

In fact, orphan drugs have a greater potential to improve and extend the lives of patients, compared to non-orphan drugs.[lvi, lvii] Therefore, by limiting orphan drug development, policymakers are not only deepening the challenges faced by rare disease patients, but limiting their current and future life expectancy.

Pricing policies limit access to existing orphan drugs by distorting already complex drug supply chains

Access to orphan drugs has historically been challenging due to drug shortages[lviii] and utilization managements tools[lix]; however, pricing policies could further limit access by distorting drug supply chains. Manufacturers, health

insurers, and providers may each face reduced financial incentives to produce and distribute drugs needed to treat rare disease patients. For example, if an MFP or UPL is set, a health insurer may be restricted in a drug's potential revenue and may change its formulary to improve access to a more profitable treatment. The IRA is already driving these decisions as 78 percent of surveyed health directors indicated plans will "restrict therapeutic options in response to" the government pricing policies and the MFP.[lx, lxi]

Similarly, providers, who may have purchased a drug at a certain price, may also be restricted in their reimbursement and may either carry the drug at a loss or decide to no longer carry the drug. For pharmacists, a survey found that nearly 90 percent of independent pharmacies may not sell Medicare-negotiated products given reimbursement concerns.[lxii] In either of these situations, patients lose access to their medicines due to pricing policies, which already come as a challenge for rare disease patients. Unfortunately, legislation like the IRA, which was passed with the intent of reducing costs and improving access, is now having the opposite effect in practice.

Policy Recommendations

Federal and state policymakers should immediately act to undo the damage done to orphan drug development. Pricing policies, like the MFP and UPLs, negatively impact rare disease patients by disrupting patient access, limiting life expectancy, delay orphan drug indications, and limit orphan drug development.

Policymakers should consider alternatives to best support rare disease patients:

- Maintain incentives for rare disease research,
- Carve out all orphan drugs from pricing policies, and;
- Develop policies to enhance orphan drug access.

Maintain incentives for rare disease research

- **Increase the Orphan Drug Tax Credit to its original 50 percent of qualified R&D costs.** The Tax Cuts and Jobs Act's reduction of the value of the Orphan Drug Tax Credit from 50 percent to 25 percent of qualifying clinical trial costs represented a break from 40 years of legislative policy that encouraged the development of treatments for rare patients. This action exacerbated issues with the underlying value proposition for rare therapies and has since discouraged investor confidence in rare innovators as compared to their non-rare counterparts.[lxiii] To counteract the negative innovation trends which have followed this policy, Congress should ensure stability and protect advances made in rare disease research by increasing the Orphan Drug Tax Credit to its original 50 percent of qualified R&D costs.
- **Reauthorize the Rare Pediatric Disease (RPD) Priority Review Voucher (PRV) program.** Without Congressional action, the RPD PRV program expired in late December 2024. Congress recently provided a short-term programmatic extension through that date using a continuing budget resolution, but a program that has been integral to the development of rare therapies should not continue to be subject to temporary fixes. At this juncture, there is enough evidence of the program's benefit to orphan drug development that Congress should make the RPD PRV program permanent.[lxiv]

Maintain incentives for rare disease research, continued…

- **Expand direct federal funding and involvement in rare disease product research and development.** Legislators increased federal funding allotments for rare disease scientific priorities through the 21st Century Cures Act, and they can continue to make similar investments that further accelerate rare disease medical research and increase patient access to novel therapeutics in future legislation. Representatives Diane DeGette (D-CO) and Larry Bucshon (R-IN) are continuing their bipartisan collaboration on these issues within new Cures legislation, and other policymakers should support their efforts to increase federal investments in rare disease treatment development.[lxv] They can also work to strengthen regulatory pathways that allow rare disease products to reach patients more quickly, such as FDA's Accelerated Approval program.

Carve out all orphan drugs from pricing policies

- **Improve the Orphan Drug Exclusion to encompass all products designated solely to treat rare diseases.** Under the current structure of the Inflation Reduction Act's Orphan Drug Exclusion, innovators are disincentivized from seeking additional orphan designations and approvals for rare disease treatments. Thankfully, there is a bipartisan solution in Congress to address this unintended consequence of the Exclusion called the "ORPHAN Cures Act." Congress should move immediately to pass the ORPHAN Cures Act, which would ensure orphan drugs treating one or more rare diseases or conditions are excluded from Medicare drug price negotiations.
- **Encourage Prescription Drug Affordability Boards to exclude drugs solely focused on rare diseases from Upper Payment Limit procedures.** PDABs are state bodies tasked with controlling prescription drug costs through cost reviews, mandatory reporting, or the implementation of ceiling prices (known as upper payment limits) that cap the amount that stakeholders can be reimbursed for certain treatments. Several states have enacted PDABs with varying authorities to impact treatment prices to date, and a small portion of these states have already exempted orphan drugs from PDAB activities.[lxvi] However, these exemptions are not universal, and given the potential treatment access issues for rare disease patients created by PDAB action, it is imperative that all PDABs provide statutory protections for solely orphan products.

