



**The Next Generation of
Rare Disease Drug Policy:
Ensuring Both Innovation and Affordability**

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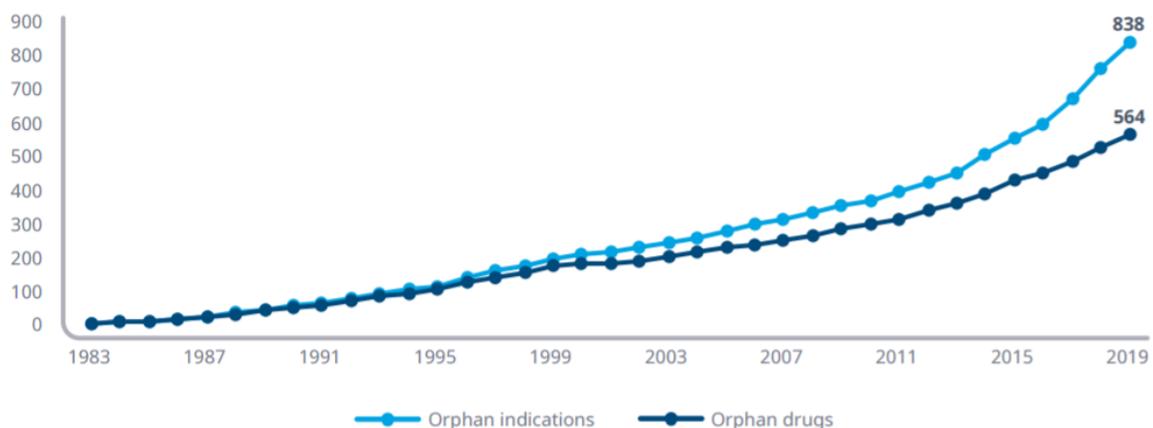
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Introduction

The United States defines a rare disease as a condition affecting fewer than 200,000 people in the country or one in which “there is no reasonable expectation” of recovering research and development costs.¹ Examples of rare diseases include genetically-linked cancers, cystic fibrosis, and debilitating pediatric conditions like Gaucher disease and spinal muscular atrophy. Despite the relatively small patient populations for each individual rare disease, there are an estimated 7,000 known rare diseases, impacting 1 out of every 10 Americans.² When available, treatments for rare diseases have been shown to provide larger health gains on average than drugs for more common conditions. Unfortunately, more than 90% of rare diseases still lack any disease-specific treatment approved by the Food and Drug Administration (FDA), and the unmet need for patients and families across many rare disease areas remains extremely high.^{3,4}

In 1983, Congress passed the Orphan Drug Act (ODA), which created financial incentives to encourage companies to develop new drugs for rare diseases. In the 1970s, prior to the ODA, there were only 10 drugs approved to treat rare diseases.⁵ Policymakers were concerned that there was no viable business model for rare disease treatments due to the inherent risk associated with drug development and the very small patient populations across which rare disease treatments could derive revenue.⁶ Henry Waxman, the author of the ODA, believed that legislation was needed to correct the structural imbalance in the risk and reward for rare disease treatments.⁷ Among other incentives, the ODA provides tax credits to offset some of manufacturers' research and development costs, and eligible products receive an extended seven-year market exclusivity.⁸

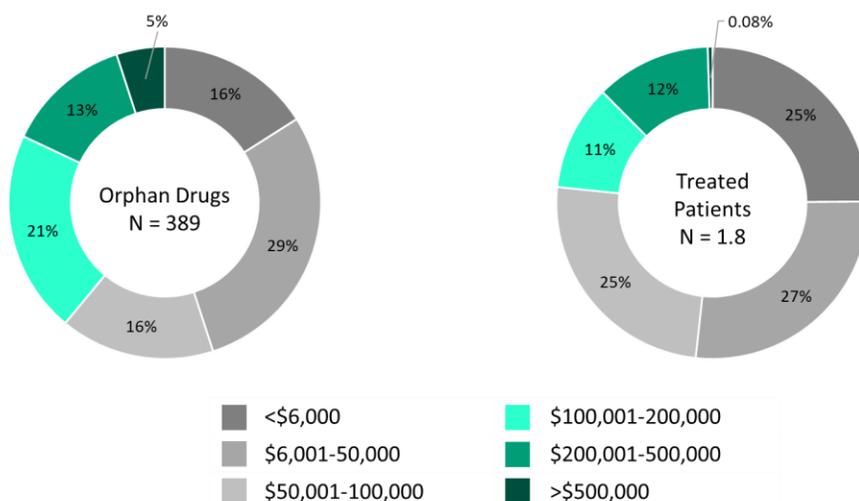
Figure 1: Cumulative Number of Approved Orphan Indications and Distinct Drugs with at Least One Orphan Indication by Year of Marketing Approval⁹



Since its passage, the ODA has been successful at increasing the number of products approved to treat rare diseases, with over 800 orphan drug indications approved between 1983 and 2019 (Figure 1).¹⁰ Many approved orphan drugs have contributed to improved treatment in the oncology space, with 42% of the 491 orphan drugs approved over the past ten years targeting rare cancers.¹¹ This progress has been spurred by advances in cell and gene therapies, among other scientific discoveries, that have revolutionized care for many rare conditions. The patient community has contributed to this success and has demonstrated its ability to spur investment, inform research, and influence policymakers at all levels.¹² Today, many new biotech companies launch with a singular focus on developing treatments for patients with orphan conditions. The ODA has played a critical role in this progress, but there remains a substantial unmet need for new treatments to address serious rare diseases affecting millions of Americans and others worldwide.

This unmet need is an enduring part of the orphan disease landscape, but it is now shadowed by a problem not foreseen by the authors of the ODA. The rapid growth in approved rare disease treatments in recent years has created concerns about the pricing of orphan drugs and their cumulative affordability to the health system. In 2019, the average annual cost of an orphan treatment per treated patient was \$32,000, with treatments ranging from \$6,000 to \$500,000 per year (Figure 2).¹³ Internal payer data suggest a growing number of patients with treatments whose cost exceeds \$1 million per year. Most orphan drugs have high list prices, with 39% of orphan drugs costing more than \$100,000 annually,¹⁴ and gene and cell therapies costing hundreds of thousands of dollars or more.¹⁵ For a drug priced at \$100,000 per year, a treated patient population of only 10,000 individuals produces revenues of \$1 billion per year – an orphan “blockbuster.”

Figure 2. Orphan Drug and Patients Treated by Drugs with an Orphan Indication in 2019 by Annual Drug Cost Bands¹⁶



Therefore, today, as the proportion of new FDA approvals gaining orphan drug designation crests above 50% each year, some people no longer see the primary challenge related to orphan drugs as that of creating a viable business model. They see a growing challenge in absorbing the cost of a growing wave of high-priced orphan drugs that may threaten sustainable insurance premium levels and throw up greater barriers to access for individual patients.¹⁷ This affordability challenge is magnified by concerns regarding the quality of the evidence being generated to support FDA approval of orphan drugs. While high drug prices are a concern across the entire spectrum of therapies, orphan products are commonly approved with more limited evidence on relative safety and effectiveness due to their reliance on non-randomized trials using short-term surrogate outcomes.

Premium pricing for orphan drugs has persisted despite other tailwinds that have helped facilitate orphan drug development—including scientific advances, new FDA approval pathways, and limited competition. Scientific advances allow for more precise targeting of treatments to underlying disease mechanisms, producing higher success rates for orphan drug applications, lowering the risk to life science companies and investors.¹⁸ Second, the creation of the accelerated approval pathway at the FDA has simplified evidence requirements for many rare disease products that qualify for this approval pathway. Lastly, insufficient potential profits and anticipated market size may not attract generic competitors to enter the market.¹⁹ Whether premium pricing at current levels is still required as an incentive to drive orphan drug development is hotly contested, but the data on orphan drug approvals suggests that the combination of scientific advances, regulatory flexibility, market conditions, and premium pricing power has made rare disease treatments an attractive market for investors and life sciences companies.

And so, the landscape for orphan drugs includes signals that innovation is flourishing but not yet near the level to meet the unmet need; that the infrastructure of incentives created by the ODA has been critical in advancing innovation, but now may be overshadowed by other factors driving investment and innovation toward rare diseases; and that the welcome success of a growing wave of orphan drugs has not led to lower prices and therefore is creating financial strain that threatens to undermine access to these treatments and the affordability of health insurance for all patients. All participants in the health care system, including patients, innovators, and payers, would agree that the goal should be to build a policy and practice infrastructure that drives innovation within a platform that is affordable to patients and the health system. Do we have the right balance in policies and practice to achieve this goal?

The purpose of this paper is to examine potential reforms to current policies and practices related to orphan drug development, pricing, and coverage. As suggested above, any reform to these policies and practices carries the risk of tilting the ecosystem too far in one direction or another. This paper will explore potential risks as well as advantages of reform options. The goal will be to

provide policymakers and others with a deeper understanding of the options to ensure innovation's future ability to successfully address the needs of patients and families with rare diseases. That success will require new insights and new action to make innovation and affordability inseparable outcomes of our health system.

Structure of This Paper

Evaluating the complexities around rare disease development, evidence generation, and payment requires a firm understanding of the ODA, including its history and qualifications for use, as well as the scientific considerations surrounding FDA approval of orphan drugs—specifically accelerated approval and the use of surrogate endpoints. This information is presented in the Background section.

We then examine the orphan drug market landscape and existing challenges, which we have organized into three elements: scientific discovery, evidence generation, and financial impact. Given limited resources of time and money for pharmaceutical innovation, we explore the current market incentives for drug development across competing priorities, including ultra-rare, rare, and population health treatments. We explore how advances such as gene sequencing and gene editing technology have fueled a new understanding of rare diseases. We then look at why generating evidence for rare diseases can be more challenging than other diseases, due to factors such as trial size and heterogeneous patient populations. Next, we explore the reason why investment in rare disease drugs has increased over recent years and how the ODA and other incentives may or may not drive manufacturer decision making.

To conclude, we examine potential policy reforms in the final section of this paper, recognizing that it is crucial to consider the trade-offs that would come with changes to the incentives and other elements of the orphan drug ecosystem that currently exist.