Develop policies to enhance orphan drug access

- **Bolster outcomes-based contracting.** Outcomes-based contracts make a certain percentage, or the entirety, of the payment for a treatment contingent on the degree of patient benefit. An approach that enables companies to negotiate a standard outcomes-based contract applied consistently across all payers could help solve uptake issues surrounding the commercialization of orphan drugs. This framework presents another opportunity to reward companies' orphan treatment innovation, while simultaneously increasing rare disease patients' access to new therapies.

About ADVI Health

ADVI is a commercial strategy and business development consulting firm that thrives on solving complicated problems in an evolving healthcare system. We are a specialized team of operators, policymakers, and clinicians with extensive experience delivering pragmatic, results-oriented approach. We deliver a comprehensive perspective by integrating business, policy, and science to find creative solutions through data, learned insight and compelling strategy to help make decisions across all segments of healthcare.

The firm represents a sophisticated client base of Fortune 500 life sciences and health care service companies as well as venture and private equity-backed companies in diagnostics, digital health, health IT, and health care services. The firm is at the forefront of health care delivery transformation, payment reform, public and private payer coverage, and healthcare merger and acquisition deal flow, within the US and abroad.

Thank you to Tyler Seville and Zack Friend for their contributions to this report.

Acknowledgements

ADVI Health thanks Alexion, AstraZeneca Rare Disease for supporting this report.

Original publication July 2025.

References

i. U.S. Food and Drug Administration. Rare Diseases at FDA. 2024, November 21. https://www.fda.gov/patients/rare-diseases-fda.

ii. Fermaglich, L.J., Miller, K.L. 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 J Rare Dis* 18, 163 (2023). https://doi.org/10.1186/s13023-023-02790-7.

iii. U.S. Government Accountability Office. Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial. 2021, October 18. https://www.gao.gov/products/gao-22-104235.

iv. EveryLife Foundation. The National Economic Burden of Rare Disease. 2021, February 25. https://everylifefoundation.org/burden-study/.

v. The Lewin Group. The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study. 2023, September. EveryLife Foundation https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf.

vi. EveryLife Foundation. The National Economic Burden of Rare Disease. 2021, February 25. https://everylifefoundation.org/burden-study/.

vii. Rees, C., Pica, N., Monuteaux, M., Bourgeois, F. Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis. PLOS Medicine, 16(11)(2019). https://pmc.ncbi.nlm.nih.gov/articles/PMC6871779/.

viii. Fogel, D.B. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemp Clin Trials Commun*. 2018, August 7. https://pmc.ncbi.nlm.nih.gov/articles/PMC6092479/.

ix. Health Capital Group. Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty. Rare Disease Company Coalition. 2023. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf.

x. Jayasundara, K., Hollis, A., Krahn, M. et al. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet J Rare Dis* 14, 12 (2019). https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0990-4.

xi. Health Capital Group. Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty. Rare Disease Company Coalition. 2023. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf.

xii. Global Genes. NEXT 2024: Rewriting the Rules. Global Genes. 2024. https://globalgenes.org/wp-content/uploads/Next-Report-2024.pdf.

xiii. 1) Orphan Drug Act (ODA) of 1983, 2) FDA Modernization Act (FDAMA) of 1997, 3) Best Pharmaceuticals for Children Act (BPCA) of 2002, 4) Rare Diseases Act of 2002, 5) Pediatric Research Equity Act (PREA) of 2003, 6) Food and Drug Administration Amendments Act (FDAAA) of 2007, 7) Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, 8) 21st Century Cures Act of 2016, 9) Advancing Hope Act of 2016, 10) FDA Reauthorization Act of 2017 (FDARA), 11) Right to Try Act of 2018.

xiv. EveryLife Foundation for Rare Diseases. Celebrating 40 years of the Orphan Drug Act (ODA). 2023, January 4. https://everylifefoundation.org/celebrating-40-years-of-the-orphan-drug-act-oda/.

xv. U.S. Food and Drug Administration. Rare Diseases at FDA. 2024, November 21. https://www.fda.gov/patients/rare-diseases-fda.

xvi. Rare Diseases Act of 2002, H.R. 4013, 107th. 2002, November 6. https://www.congress.gov/bill/107th-congress/house-bill/4013#:~:text=Shown%20Here:,for%20FY%202003%20through%202006.