Methods

This paper relies on information, data, and perspectives gathered from a targeted literature review, as well as interviews with health plans and drug manufacturers from the Policy Leadership Forum, rare disease patient groups, and investors.

The targeted literature review included keyword and hand searches for peer-reviewed and gray literature articles focusing on the U.S. policy landscape surrounding rare and ultra-rare disease drugs.

We used a structured discussion guide to collect input during interviews with 13 experts from large and small pharmaceutical manufacturers, investors, health plans, pharmacy benefit managers (PBMs), and patient groups about their views on the challenges around rare and ultra-rare disease drug innovation, assessment, payment, treatment, and potential policy solutions.

Based on the primary and secondary research, the ICER research team developed a set of potential policy solutions that respond to identified themes and challenges. Representatives from patient organizations joined senior policy leaders from 29 payer and life science companies at a two-day meeting in December 2021 to deliberate on the potential benefits and the risks presented by these policy reforms and provide suggestions for revisions to a draft version of this paper. The participants in this meeting are shown in Appendix A. None of these participants or their organizations should be considered as having approved of any element of this paper.

Background

There are an estimated 7,000 rare conditions, most of which have no disease-modifying treatment options.²⁰ Because many of these conditions are relatively unknown to clinicians and may have a wide variety of presentations and courses, many patients experience long diagnostic odysseys that may conclude with few treatment options or with barriers accessing treatments. According to the National Organization for Rare Disorders (NORD), in 2016, only 36% of people with a rare disease were diagnosed within the first year, while 28% say it took seven or more years to accurately diagnose their condition.²¹ The mean time to diagnosis is about six years, with many patients receiving several incorrect diagnoses throughout the process.²²

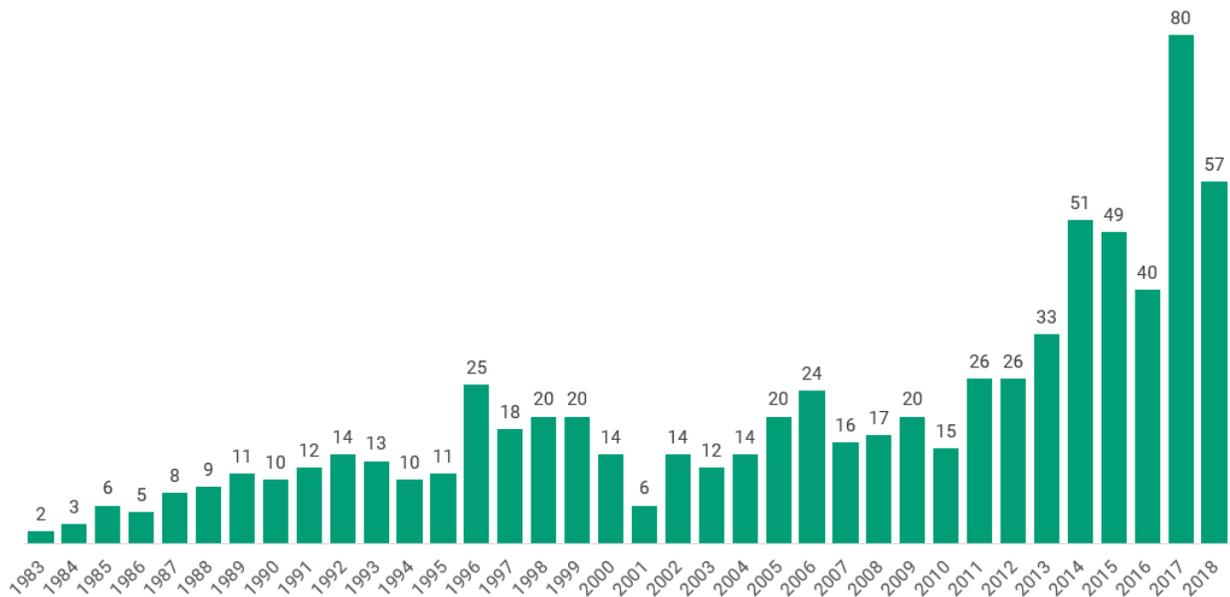
Many rare diseases are life-threatening or life-limiting, and patients and caregivers face unique challenges. Individuals with rare diseases face significant economic burdens due to higher medical needs, often requiring the assistance of a caregiver, and having to miss work. In 2019, it was estimated that the total economic burden of 379 rare diseases was \$966 billion, including \$418 billion in direct medical costs and \$548 billion in indirect and non-medical costs.²³ It is an unchallenged fact that increased drug development for rare diseases has provided patients, and often their families, with more opportunities to live their best lives. Of drugs approved between 1999 and 2015, seven of the top ten drug indications with the largest survival and quality of life gains combined were orphan drugs.²⁴ One estimate suggests that from 1999-2007, the potential years of life lost to rare diseases before age 65 declined at an average annual rate of 3.3%, whereas in the absence of new drug approvals an increase of 0.9% per year would have occurred.²⁵

While there has been an increase in the number of drugs that have come to market to treat rare diseases, some health plans have restricted access to these treatments. As of 2018, an analysis of private health plan coverage decisions for specialty products found that plans excluded coverage for orphan products only 1% of the time, but coverage for all orphan drugs was restricted in 29% of coverage policies, ranging from 11% to 65% across plans.²⁶ However, coverage for orphan products was less restrictive than for non-orphan specialty drugs, which faced coverage restrictions 41% of the time and exclusions 6% of the time. From diagnosis to treatment availability, to plan coverage, people with rare diseases face many challenges to gaining effective, timely, and affordable treatment for their condition.

Scientific Developments Related to Orphan Drug Development

In the years since the ODA passed, orphan drug development has been buoyed not only by incentives within the inaugural legislation, but by additional scientific and policy developments that directly or indirectly reduce the costs of discovery while increasing expected profits for rare disease products. One significant scientific factor that has enabled more orphan products is the completion of the Human Genome Project in 2003. This fueled a new understanding of the genetic and biological underpinnings of rare diseases, enabling scientists to target therapies more precisely for patient populations based on new biomarkers. It is estimated that >70% of rare diseases are genetic,²⁷ and as of 2020, a third of all cell and gene therapies in development are for rare diseases.²⁸ This science makes it easier to focus on and develop products for many rare diseases, where the mechanisms of action are now better understood, and the patient population is less heterogeneous than in disease areas with larger patient populations. Figure 3 shows how annual approvals of orphan indications have increased over time.

Figure 3: Number of Orphan Indications Approved in the United States, 1983 - 2018²⁹



Federal Policies Related to Orphan Drug Development

Because few individuals are affected by any single rare disease, pharmaceutical companies historically had a disincentive to invest in orphan drugs. In June of 1980, Congress held a hearing on the issue, remembered later by the primary author of the ODA, Henry Waxman (D-CA):

It was as if someone had pulled back a curtain to reveal an entire segment of society that no one knew was there. Gathered together in a congressional hearing room before the national media were human beings with diseases so disabling or disfiguring that they never came out in public. – Henry Waxman, The Orphan Drug Act³⁰

Lawmakers wanted to understand the full extent of the problem. Waxman went on to explain that in addition to serving markets too small to make desirable targets, many orphan drugs were not patentable or their patents had expired, thus offering much smaller profit potential. Some lawmakers made compelling arguments that the NIH should develop treatments for rare diseases instead of industry. Waxman's analysis instead concluded that the NIH had no experience developing drugs for the commercial market and that the expertise and resources lay in the private sector.³¹

Waxman led the effort to design the ODA in order to create an incentive structure adequate to support the development of drugs for rare diseases. It aimed to establish a new balance in the market ecosystem by reducing the financial risk associated with industry-sponsored rare drug development and increasing potential on-market revenues through extended exclusivity.³² As Waxman stated in 1986, "The [ODA] is meant to demonstrate that society puts a higher value on helping victims of rare disease than does the pharmaceutical marketplace".³³

While the initial ODA did not include a specific prevalence threshold by which to define a condition as a rare disease, the law was amended in 1984 to include a threshold of fewer than 200,000 people in the U.S. (equivalent to 6 in 10,000 Americans at the time it passed).³⁴ This threshold was set to align with the estimated prevalence of narcolepsy and multiple sclerosis and has not been updated since.³⁵ The 200,000 patient threshold that the U.S. set for orphan status is not indexed to increase with U.S. population growth over time, meaning that the effective incidence rate for orphan status continues to decrease.

A recent survey of definitions of rare diseases from over 1,100 organizations worldwide found significant variation, ranging from prevalence thresholds of 5 to 76 cases per 100,000 population.³⁶ Variation was correlated with stakeholder type, with patient groups and payers employing the most liberal and restrictive definitions, respectively. The U.S. regulatory threshold of 200,000 people translates into a threshold of approximately 64 per 100,000, higher than the global average of 40 cases per 100,000. The European Union's definition, which affects public health actions and regulatory submissions to the European Medicines Agency (EMA), is 50 per 100,000.

The choice of a prevalence threshold is a critical element of policies to focus incentives on rare diseases. Whatever rationale is used to justify any special incentives or market treatment of drugs for rare diseases, the threshold selected should be viewed as an arbitrary dividing line intended to balance the benefits of targeting more favorable regulatory and market policies to certain drugs with the risk that these incentives are spread too broadly, inducing “too much” investment in rare disease treatments versus treatments for other conditions, ultimately creating an inefficient market that leads to higher costs and less health benefits for the nation. Below, we describe the current added incentives provided for all rare disease drugs in the U.S. We then discuss potential advantages and disadvantages of limiting these incentives, including the option of limiting or removing them for some treatments while increasing them for a narrower set of treatments for “ultra-rare” conditions.

Benefits Provided Through the Orphan Drug Act of 1983. The ODA confers several important benefits on products approved with an orphan indication, including assistance to manufacturers developing drugs for rare diseases. Congress and the FDA have built on the ODA’s original provisions to establish additional incentives and programs favoring orphan drug development. Table 1 below provides an overview of the benefits provided by orphan drug designation. Each benefit is further described, below.

Table 1: Policies that Support Orphan Drugs

Policies/Programs	
Longer market exclusivity	7 years of market exclusivity for approved orphan indications
Tax credits for expenditures incurred in conducting clinical trials	25% federal tax credit for expenditures incurred in conducting clinical research within the U.S.
User fee waiver	Waiver of Prescription Drug User Fee Act (PDUFA) fees
Research grants	Ability to compete for research grants from the Office of Orphan Products Development (OOPD) to support clinical studies for orphan drugs

- Market Exclusivity:** Seven years of market exclusivity to sponsors of approved orphan indications. The market exclusivity in the U.S. is typically five years for a new chemical entity. ODA market exclusivity begins on the day of FDA approval of an orphan indication and differs from patents that usually start early in the development process. The ODA exclusivity allows manufacturers a guaranteed period without head-to-head generic competition for the indication, though it does not prevent generic drugs from launching for other non-orphan indications of the product and thereafter being used off-label to compete with the brand drug.

- Tax Credits:** Developers of orphan products receive a 25% federal tax credit for expenditures associated with “qualified clinical testing expenses” for orphan drugs. Tax credits may be applied to the prior tax year or up to 20 years of future taxes. Because companies must be profitable to owe corporate income taxes, early-stage companies that do not yet have tax liability (e.g., those with no on-market products) can “bank” their tax credits to apply in future years. Prior to 2017, the federal tax credit was 50% of the drug’s clinical trial costs, but the Tax Cut and Jobs Act (TCJA) of 2017 reduced the tax credit to 25%.³⁷ This cut was estimated to reduce the average per-product value of the tax credit by \$25 million.³⁸ Additionally, companies may also be eligible for the standard Research and Development (R&D) tax credit for qualified research expenses (QRE), which typically results in a tax credit of 10% of QRE. Since the potential savings are greater for the orphan drug tax credit, a company with an orphan drug designated indication would likely pursue that over the R&D credit.³⁹
- User Fee Waiver:** Waiver of Prescription Drug User Fee Act (PDUFA) fees unless the application includes an indication for other than a rare disease or condition, even if the drug has a previous indication for a rare disease or condition. If the application requires clinical data, the application and program fee is about \$3.2 million. For applications that don’t require clinical data, the application fee is about \$1.8 million.⁴⁰
- Research Grants:** Ability to compete for research grants from the Office of Orphan Products Development (OOPD) to support clinical trials and natural history studies for orphan drugs.

Exemption From 340B Drug Pricing to Certain Providers. The 340B program requires pharmaceutical manufacturers participating in Medicaid to sell outpatient drugs at discounted prices to qualifying health care organizations—primarily those that serve many uninsured and low-income patients. The maximum price (ceiling price) must be no more than the best price offered to State Medicaid programs, which is at least the wholesale acquisition cost minus the applicable rebate percentage (23.1 percent discount for brand-name drugs).⁴¹ The Affordable Care Act (ACA) expanded eligibility for 340B discounts to freestanding hospitals, critical access hospitals, rural referral centers, and sole community hospitals. For these additional covered entities, manufacturers are not required to provide 340B discounts for products with orphan designations, regardless of whether or not the products are prescribed to treat a non-orphan disease.⁴²

Clarifying the 340B Orphan Drug Exemption

The ACA added several new categories of covered entities to the 340B program (free-standing cancer hospitals, critical access hospitals, rural referral centers, and sole community hospitals) and was later amended by the Health Care and Education Reconciliation Act (HCERA) to exclude these newly covered entities from accessing “a drug designated... for a rare disease or condition” at a 340B discounted price. This exclusion does not pertain to pre-existing 340B covered entities.

In July 2014, the Health Resources and Services Administration (HRSA) issued an interpretive rule claiming that the 340B exclusion applied only to the orphan indication and that manufacturers were required to provide 340B discounts when a drug with an orphan designation was used for other, non-orphan indications. HRSA claimed that “interpreting the statutory language to exclude all indications for a drug that has an orphan drug designation would be contrary to the Congressional intent of section 340B(e) to balance the interests of orphan drug development and the expansion of the 340B Program to new entities.”⁴³

This HRSA rule was challenged in U.S. District Court by the Pharmaceutical Research and Manufacturers of America (PhRMA) and was overturned on October 14, 2015.⁴⁴ The court found that the 340B statute included in HCERA unambiguously applies to all drugs carrying an orphan designation, regardless of whether the drug is used for an indication other than the rare condition or disease for which the drug was designated.⁴⁵ As such, manufacturers have the option, but are not required, to offer 340B discounts for drugs carrying an orphan designation to the covered entities included in the ACA.

In February 2021, Representative David McKinley (R-WV) and Peter Welch (D-VT) introduced legislation to address what they refer to as the “Orphan Drug loophole”. The Closing Loopholes for Orphan Drugs Act seeks to close this “loophole” by limiting the orphan drug exclusion to only apply in instances where the drug is used for the rare condition or disease for which it was designated.⁴⁶ The bill was referred to the House subcommittee on Health.⁴⁷

FDA Accelerated Approval. In addition to the explicit financial benefits granted to orphan products, development costs for many products have decreased as a result of the FDA accelerated approval process. In 1992, the FDA instituted an accelerated approval pathway to allow for faster approval of drugs that treat serious conditions and fill an unmet medical need.⁴⁸ While not specific to orphan drugs, given the frequent linkage of biomarkers to defined orphan diseases, and the lack of available treatments for many rare conditions, orphan drugs are more likely to qualify for the accelerated approval pathway. Since the introduction of the accelerated approval pathway, about 1 in 7 orphan indications has received accelerated approval.⁴⁹ And, since the introduction of the original accelerated pathway nearly three decades ago, 41.9% of all accelerated approvals have been for orphan indications.⁵⁰

Accelerated approval is conferred based on surrogate endpoints, rather than clinical endpoints, reducing the overall length and expense of clinical trials needed for regulatory approval.⁵¹ Surrogate endpoints are biomarkers that are “reasonably likely” to predict a clinical benefit of a drug. The

fundamental assumption of the accelerated approval pathway is that properly selected surrogate endpoints can predict improvement in health outcomes that are clinically relevant and matter to patients. The advantage of surrogate endpoints is that they can be measured over a shorter timeframe in less expensive or smaller studies.⁵² As noted, while accelerated approval is an option for some non-orphan products, orphan drugs are more likely to qualify and therefore benefit from these efficiencies.

Some stakeholders have expressed concern about the level of uncertainty associated with accelerated approval. Many have also expressed concerns about delays in companies completing post-market, confirmatory trials of clinical outcomes. For more information and proposed policy reforms to strengthen the accelerated approval pathway, please see the ICER paper, [“Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation and Costs”](#).

When a drug receives initial approval via the accelerated approval pathway, the FDA requires manufacturers to complete post-marketing studies to generate confirmatory evidence before receiving full approval for the drug. One analysis found that results from confirmatory trials for over half of indications granted accelerated approval between 2009 and 2013 were not available after a median of five years of follow-up.⁵³ Accountability for disclosing the results of studies, either in peer reviewed journals or on clinicaltrials.gov, also appears to be underenforced.⁵⁴ Serious concerns about these issues and other areas of lax oversight were documented in a 2009 U.S. Government Accountability Office (GAO) report criticizing the FDA for failing to ensure that treatment effects estimated through surrogate endpoints are eventually verified.⁵⁵ The FDA can fine companies or withdraw approval to penalize non-compliance with confirmatory trial requirements, but the agency rarely deploys these measures. Additionally, the FDA has been lenient in setting evidence development timelines for confirmatory trial commitments. This creates a financial incentive for manufacturers to place a low priority on obtaining confirmatory evidence in a timely manner, particularly for treatments that have few, if any, competitors. While not unique to orphan drugs, this issue is important given the large number of orphan drugs that are approved under the accelerated approval pathway (106 orphan indications since the introduction of the accelerated approval pathway in 1992).⁵⁶

Proposals in the *Build Back Better Act* to Modify the ODA

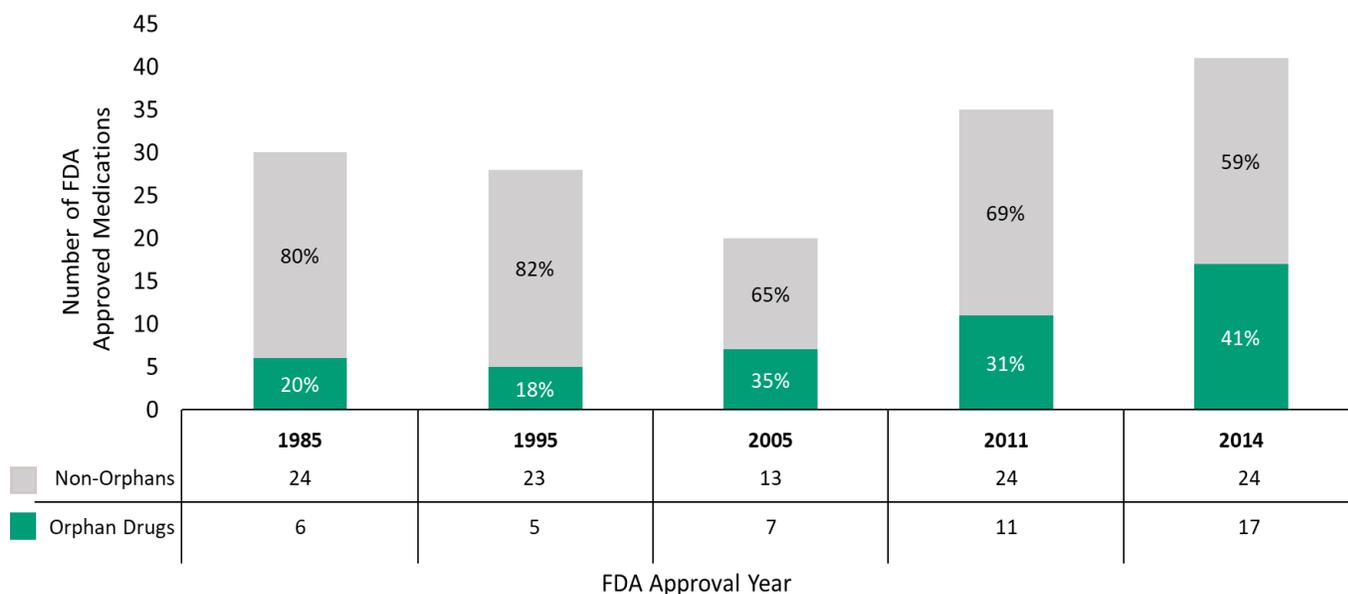
The reconciliation bill (aka the “Build Back Better” Act) debated in Congress in the Fall of 2021 considered policy changes that would impact orphan drugs. The draft legislation proposed limiting the 25% ODA tax credit for clinical testing expenses to only the first use or indication for an orphan drug to prevent companies from stacking up multiple tax credits on a single product. The Joint Tax Committee estimated that the policy would reduce manufacturer credits by \$2.7 billion over the next 10 years.⁵⁷ Experts argued that the change would not impact drug development because manufacturers would still generate significant revenue by securing additional indications for orphan products.⁵⁸ Patients and providers disagreed, suggesting the change would have a devastating impact on orphan drug development. They also maintain that adding indications to a drug’s label ensures that the drug is safe and effective for them, and is thus critical.⁵⁹