References

xvii. Rare Disease Company Coalition. Impact of the Priority Review Voucher Program on Rare Pediatric Disease Drug Development. Rare Disease Company Coalition. 2024, May. https://www.rarecoalition.com/wp-content/uploads/Impact-of-the-Priority-Review-Voucher-Program-on-Rare-Pediatric-Disease-Drug-Development-1-1.pdf.

xviii. NORD. Senate Passes Landmark 21st Century Cures Act [Press release]. 2016, December 7. https://rarediseases.org/senate-passes-landmark-21st-century-cures-act/.

xix. Shaikh, M., Del Giudice, P. Kourouklis, D. Revisiting the Relationship Between Price Regulation and Pharmaceutical R&D Investment. *Appl Health Econ Health Policy* 19, 217–229 (2021). https://doi.org/10.1007/s40258-020-00601-9.

xx. Golec, J., Hegde, S., Vernon, J.A. Pharmaceutical R&D Spending and Threats of Price Regulation. *Journal of Financial and Quantitative Analysis.* 2010.

xxi. Golec, J., Vernon, J.A. Financial effects of pharmaceutical price regulation on R&D spending by EU versus US firms. *Pharmacoeconomics.* 28(8):615-28 (2010). https://pubmed.ncbi.nlm.nih.gov/20617857/.

xxii. Long, T., Ezell, S. The Hidden Toll of Drug Price Controls: Fewer New Treatments and Higher Medical Costs for the World. ITIF. 2023, July 17. https://itif.org/publications/2023/07/17/hidden-toll-of-drug-price-controls-fewer-new-treatments-higher-medical-costs-for-world/.

xxiii. Philipson, T., Durie, T. The Impact of HR 5376 on Biopharmaceutical Innovation and Patient Health. University of Chicago. 2021, November 29. https://bpb-us-w2.wpmucdn.com/voices.uchicago.edu/dist/d/3128/files/2021/08/Issue-Brief-Drug-Pricing-in-HR-5376-11.30.pdf.

xxiv. David, F., Belogolovsky, G. A Strategic Approach to Pharma R&D Portfolio Planning. PharmExec.com. 2019, April 23. https://www.pharmexec.com/view/strategic-approach-pharma-rd-portfolio-planning.

xxv. Schuhmacher, A., Gassmann, O., Hinder, M. Changing R&D models in research-based pharmaceutical companies. J Transl Med 14, 105 (2016). https://doi.org/10.1186/s12967-016-0838-4.

xxvi. Incubate Coalition. Life Science Investment Tracker. 2023. https://lifesciencetracker.com/.

xxvii. Philipson, T. The Deadly Side Effects of Drug Price Controls. The Wall Street Journal. 2023, April 5. https://www.wsj.com/articles/medicare-drug-price-controls-will-make-america-sicker-research-innovation-negotiations-private-insurers-b503b4ba.

xxviii. Health Capital Group. Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty. Rare Disease Company Coalition. 2023. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf.

xxix. Global Genes. NEXT 2024: Rewriting the Rules. Global Genes. 2024. https://globalgenes.org/wp-content/uploads/Next-Report-2024.pdf.

xxx. Health Capital Group. Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty. Rare Disease Company Coalition. 2023. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf.

xxxi. Aartsma-Rus, A., Dooms, M., Le Cam, Y. Orphan Medicine Incentives: How to Address the Unmet Needs of Rare Disease Patients by Optimizing the European Orphan Medicinal Product Landscape Guiding Principles and Policy Proposals by the European Expert Group for Orphan Drug Incentives. *Front Pharmacol*. 2021, December 16. https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.744532/full.

References

xxxii. Long, T., Ezell, S. The Hidden Toll of Drug Price Controls: Fewer New Treatments and Higher Medical Costs for the World. ITIF. 2023, July 17. https://itif.org/publications/2023/07/17/hidden-toll-of-drug-price-controls-fewer-new-treatments-higher-medical-costs-for-world/.

xxxiii. Crane, B. The Effect of Reference Pricing on Pharmaceutical Innovation. The Center for Strategic and International Studies. 2023, July 12. https://www.csis.org/blogs/perspectives-innovation/effect-reference-pricing-pharmaceutical-innovation.

xxxiv. Congressional Budget Office. Research and Development in the Pharmaceutical Industry. 2021, April. https://www.cbo.gov/publication/57126.