The proposed legislation would also have excluded drugs with only one orphan indication from Medicare price negotiation. Another way that this legislation sought to create special protections for orphan drugs was to exclude from negotiated pricing drugs whose total Medicare spending is less than \$200 million.⁶⁰

Trends in Orphan Drug Approvals, Pricing, and Coverage

The regulatory changes and scientific advancements described above have combined to produce a dramatic increase in the number of orphan drugs in the market. Prior to passage of the ODA, only 38 drugs had been approved in the entire history of the FDA to treat a rare disease.⁶¹ Figure 4 shows the increase in both the number and percent of orphan drugs in the past two decades. Since the ODA passed, 599 orphan products have been approved by the FDA, as of mid-2020.⁶² Half of all orphan drugs approved in the U.S. are first in their class, which is a rate much higher than non-orphan drugs.⁶³ Clearly, the incentives for drug development created by the regulatory landscape, scientific advances, and market pricing expectations have succeeded at bringing more drugs to market to the benefit of patients who need them.

Figure 4. Percent of Novel New Orphan and Non-Orphan Drugs Approved by FDA⁶⁴



Evolution of Disease Targeting. One concern about the ODA is that with scientific advancements in personalized medicine, more products will qualify for orphan status over time, worsening affordability concerns. Particularly in oncology, these advances have naturally begun to move treatments from single, broad indications (e.g., melanoma or non-small cell lung cancer) to narrower, genetically-specified subpopulations (e.g., BRAF V600 mutated melanoma, or anaplastic lymphoma kinase-positive non-small cell lung cancer). From 2009 to 2015, 16% of orphan drug approvals were based on biomarker-defined subsets of diseases.⁶⁵

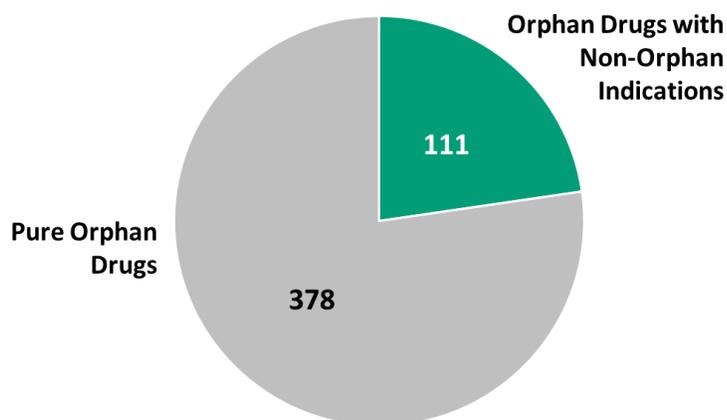
[T]he convergence of [the organ and gene models of cancer detection] means that almost any cancer medication can be maneuvered into an orphan disease category. For example, the proto-oncogene HER2 is most commonly associated with breast cancer. However, HER2 can also be found in glioblastomas, non-small cell lung cancer, gastric tumors, adenoid cystic carcinomas of the parotid gland, pancreatic cancer, and ovarian cancer. Each one of these organ-based cancer types can be further substratified by classifying them into HER2+ and HER2- cancers.⁶⁶

Increasingly as drug development focuses on these subdivisions of more common conditions—a practice sometimes known as salami-slicing—more drugs are likely to qualify for orphan indications.⁶⁷ While some industry critics have characterized salami-slicing as an intentional strategy to exploit ODA benefits, others point out that this evolution is the natural outcome of scientific advancement in treating biomarker-driven and genetically-linked conditions. Further, FDA

regulations ensure orphan approvals and exclusivity are only granted for distinct diseases. Over time, given the rise of narrowly-focused genetically linked diseases, the FDA may need to revisit how it defines distinct diseases and their impact on orphan drug status, a question also related to the prevalence threshold for designation as a “rare” or “ultra-rare” disease.

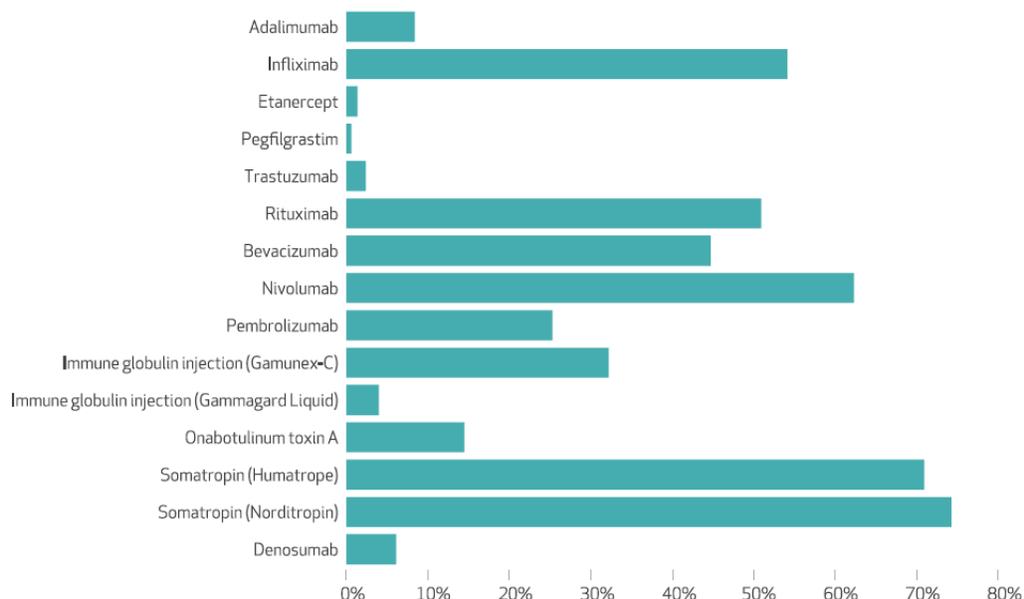
Partial Orphan Products. Many orphan products also secure FDA approval for non-orphan indications, products sometimes referred to as “partial orphans.” As of 2018, 23% of approved orphan drugs also had non-orphan indications (Figure 6).⁶⁸ While ODA exclusivity benefits apply only to orphan indications, once a product receives approval for an expanded indication, manufacturers almost always maintain the initial high “orphan-level” pricing while expanding their product sales and revenue.⁶⁹

Figure 6. Approved Orphan Drugs before January 1, 2018⁷⁰



Partial orphans are particularly common among drugs with the highest overall revenue. In 2018, five of the six top selling drugs in the U.S. were partial orphan drugs, and a recent OIG report found that a majority of the highest-expenditure drugs in Medicare have been granted at least one orphan designation.^{71, 72} Figure 7 below shows the percent of spending on the orphan indications of partial orphan drugs with high U.S. spending in 2018. For most of these drugs less than 50% of expenditures were for their orphan indications. As one extreme example, pegfilgrastim (Neulasta®) had the fourth highest spend among partial orphan drugs currently on the market, but only 0.6% of this amount was for its orphan indication of acute radiation syndrome.⁷³

Figure 7. Percent of Spending on Orphan Indications for 15 Drugs with Both Orphan and Non-Orphan Indications, 2018⁷⁴



A recent drug pricing investigation conducted by the House Committee on Oversight and Reform found that Mallinckrodt leveraged its orphan drug designation for Acthar as a justification for the drug’s high price and then aggressively expanded sales to non-orphan indications at the same price, with the specific objective of bringing in “top-level shareholder returns.”⁷⁵ The U.S. House and Senate tried to address concerns about the growth in partial orphans in 1990 by passing legislation that would have ended market exclusivity once an orphan drug was used by more than 200,000 people, arguing that the drug no longer qualifies for the government-sponsored benefits under the ODA. President George Bush pocket vetoed this amendment to the ODA for fear of disrupting the incentives for pharmaceutical companies to invest in rare diseases.⁷⁶

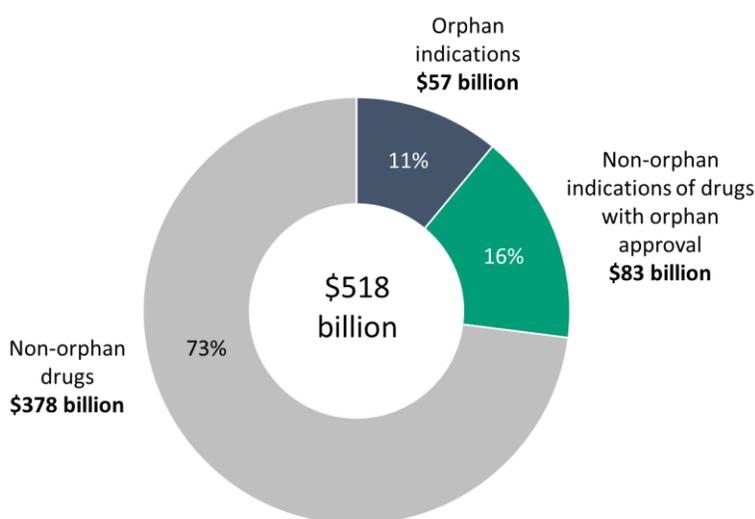
Competition Within Orphan Drug Classes. For a variety of reasons, many orphan drugs have natural monopolies with few or no brand-name competitors. Research has also shown that orphan drugs are significantly less likely to have at least one generic approval when compared to non-orphan drugs.⁷⁷ Even after the ODA exclusivity period ends, orphan drugs tend to face a lower threat of generic competition since the barrier to entry is high and potential returns are low.⁷⁸ In addition, barriers in the U.S. to rapid development and uptake of biosimilars protect many orphan drugs from competition.