xxxv. O'Neil, D. A better fit? Biotech versus Big Pharma in orphan/rare disease drug research. *Expert Opinion on Orphan Drugs.* 2014, March 12. https://www.tandfonline.com/doi/pdf/10.1517/21678707.2014.900433.

xxxvi. Vital Transformation. The Historical Impact of Price Controls on the Biopharma Industry. 2022. https://vitaltransformation.com/2021/11/the-historical-impact-of-price-controls-on-the-biopharma-industry/.

xxxvii. Proudman, D., Desai, U., Gomes, D. A., Khomenko, M., Martin, S., Nellesen, D., Neumann, U., Grabowski, H. Public sector replacement of privately funded pharmaceutical R&D: cost and efficiency considerations. *Journal of medical economics*, 27(1), 1253–1266 (2024). https://doi.org/10.1080/13696998.2024.2405407.

xxxviii. Mingorance, A. Drivers of Orphan Drug Development. *ACS Med Chem Lett*. 2018, October 1. https://pmc.ncbi.nlm.nih.gov/articles/PMC6187403/.

xxxix. Miller, K. Orphan Drug Label Expansions: Analysis Of Subsequent Rare And Common Indication Approvals. *Health Affairs*, 43(1)(2024). https://doi.org/10.1377/hlthaff.2023.00219.

xl. Landscape Analysis: Investing in the Development of Rare Disease Treatments. Save Rare Treatments Task Force. 2024. https://www.saveraretreatments.org/wp-content/uploads/2024/09/Save-Rare-Treatments-Task-Force-Landscape-Analysis-on-Declining-Investment-in-Rare-Disease-Treatments.pdf.

xli. Incubate Coalition. Investors Warn: Biotech's Growth Stifled By Policy Missteps. 2025. https://www.incubatecoalition.org/post/survey-investors-warn-biotech-s-growth-stifled-by-policy-missteps.

xlii. Gassul, D., Bowen, H., Schulthess, D. IRA's Impact on the US Biopharma Ecosystem. VitalTransformation. 2023, May. https://vitaltransformation.com/wp-content/uploads/2023/10/VT-BIO_IRA_v14.pdf.

xliii. IQVIA. Orphan Drugs in the United States. 2020, December. https://rarediseases.org/wp-content/uploads/2021/03/orphan-drugs-in-the-united-states-NRD-2020.pdf.

xliv. Gassul, D., Bowen, H., Schulthess, D. IRA's Impact on the US Biopharma Ecosystem. VitalTransformation. 2023, May. https://vitaltransformation.com/wp-content/uploads/2023/10/VT-BIO_IRA_v14.pdf.

xlv. Landscape Analysis: Investing in the Development of Rare Disease Treatments. Save Rare Treatments Task Force. 2024. https://www.saveraretreatments.org/wp-content/uploads/2024/09/Save-Rare-Treatments-Task-Force-Landscape-Analysis-on-Declining-Investment-in-Rare-Disease-Treatments.pdf.

xlvi. Agency for Healthcare Research and Quality. Off-Label Drugs: What You Need to Know. 2015, September. https://www.ahrq.gov/patients-consumers/patient-involvement/offlabel-drug-usage.html.

xlvii. Van Norman, G.A. Off-Label Use vs Off-Label Marketing of Drugs: Part 1: Off-Label Use-Patient Harms and Prescriber Responsibilities. *JACC Basic Transl Sci.* Feb 27;8(2):224-233 (2023). doi: 10.1016/j.jacbts.2022.12.011. PMID: 36908673; PMCID: PMC9998554.

References

xlviii. Eguale, T., Buckeridge, D., Verma, A., Winslade, N., Benedetti, A., Hanley, J., Tamblyn, R. Association of Off-label Drug Use and Adverse Drug Events in an Adult Population, *JAMA Internal Medicine*, 176 (1) (2016). https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/ 2467782.

xlix. Congressional Research Services. Off-Label Use of Prescription Drugs. 2021, February 23. https://crsreports.congress.gov/product/pdf/R/R45792/3#:~:text=Unchecked%20off%2Dlabel%20prescribing%20may,FDA%20process%20to%20win%20approval.

l. Fung, A., Yue, X., Wigle, P.R., Guo, J.J. Off-label medication use in rare pediatric diseases in the United States. *Intractable Rare Dis Res*. 2021, November. https://pmc.ncbi.nlm.nih.gov/articles/PMC8630459/.

li. Van Norman, G.A. Off-Label Use vs Off-Label Marketing of Drugs: Part 1: Off-Label Use-Patient Harms and Prescriber Responsibilities. *JACC Basic Transl Sci*. 2023, February 27. https://www.sciencedirect.com/science/article/pii/S2452302X23000116?via%3Dihub.

lii. Philipson, T., Ling, Y., Chang, R., Di Cera, G., Onogi, K., Vakil, A., Kataria, A. The Potentially Larger Than Predicted Impact of the IRA on Small Molecule R&D and Patient Health. The University of Chicago. 2024, June 25. https://bpb-us-w2.wpmucdn.com/voices.uchicago.edu/dist/d/3128/files/2024/06/Small-Molecule-Paper-20240625.pdf.

liii. Philipson, T., Ling, Y., Chang, R., Di Cera, G., Onogi, K., Vakil, A., Kataria, A. The Potentially Larger Than Predicted Impact of the IRA on Small Molecule R&D and Patient Health. The University of Chicago. 2024, June 25. https://bpb-us-w2.wpmucdn.com/voices.uchicago.edu/dist/d/3128/files/2024/06/Small-Molecule-Paper-20240625.pdf.

liv. Moreno, G., Van Eijndhoven, E., Benner, J., Sullivan, J. The Long-Term Impact of Price Controls in Medicare Part D. *Forum Health Econ Policy*. 2017, January 20. https://pubmed.ncbi.nlm.nih.gov/31419906/.

lv. Chambers, J.D., Silver, M.C., Berklein, F.C. et al. Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs. *J Gen Intern Med* 35, 2629–2636 (2020). https://link.springer.com/article/10.1007/s11606-020-05805-2.

lvi. National Organization for Rare Disorders. Inequities in the Rare Disease Community. 2024, June. https://rarediseases.org/wp-content/uploads/2024/08/RDDC-Survey-Report.pdf.

lvii. Chambers, J.D., Silver, M.C., Berklein, F.C. et al. Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs. *J Gen Intern Med* 35, 2629–2636 (2020). https://doi.org/10.1007/s11606-020-05805-2.

lviii. Delivering Hope for Rare Diseases [Pamphlet]. National Center for Advancing Translational Services. 2023. https://ncats.nih.gov/sites/default/files/NCATS_RareDiseasesFactSheet.pdf.

lix. Jarosławski, S., Azaiez, C., Korchagina, D., Toumi, M. Quantifying the persisting orphan-drug shortage public health crisis in the United States. *J Mark Access Health Policy*. 2016, December 23. https://pmc.ncbi.nlm.nih.gov/articles/PMC5560412/.

lx. Yehia, F., Segal, J., Anderson, G. Predictors of Orphan Drug Coverage Restrictions in Medicare Part D. *The American Journal of Managed Care*. 2020, September. https://www.ajmc.com/view/predictors-of-orphan-drug-coverage-restrictions-in-medicare-part-d.

lxi. Magnolia Market Access. IRA Payer Insights Report: Chartbook. 2024, July 31. https://www.magnoliamarketaccess.com/wp-content/uploads/MMA_IRA-Payer-Insights-Survey-4.0_Chartbook_2024.07.31.pdf.

References

lxii. National Community Pharmacists Association. Report for Fall Survey of Independent Pharmacy Owners/Managers. 2024, October 11. https://ncpa.org/sites/default/files/2024-10/NCPA-FallSurvey2024-ExecSummary.pdf.

lxiii. Health Capital Group. Rare Disease Companies in the Public Markets: Challenging Performance Against a Backdrop of Policy Uncertainty. Rare Disease Company Coalition. 2023. https://www.rarecoalition.com/wp-content/uploads/Health-Capital-Group-White-Paper-FINAL-1.pdf.

lxiv. Rare Disease Company Coalition. Impact of the Priority Review Voucher Program on Rare Pediatric Disease Drug Development. Rare Disease Company Coalition. May, 2024. https://www.rarecoalition.com/wp-content/uploads/Impact-of-the-Priority-Review-Voucher-Program-on-Rare-Pediatric-Disease-Drug-Development-1-1.pdf.

lxv. Office of Representative Diana Degette. Reps. DeGette, Bucshon Seek Stakeholder Input on Next-Generation Cures Bill [Press release]. 2024, June 6. https://degette.house.gov/media-center/press-releases/reps-degette-bucshon-seek-stakeholder-input-next-generation-cures-bill.

lxvi. Currently, 8 states (Colorado, Maine, Maryland, Minnesota, New Hampshire, New Jersey, Oregon, and Washington) have enacted prescription drug affordability boards (PDABs), while Massachusetts and New York also have drug review boards with the authority to identify high cost medicines and require companies to submit data to justify their price, or subsequently face additional administrative penalties or supplemental rebate requirements.