However, while generic manufacturers may not be drawn to pure orphan products because of the small patient populations, partial orphans may prove financially attractive to generic manufacturers. Through a practice known as “skinny labeling,” generic manufacturers can produce a generic medication of a partial orphan drug with a label limited to the drug’s non-orphan indication(s). But physicians may be able to prescribe the generic drug off-label for the non-orphan indication.⁷⁹ Whether this approach undermines the incentives for orphan drug development or not, it does increase competition and helps improve affordability for patients. A recent study found that by achieving timely entry into the market, skinny labeling facilitated lower drug prices for patients by decreasing their out-of-pocket costs.⁸⁰

Drug Pricing and Access: Commercial Insurance. Increased spending on orphan drugs has paralleled the growth in orphan drug development. Spending for orphan indications increased from 2% of invoice spending on drugs in 1992 to 11% in 2019 (Figure 5).⁸¹ An additional 16% of drug spending was on non-orphan indications of drugs that also had orphan indications.⁸² Such spending increases are driven not just by increases in the volume of orphan drugs, but also because these products have higher prices. In 2017, the average annual cost of orphan drugs at launch was 25 times higher than the annual cost of treatment for non-orphan drugs.⁸³ Another analysis found that among the top 100 drugs by U.S. sales, the average cost of treatment for orphan drugs is 4.5 times that of non-orphan drugs (\$150,854 vs. \$33,654 per year), a difference of \$117,200 on average.⁸⁴

While orphan products range widely in price, a small proportion carry an extremely high price, usually linked to very small (e.g. < 10,000) eligible patients. Research shows that orphan drugs costing over \$500,000 per year represent 5% of all orphan drugs and treat 0.08% of patients taking orphan medications.⁸⁵

Figure 5: Invoice Spending on Orphan Drugs in the United States 1992 – 2019, U.S. \$B⁸⁶



Payers have limited tools with which to manage the high costs for orphan drugs. Medicare Part D and the ACA rules for individual and small-group products generally require coverage for prescription drugs that are the only product available in the class, a common occurrence with orphan drugs. Coverage requirements that align with compendia rules further restrict plans' ability to deny coverage for oncology products. In addition, while drugs in competitive classes often provide rebates and discounts to offset list price, payers report that these price concessions are uncommon for orphan drugs, even when there are one or two competitors.

However, payers usually do apply utilization management restrictions on orphan products in an effort to encourage evidence-based prescribing and manage costs. In Medicare Part D, 76% of orphan drugs were subject to prior authorization in 2016.⁸⁷ Higher priced orphan drugs (those over \$50,000 per year) and partial orphans were more likely to be subject to prior authorization.⁸⁸ While such access restrictions may be necessary to ensure appropriate evidence-based prescribing, they also may cause delays or other challenges for patients seeking treatment, and their utility in managing overall health care costs is uncertain.

As the portion of employers who self-fund their insurance continues to rise⁸⁹, many have adopted stop loss or reinsurance policies as one mechanism to help manage extremely high, unanticipated costs that can be associated with some orphan treatments, particularly cell and gene therapies. However, not all employers can afford benefit designs including stop loss insurance. In addition, a recent report suggests that the current contracts between self-insured companies and stop loss carriers may no longer be cost-effective in mitigating the financial risk associated with gene and cell therapies, particularly as a wave of new gene and cell therapies enter the market in the coming years.⁹⁰

In the absence of effective and affordable mechanisms to manage spending for extremely high-cost, low-utilization products, some plan sponsors have resorted to the extreme of stripping out cell and gene therapies entirely from their health benefits. Health plan and PBM executives interviewed for this report indicated that they experience regular and growing pressure from self-insured employers to exclude coverage for these products, and anticipate that this trend will only increase as the numbers of these treatments add further to the actuarial impact of pharmaceutical coverage.

Drug Pricing and Access: Medicaid. As the largest single insurer of children in the U.S., Medicaid has a particularly important role in coverage and reimbursement for many orphan drugs, especially those that treat ultra-rare conditions. Among the 50 most costly drugs to state Medicaid programs, 11 (22%) had orphan drug status at some point.⁹¹ Financial pressures associated with orphan drugs have led some states to adopt prior authorization policies that have been legally challenged as being inconsistent with laws requiring Medicaid not to deny access to any medically necessary drug whose manufacturer participates in the Medicaid drug rebate program.⁹² For example, Arkansas Medicaid instituted prior authorization criteria for a new orphan drug for cystic fibrosis that required patients to have first demonstrated insufficient benefit from older, less expensive

therapies;⁹³ the state reached a legal settlement to ensure access to patients with a demonstrated need for the drug. Similarly, Pennsylvania Medicaid added severity requirements for coverage of a prophylactic treatment for hereditary angioedema that were not in the FDA label or clinical guidelines.⁹⁴

Distinctive Challenges of Evidence Generation and Technology Assessment of Orphan Drugs

Evidence Generation. A prior ICER white paper examined in depth the issues related to evidence generation and value assessment of orphan drugs.⁹⁵ There are many ways in which orphan drugs, particularly treatments for very low-incidence, ultra-rare conditions, face distinctive challenges in generating the same type of body of evidence as drugs for more common conditions. Orphan drugs often lack regulatory precedent, have small trial populations, and/or suffer from limited understanding of the natural history associated with the disease. These factors can combine to create special challenges in developing feasible clinical trial endpoints that capture outcomes that matter to patients. Researchers have found that the time from patent filing to product launch is 2.3 years longer for new orphan molecules compared to all drugs.⁹⁶ The FDA recently recognized the specific challenges that orphan drugs face when determining endpoints for clinical trials through the announcement of the Rare Disease Endpoint Advancement pilot program.⁹⁷

Research has noted that clinical trials of orphan drug have about a third as many participants (median = 96) compared to trials involving non-orphan treatments (median = 290).⁹⁸ The sheer geographic dispersion of these small patient populations often means that rare disease trials must operate at many provider sites to achieve necessary enrollment. Some patient groups are building registries to support improved clinical trial enrollment. The FDA awarded NORD a grant in 2015 to develop several natural history registries, and stakeholders suggest that additional funding in the space could help strengthen rare disease research.⁹⁹ The proposed 21st Century Cures 2.0 Act (Cures 2.0) also includes provisions for grant money to support innovative and novel clinical trial designs.¹⁰⁰

In addition to being smaller, trials of orphan drugs are also more likely to be designed as single-arm trials compared to trials for non-orphan drugs (96% vs. 67%).¹⁰¹ Patient advocates and other policymakers often raise ethical concerns about having a control arm in orphan drug studies, particularly when the condition is severe and progressive; patients may not be interested in participating in trials where they may be receiving a placebo. Because orphan drugs have a higher frequency of non-randomized, non-blinded trials, some academics have raised questions about the robustness of the data.¹⁰² Cures 2.0, legislation introduced in the U.S. House of Representatives in November 2021, also includes provisions to address these data related challenges, including

ensuring availability of Medicare claims data to link with clinical data in registries and increasing the use of real-world evidence to support post-approval requirements.¹⁰³

Value Assessments. The challenge of generating evidence comparable to that required for non-orphan conditions presents difficulties when health technology assessment groups and payers assess the value of orphan drugs. Smaller studies, often unrandomized, with frequent use of surrogate outcomes, may be judged adequate by regulators to demonstrate that new orphan drugs are “safe and efficacious,” but the potential biases in the data create higher uncertainty in longer-term safety, the magnitude of patient-centered clinical benefits, and the comparative effectiveness versus other treatment options that are the principal questions asked in value assessment. For payers, this higher uncertainty often frustrates their hopes of using clinical trial evidence to frame coverage criteria that can reasonably restrict access to those patients for which the risk-benefit ratio has been demonstrated. And payers also criticize a system in which the degree of uncertainty does not seem reflected in any way in moderation of launch pricing for new orphan drugs.

Less robust data complicate the process of designing cost-effectiveness models to evaluate the long-term value for money of orphan drugs. Clinical experts and patients and their families often have to supply model inputs in lieu of good data from clinical trials and broader epidemiological studies. Nonetheless, cost-effectiveness analysis of orphan drugs is commonly performed by academics and some health technology agencies. Some HTA agencies explicitly acknowledge that higher uncertainty in the data on orphan drugs should be viewed as more potentially appropriate given the constraints on evidence generation. When these analyses are done, despite recent research finding that orphan drugs provide greater health gains on average than non-orphan drugs,¹⁰⁴ the high prices of orphan drugs often drive unfavorable cost-effectiveness results.¹⁰⁵ Application of higher cost-effectiveness thresholds for orphan drugs is not supported by broad academic or HTA consensus, but national HTA assessments of treatments for *ultra-rare* conditions are frequently managed using alternative methods that may include higher thresholds.¹⁰⁶ As is true of all drugs, value assessment of orphan drugs need to be sensitive to whether quality of life measures are adequate to capture benefits that matter to patients and their families, and should look to incorporate consideration of the broader benefits to patients, families, and society that can accrue outside the health system.

In 2017, ICER published an analysis of the challenges of value assessment for treatments of rare and ultra-rare disorders and adopted several specific modifications to its value assessment framework.¹⁰⁷ ICER did not change its approach to rating evidence, rather it modified the assessments to be able to provide specific context and additional information so that decision-makers will be adequately informed of the distinctive character of the evidence and the broader considerations that should be part of policy decisions regarding these treatments. Other HTA groups around the world have been rethinking how best to adapt their procedures and methods for orphan drugs as well. A workgroup organized by Health Technology Assessment International

(HTAi) has proposed an approach that includes collaborating with both patients and clinicians to help develop robust patient-based evidence for an assessment.¹⁰⁸ In this model, clinical and patient experts meaningfully contribute at all levels of the assessment, from gaining an understanding of the disease, the potential role in therapy of a new agent, what outcomes matter most to patients, how clinical trial effects can be interpreted in real-life, and how to develop reasonable stopping protocols should treatments not show intended benefits. HTAi agencies are also working in partnership with public payers to develop frameworks for decision-making, thresholds for economic impact, and reimbursement policies for orphan drugs.

How Effective Is Drug Development for Ultra-Rare Diseases?

While the ODA and other factors have resulted in tremendous growth in rare disease products more generally, payers and manufacturers alike believe that new incentives and business models may still be needed to support the development of treatments for ultra-rare diseases. There have been a few notable regulatory and commercial successes of ultra-rare treatments, such as Zolgensma® for spinal muscular atrophy and Luxturna® for a genetic form of childhood blindness, but treatments for ultra-rare diseases are viewed by many stakeholders as too commercially risky. Outside of the U.S., the struggles for reimbursement experienced by Glybera¹⁰⁹ and, more recently, Zynteglo,¹¹⁰ suggest to many that treatments of ultra-rare disorders remain at substantial risk of commercial failure. Indeed, many experts, including investors, drug makers, and health plans interviewed for this project, believe that very small disease areas may never be commercially viable targets for private pharmaceutical companies without new significant incentives or development pathways.¹¹¹ Potential solutions could include new public-private partnerships, additional incentives scaled based on the size of the patient population, or broader publicly-sponsored research efforts, which will be discussed more below.

One of the key challenges in developing a policy platform to promote ultra-rare drug development would be to settle on a working definition of what constitutes a “rare” as opposed to an “ultra-rare” condition.¹¹² Such a regulatory definition or distinction does not now exist in the U.S. nor in other countries. However, many non-US countries have established separate procedures for value assessment and funding of therapies for patient populations that are much smaller than the lower bounds of the standard orphan population size.¹¹³ For example, the Health Technology Assessment (HTA) agency in Italy considers a disease prevalence of one per million to represent an ultra-rare disease, while the National Institute for Health and Care Excellence (NICE) in England restricts entry into a separate assessment track named the Highly Specialized Technologies (HST) program to diseases with a prevalence of 2 per 100,000 or less.^{114,115} Similarly, in 2018, the Scottish Medicine Consortium (SMC) introduced an ultra-orphan pathway in 2018, defining ultra-rare as fewer than 1 in 50,000 people.¹¹⁶

The Stress on the System

Patients living with rare diseases want access to more and better treatments. Since 90 percent of rare diseases have no FDA-approved treatment today, patient access to new treatments depends on ongoing innovation combined with broad and affordable insurance coverage. As science delivers more targeted therapies for increasingly-specific and rare conditions, the favorable orphan drug pricing conditions support robust investment from venture capital firms, and biotech startups are seeing higher early rounds of funding with average fundraising more than doubling to \$43 million over the past 5 years.¹¹⁷ More orphan drugs are needed, but the system has been successful in producing solid growth and outstanding future prospects, at least for drugs with large enough patient populations not to be considered ultra-rare.

But this success is not coming without strain on the health care system and without affordability problems already affecting patients and plan sponsors in both the public and private insurance system. While high drug prices are not unique to orphan drugs, and spending for rare diseases is not a dominant component of overall health care costs today, the trend toward higher prices and growing numbers of orphan drugs represents a rapidly escalating part of health care spending whose overall budgetary impact is likely to grow substantially in coming years.

The area of cystic fibrosis is one example of what payers and some policymakers see as a herald of growing affordability concerns. Since 2012, the drug maker Vertex has transformed the treatment of cystic fibrosis (CF) by launching several new drugs that target specific underlying gene mutations in different ways. Vertex's latest CF treatment is Trikafta[®], a drug that garnered a rare "A" rating in an ICER review for the magnitude and certainty of its added health benefits. CF has been a major success story in its development of new, clinically meaningful innovations. But that innovation has come at a high price, leading to access challenges around the world. The first drugs for CF made by Vertex started out at above \$300,000 per year when the number of patients eligible were a small percentage of those with CF. But as others were added the costs did not come down, and now with Trikafta bringing the eligible patient population up to 90% of all patients with CF, its price was also set above \$300,000 per year. Analysts estimate that Trikafta will reach \$6.6 billion in sales by 2025.¹¹⁸ Mega-blockbusters within the orphan drug space were not original vision of the ODA, and with this phenomenon comes the growing sense that the system is unsustainable.

With the stress between innovation and affordability now visible and growing, it is reasonable to consider the potential benefits and risks of policy reforms that might seek different approaches to establishing a different balance in the orphan (and ultra-orphan) drug market. This paper now turns to consideration of potential policy reforms that may offer a way to keep the robust innovation that patients and all stakeholders desire while improving the long-term affordability that

will secure improved access to these products in the future.

Analysis of Potential Policy Reforms

When considering policy proposals that address rare disease products, there are tradeoffs between measures taken to improve affordability and innovators' incentives for new drug development. Our research with stakeholders and analysis of historical regulatory and market trends suggests that recent growth in orphan drug development is likely to prove resilient should modest reforms be made to address equity and affordability. However, policymakers must be aware that any efforts to improve affordability will change the economic model for rare disease product developments, potentially resulting in fewer drugs for rare diseases. In addition, if policymakers consider the idea of adding new private market incentives or federal government investment and reimbursement changes to encourage development of ultra-rare treatments, risk exists in that interest and investment in other orphan drugs could be siphoned away.

Therefore, in presenting an analysis of potential policy reforms we seek to convey that any potential policy reform carries both potential benefits and potential risks. These effects are likely to have ramifications for orphan drug development and access not only in the U.S. but internationally as well given the strong preponderance of profits made on orphan drugs in the U.S. market. Thus, for stakeholders who see the current market ecosystem as striking the right balance between innovation and affordability, with adequate incentives and structures in place to generate appropriate evidence and keep overall investment balanced between orphan and non-orphan conditions, no change is likely to appear desirable. But, given the current stresses in the system and concerns from many stakeholders about the potential for even greater problems in the future, we believe that policymakers should consider reforms aimed at striking a more sustainable balance between the incentives and structures that favor orphan drugs and the need of the health system for sustainable affordability.

Table 2 below gives a high-level summary of a list of potential policy reforms that emerged from our research and analysis. In the sections that follow, we aim to present the advantages and risks of each policy to guide future discussions and decisions.

Table 2. Summary of Policy Options

Encouraging Ultra-Rare Drug Development	Establish a definition of ultra-rare disorders
	Increase incentives to develop treatments for ultra-rare disorders
	Use value-based pricing and reimbursement for ultra-rare treatments
Limiting Incentives for Partial Orphans	Establish a maximum revenue threshold to be eligible for ODA incentives
	Assess FDA standards for defining distinct diseases
	Eliminate 340B exclusions for partial orphans
Strengthening Evidence Generation	Update ICD-10 codes to reflect rare disease
	Fund patient registry development
	Clarify evidence expectations
Reducing Prices for Rare Disease Products	Expand outcomes-based contracts
	Consider indication-based pricing
	Pursue value-based pricing
	Volume based contracts

Encouraging Ultra-Rare Drug Development

Establish a Definition of Ultra-Rare Disorders. Conditions that affect a very small number of potential patients in the U.S. face special challenges in attracting innovator and investor interest. Most stakeholders agree that we need new solutions to target research, development, and commercialization of drugs to treat these kinds of ultra-rare conditions. A necessary step in this process requires agreement on a definition of “ultra-rare” disease to help guide efforts to target special incentives or direct investment by the government. However, with no U.S. or global standard for ultra-rare diseases, stakeholders have struggled to agree on an appropriate threshold and remain reticent to pick an arbitrary number.

One reasonable threshold for ultra-rare diseases, following European approaches, would be for conditions with fewer than 10,000 patients in the U.S.¹¹⁹ Most stakeholders concur that products with fewer than 10,000 patients in the U.S. struggle to be commercialized in today’s market even with expectation of extremely high prices.¹²⁰ Some observers have argued that population standards should consider not just the U.S. but the global patient population in order not to overapply special incentives where they are not needed. In particular, while some diseases are relatively evenly dispersed across countries, there are conditions that are ultra-rare in the U.S. but which have higher global prevalence, due to genetic, biologic, or environmental differences across international patient populations.

It should be noted that patient advocates for rare conditions have not favored the idea of separately identifying a narrower “ultra-rare” group. They argue that even if ultra-rare conditions receive a boost to support innovation, such a separation over time would give policymakers too much leeway to decrease incentives that are still vital for future innovation across the broader range of orphan conditions. If such a distinction is to be drawn, however, advocates underscore the importance of considering not only absolute patient numbers but patient-level quality-of-life indicators, such as disease severity, level of disability, and premature mortality. They argue that these factors should also be considered if a subset of orphan conditions is to be carved out and given special incentives. Policymakers, however, would need to weigh the potential advantages of including additional, less objective criteria, with its requisite more complicated – and potentially contentious – algorithm for designating which indicators are applicable to which conditions for the purposes of eligibility for incentives.

Increase Incentives to Develop Treatments for Ultra-Rare Disorders. Unless development of ultra-rare treatments is taken over by government-directed programs, enhanced financial incentives are needed to stimulate more research and development of these treatments. One option is to increase ODA tax credits or other subsidies specifically for products treating ultra-rare disorders. For instance, the research and development tax credit for ultra-rare products could be increased from 25% back to 50%, the original tax credit set in the ODA. Such a change would explicitly prioritize ultra-rare diseases as requiring more incentives than products for other rare conditions, though some stakeholders worry this could create too strong an incentive to move resources toward conditions that impact fewer people. Regardless, changes to the tax credits may be insufficient to overcome the market challenges faced by ultra-orphan drugs, and enhancements to the tax credit may not be immediately useful for early-stage companies because of the structure of a tax credit.

Another, more direct, approach to support the development of ultra-rare drugs would be to expand direct federal funding for and involvement in ultra-rare drug research and development. One option would be to establish a new federal authority to conduct critical research and development for ultra-rare conditions, akin to what Defense Advanced Research Projects Agency (DARPA) does for technology and military innovation. DARPA does not have its own laboratories or research facilities, instead directing promising research pathways through grant making and partnerships with scientists. In a similar model, the government could pursue public-private partnerships to underwrite focused research and development of drugs for ultra-rare conditions that otherwise may not receive the attention of commercial pharmaceutical companies. The Bespoke Gene Therapy Consortium (BGTC) is an example of a public-private partnership that supports the commercial viability and sustainability of gene therapies for very rare diseases. This partnership between the NIH, FDA, industry, and non-profit partners seeks to foster development of gene therapies by developing tools to streamline the development process.¹²¹

Operation Warp Speed, which accelerated the COVID-19 vaccine development, is another potential model. In that example, the federal government directly subsidized research and development costs, contracted to support manufacturing capacity, purchased necessary ingredients and supplies, and provided advance-purchase commitments to underwrite market risk.¹²² While the threat of the COVID-19 pandemic demanded a significant federal investment in Operation Warp Speed, and acknowledging that the focus was only on one disease (COVID-19), the same general model could be applied in the ultra-rare disease space. The federal government could encourage ultra-rare drug development through (1) increasing NIH funding for basic research in ultra-rare conditions; (2) creating a loan or other system to offset manufacturing expenses; (3) establishing subsidies to underwrite commercialization costs; and (4) guaranteeing market access via pre-established coverage and reimbursement expectations in Medicare and Medicaid.

Looking abroad, another option for creating special arrangements for ultra-orphan drugs has been to create special assessment pathways and reimbursement mechanisms at the national level. As noted earlier, NICE in the UK has a separate pathway for assessment of “Highly Specialized Technologies” that in principle is willing to accept much higher cost-effectiveness thresholds for treatments for ultra-rare conditions. Similarly, the Scottish Medicines Consortium (SMC) implemented a rule in 2018 that creates a lower bar to reimbursement for treatments of ultra-rare conditions through which treatments judged effective by the national HTA body are funded at the national level for at least three years while additional information on its effectiveness and cost-effectiveness is gathered.¹²³ Congress could consider creating a similar national coverage structure for ultra-rare treatments through CMS that would leverage the existing Coverage with Evidence Development (CED) mechanism to accelerate access to these treatments with a corresponding evidence development requirement. This mechanism could also be linked with a requirement for value-based pricing (see below), at least during the evidence generation phase of coverage. If this approach, with or without a pricing component, were limited expressly to treatments for ultra-rare conditions, the resulting improvement in access might spur additional interest in developing these treatments while creating manageable increases in spending.

Whether policymakers favor the idea of using private market incentives or federal government investment and reimbursement changes to encourage development of ultra-rare treatments, the major potential risk is that additional resources will go to ultra-rare conditions, perhaps in some way siphoning away interest and investment in other orphan drugs. Public investments in health are needed in other areas, including antimicrobial development and chronic diseases, so every investment has a potential opportunity cost that should be considered. That being said, the current market system is viewed by many as inadequate to support development of treatments for patients with truly ultra-rare conditions, and policy changes may be possible to support that area without undermining either broader innovation or affordability.

Value-Based Pricing and Reimbursement for Ultra-Rare Treatments. Once a product to treat an ultra-rare condition is brought to market, whether developed by industry or government, its price will determine its cost-effectiveness. If developed by government, pricing can be done by administrative fiat. If developed or co-developed by industry, the product's price, shaped as described above, underpins the economic incentives for innovation. As such, prices paid by payers for products that treat ultra-rare conditions, especially those with the lowest prevalence, may need to exceed typical thresholds used in cost-effectiveness assessments.

Instead of relying on traditional cost-effectiveness assessments, prices for ultra-rare products could be developed on the basis of a different pricing paradigm based on the idea that rates of return for investments in developing orphan drugs should not be greater than the industry average.¹²⁴ In this approach, a calculation would be done of the maximum allowable price society should be willing to pay. Such a change would represent a major departure from current U.S. reimbursement models in which the government does not set prices. A downside of this approach is that it could reward inefficient research and development programs while under-incentivizing the kinds of risk taking needed on early assets that promise substantial clinical gains. Nonetheless, a rate-of-return approach could potentially be twinned with cost-effectiveness, with the greater price calculated through either paradigm the one that would be accepted by payers. Ultimately, by managing the balance between innovation and affordability more explicitly and consistently, a reasonable rate-of-return methodology could generate pricing recommendations that would do a better job of balancing the need for greater incentives for ultra-rare treatments within a more predictable and affordable framework.

Limiting Incentives for Partial Orphans

There are clear benefits for manufacturers to test the viability of promising pharmaceutical agents first within narrowly targeted patient populations and, if found successful, to expand development more broadly to additional indications. As such, it is neither surprising nor problematic that some products launch as an orphan drug before gaining non-orphan indications. However, the evident commercial success of partial orphans, in part derived from their sustained "orphan pricing" as patient populations expand, suggests that ongoing federal research and development tax credits and waived user fees may not be necessary or appropriate. Specific policy options for modulating orphan drug benefits for partial orphans are described below.

Establish a Maximum Revenue Threshold to be Eligible for ODA Incentives. One potential policy reform would be to limit or remove orphan drug incentives once a product is approved for non-orphan indications or once it exceeds a given threshold of revenue indicative of relative commercial success (e.g., \$200 million). Such a change would tend to focus orphan drug incentives on products that need it most – those treating very small patient populations and/or for which competition has limited its market share. The potential risk in this approach is that a reduction in ODA benefits tied

to revenue might discourage companies from taking the risk of conducting additional clinical trials to assess the effectiveness of a product for a broader population, thus limiting the ultimate clinical benefit to the broader population of some treatments that start out as orphan drugs.

Assess FDA Standards for Defining Distinct Diseases. Another option to rebalance incentives for partial orphan drugs would be to reassess and sharpen the FDA’s definition of distinct diseases. Increased use of new molecular biomarkers to diagnose and treat conditions is resulting in narrower definitions of distinct diseases, and thus some heterogeneous conditions that did not qualify as rare are now being subdivided into multiple “new” rare diseases. As this trend continues, the FDA could change their approach to defining distinct diseases to favor the preservation of broader indications. A broader definition would reduce the incentive for manufacturers to start their development program targeting a very narrow population, potentially blunting the trend of leveraging early orphan pricing into larger populations over time. As with any narrowing or reduction of ODA benefits, however, this policy option might increase uncertainty regarding the scientific and commercial success of some emerging treatments, producing less investment and innovation in new treatments for rare diseases.

Eliminate 340B Exclusions for Partial Orphans. Policymakers could restrict the 340B exemption for ACA-expanded covered entities to include only the utilization of partial orphans for their orphan indications, which would dramatically reduce the financial incentives for partial orphan products.¹²⁵ This change would likely require legislation to surmount the U.S. District Court decision that struck down HRSA’s interpretive rule. However, as with all potential narrowing of ODA benefits, this policy change harbors some risk of driving investment and innovation away from certain rare disease areas, and it would also be challenging to implement, as it would require participating providers to document, monitor, and report their 340B drug utilization by indication. While such reporting is conceptually possible in the context of well-integrated electronic medical records and data systems, in practice it could create a significant operational burden on 340B entities.

Strengthening Evidence Generation

To improve the efficiency and effectiveness of research on rare disease treatments, policymakers can support efforts to facilitate clinical trials and more efficient evidence generation. Expanding registries can improve the quality of real world evidence (RWE) and support more rigorous post-market surveillance for rare disease treatments. Among drugs receiving accelerated approvals from 1992 to 2016, only 76.5% have converted to full approval, with the remaining 23.4% either withdrawn or not yet converted (after a median of 9.5 years without having evidence allowing them to move to full approval).¹²⁶ For orphan products that are often approved based on surrogate endpoints or with alternative trial designs (e.g., non-randomized controlled trials), ongoing evidence generation is critical to validate their long-term safety and effectiveness. Federal investment is needed to spur the development of more robust systems for capturing and analyzing

observational data to meet the needs of patients, clinicians, and payers. These data systems should be developed so that they can capture patient-reported outcomes reflecting broader patient and family effects of treatment.

Federal funding, along with help from disease and patient groups, can accelerate efforts to improve evidence generation by sponsoring rare condition registries. Broadening rules on data ownership and using federally funded program claims data (e.g., Medicare and Medicaid) to augment registry data could further enhance these resources. The federal government should consider additional strategies to expand registry development for rare conditions, including supporting their development by patient and disease groups, and by requiring registry participation by entities delivering services to Medicare or Medicaid patients with the associated rare condition. Finally, stakeholders should consider how to employ ICD-10 codes to increase data granularity to support characterization of rare conditions. Without up-to-date and well-targeted diagnosis codes, it is challenging to identify potential patients with a rare condition and to recruit them for research. Payers indicate that improved coding would also support simplified billing, claims adjudication, and clinical utilization reviews.

Improved evidence generation also supports innovation and affordability and equity if the FDA and evidence assessment entities like ICER continue to refine and communicate their expectations about how alternate forms of evidence will be considered in their regulatory and value assessments. As part of the PDUFA reauthorization act, the FDA has committed to developing a program focused on Advancing RWE use in regulatory decision making. The Advancing RWE Program seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements.¹²⁷

While more data based on robust observational data will be useful to all stakeholders, there is an attendant risk that policy makers should consider. RWE has become a catch-all term and lionized by some as the solution to limitations in the evidence available at launch of new drugs. However, the other part of the solution to this problem is to reinvigorate the evidence standards required of all drugs to gain FDA approval. RWE as a policy option, taken to an extreme, might further undermine efforts to establish reasonable requirements for randomized trials, or for trials of adequate duration and comprehensiveness to understand the risks and benefits of an emerging treatment. For patients and clinicians, as well as for payers, it will be important that efforts to expand the generation and use of RWE not be done in a way that undermines the broader social good of requiring rigorous evidence of safety and effectiveness before allowing the widespread use of a new treatment.

Policy Options Related to Accelerated Approval

As mentioned above, 41.9% of all accelerated approvals have been orphan drugs. While the goal of the accelerated approval pathway can be stated as providing faster access to treatments that offer meaningful advantages to patients with serious conditions, there is debate as to whether the pathway is achieving that goal and whether its implementation lost the balance needed to ensure overall benefits to patients and society. For more detail and information about the advantages, disadvantages, and an analysis of potential policy reform proposals, please see the ICER paper titled [“Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation and Costs.”](#)

Improving the Affordability of Orphan Drugs

There are a range of potential policy reforms to address the high prices of products that treat rare conditions, including use of outcomes-based contracts, indication-based pricing, and value-based pricing, each of which are described below. Separately, we also discuss approaches to pooling the financial risk of rare conditions across insurers—either across states in a program like Medicaid or among and between payers (e.g., from commercial insurance to Medicare or Medicaid). The Medicaid and CHIP Payment and Access Commission (MACPAC), among others, has recommended carving-out high-cost, orphan treatments, such as cell and gene therapies, into a consistent national benefit, described below.¹²⁸

Outcomes-based contracts. Outcomes-based contracts make some or all of the payment for a treatment contingent on the degree of patient benefit.¹²⁹ Such a model could take several forms, with sliding scale bonuses or refunds depending on outcomes.¹³⁰ These contracts require manufacturers and payers to agree on a set of measurable outcomes and to track those outcomes in order to adjudicate the contract. Experience has proven that this effort to track and adjudicate outcomes can be administratively burdensome and expensive to negotiate and implement. Nonetheless, payers are attracted by the general principle of modulating payment (and, indirectly, pricing), by linking it to outcomes achieved in real world use. This approach has the benefit of appearing to address the interlocked concerns about the pricing of orphan drugs with those regarding the uncertainty of the evidence on their effectiveness.

One potential policy reform option to leverage outcomes-based contracts would be to require this kind of contract be applied for orphan drugs (particularly those approved through the accelerated approval pathway) in exchange for insurance coverage. Many gene and cell therapies are already launching with outcomes-based contracts negotiated with certain private payers. However, many payers are skeptical that they have the negotiating leverage to get manufacturers to agree to outcomes-based contracts yielding meaningful financial savings, especially after considering the high administrative costs of negotiating and adjudicating these contracts. Historically, Medicaid

best price rules have limited the magnitude of price concessions in commercial outcomes-based contracts, since contracts that offered outcomes-based prices lower than Medicaid best price would trigger higher rebates across all Medicaid utilization. Recent regulations modified the best price rules to allow more outcomes-based contracts across payers, but the impact of these changes remains uncertain.

Manufacturers and payers alike agree that outcomes-based contracts, as currently designed, are unlikely to dramatically reduce overall spending or increase affordability for orphan drugs. However, one option for policymakers is to create a new process through which contracts can be negotiated at a national scale. Specifically, Medicare could create a demonstration program in which coverage for certain orphan products, such as cell and gene therapies, could be conditioned on negotiation of an outcomes-based contract. This program could include a formal pricing function in which Medicare could set a value-based price and, in conjunction with the manufacturer and other stakeholders, select endpoints and the timing and mechanism of linking rebates from the manufacturer back to CMS when the drug does not perform up to expectations. This program could also serve as a model for private payers. Some manufacturers might welcome the opportunity to negotiate a standard outcomes-based contract applied consistently across all payers. This approach might solve many of the barriers to rapid uptake of cell and gene therapies that have plagued the launch of the first generation of these treatments. However, many manufacturers and stakeholders are likely to view any centralized process that includes some regulation of price as a slippery slope to broader application of federal price controls that would cast a pall over investment and innovation.

Volume-based contracts. Volume-based contracts are another approach that could support rare product commercialization by guaranteeing coverage, promoting patient and provider education, assuring equitable access and utilization, and simplifying contracting.¹³¹ While volume-based contracts have historically been used by the government to purchase large volumes of drugs (e.g., vaccines), a similar model could be employed in the orphan drug space. To achieve the necessary product volumes for rare conditions at an affordable price requires a single-purchaser model. Under this model, the federal government or a consortium of private payers could directly negotiate to purchase enough orphan product volume to cover all eligible patients with a given rare condition. The contract would enable the government or private consortium to set a price unique to the orphan indication, distinct from the (lower) price for the product for non-orphan indications. Manufacturers would benefit from a single contract, improved patient access, and predictable utilization.

Volume-based contracts could also be structured to ensure that product prices fall as utilization expands. For instance, the volume-based contract could establish a graduated pricing arrangement tied to the total amount of product utilization. When products launch for small patient populations, they are guaranteed a premium price. As utilization expands (due to uptake, off-label use, or label

expansions) rebates would increase and the net price of the drug would fall. Such a proposal would likely appeal to payers and could have the support of patient groups, if it encourages broader access and utilization. However, manufacturers would likely be concerned about granting power to another entity or agency to set long-term prices, and they would want to ensure long-term profit growth even as prices decline.

Indication-Based Pricing. As noted earlier, high prices for drugs that are first approved with an orphan indication usually stay high, even after additional, broader indications are approved. If indication-based pricing could be effectively implemented, it would enable payers to negotiate higher prices for rare indications and lower prices for broader indications or those for which the product demonstrates less clinical value.¹³² Independent value assessment entities could help establish a value-based price for a given rare condition and indication, based on the clinical benefit and strength of the evidence by disease area. While indication-based pricing would help expand access, one potential risk is that this pricing flexibility would allow manufacturers to increase prices for high-value indications, which could increase cost-sharing for rare disease patients.¹³³

Unfortunately, operationalizing indication-based pricing has been extremely challenging for payers in the US, given the current pharmaceutical supply chain and rebate model. Some experts have even warned that indication-based pricing could lead to unintended consequences such as higher prices for patients with rare diseases, higher overall spending, and higher manufacturer profits.¹³⁴

Value-based Price Regulation. As noted earlier in regard to several policy options, value-based price regulation could be a complement to other policies seeking to realign incentives and improve affordability. There are numerous mechanisms available, including the use of international reference pricing, or pricing based on cost-effectiveness thresholds and algorithms suggested by value assessment by groups such as ICER.¹³⁵ One benefit of this approach is that the value-based price setting methodology could shift over time as additional evidence is generated. Further, value-based price setting creates incentives for investment in evidence development to demonstrate the clinical benefits of emerging treatments and provides handsome market rewards for products bringing significant added benefits to patients while scaling those rewards down for drugs that do little to improve patient outcomes.

In adopting a value-based price setting mechanism for orphan products, policymakers must consider whether products that treat rare and ultra-rare conditions should be afforded different standards for cost-effectiveness. ICER addressed this question as part of its consideration of adapted assessment methods for treatments of ultra-rare disorders.¹³⁶ While the custom of accepting higher prices for ultra-rare disease products suggests a societal willingness to pay more for these products, ICER concluded that the logic and ethics of opportunity costs suggested that cost-effectiveness thresholds should not shift systematically solely on the basis of rarity, and that such shifts threaten the goals of health equity. However, absent a comprehensive approach to

encourage affordable pricing for rare diseases while encouraging investment in ultra-rare treatments, ICER could consider adjusting its cost-effectiveness thresholds (or granting higher weights to health gains for patients with ultra-rare disorders) to achieve the policy aim.

As with any policy that would lead to lower prices for some orphan products, value-based pricing mechanisms may result in pushing prices too low to incentivize investment in areas in which success is less certain, or in which the clinical gains from treatment would be relatively small. Some would argue that progress in the treatment of orphan diseases often seems to come in small steps, and that prices generated by value-based mechanisms would not be adequate to keep the field moving forward. The contrasting argument is that patient populations between 10,000 and 200,000 appear large enough to generate sufficient revenue to keep investments and risk-taking at robust levels. For example, a product that treated only 10,000 patients, at a price of \$100,000 per year (22% of treated patients today receive an orphan drug that costs \$100,000 or more¹³⁷) would generate an annual revenue stream of \$1 billion for the manufacturer. Nonetheless, judging the impact of value-based prices on the broad range of orphan drug development remains a hypothetical exercise, with the potential benefits and negative consequences frequently debated.

National Treatment Benefit for Rare Conditions. Insurance structures depend on the presence of shared risk pools large enough that diseases are distributed relatively evenly across the risk pools. For common conditions, with reasonably modest costs, risk pools can be small, down to the level of the individual self-insured employer and its employees. But for rare and ultra-rare conditions with extremely high costs, risk pools need to be very large – otherwise the individual employer or small group of plan sponsors might not be able to absorb the unexpected cost shock of an unanticipated number of patients with rare and expensive conditions.

Many national health plans are now trying to create insurance products to manage the extreme risk of unanticipated high-cost orphan drug treatments. Some federal policymakers have supported this approach.¹³⁸ One example of these efforts is Embarc Benefit Protection, offered by Cigna. The program carves out coverage for cell and gene therapies into a set per-member, per-month premium for employers and other plan sponsors who join the network. This premium structure protects the individual employer from the financial burden of an unanticipated high-cost therapy while allowing individual patients to access therapies without any out-of-pocket payment.¹³⁹

Although the commercial experience with these carve-out programs is limited, policymakers may wish to consider launching one at even larger scale at the national level. A new national benefit for cell and gene therapies for orphan diseases would create a single national risk pool for all identified rare conditions. Such a program would carve-out payment for orphan products generally, or cell and gene therapies specifically, from other public or private coverage. Carve-outs and national risk pools have been proposed in several forms by some policy making bodies, including the Medicaid and CHIP Payment and Access Commission (MACPAC).¹⁴⁰ Others have proposed carving these products out of Medicare's hospital payment system to ensure adequate reimbursement.¹⁴¹

One key design question for these carve-out options pertains to the scope. A carve-out could include a single program (e.g., Medicaid) or could aggregate multiple public or private purchasers via optional or mandatory participation. In its most expansive form, a carve-out program would constitute a new federal entitlement for all Americans. While more limited carve-outs would be more politically feasible in the near-term, fragmenting a diffuse risk pool could create unintended consequences that result in some payers seeking to deny coverage for these products in order to drive coverage into the carve-out. Such incentives would need to be carefully managed to prevent cost-shifting or increasing barriers to patient access.

A second major design issue of a potential national benefit for rare conditions is determination of which products are covered, and at what price. At minimum, the national benefit could act as a standardizing mechanism that still allows broad flexibility for participating payers to set prices. Alternatively, a standardized national benefit for rare disease products generally, or cell and gene therapies specifically, could create uniform coverage and risk pooling arrangements across the patient population, giving payers the opportunity to compete on providing patients with fair and equitable access to products, and appropriate care and home support services. Pricing could be based on an outcomes-based contract or a value-based pricing arrangement, as described above. Such a proposal would be a significant change to current insurance coverage that would have widespread effects on stakeholders. While many details would need to be explored, however, such an approach may be preferable to the weakening sustainability of the private insurance model.

Conclusion

Since its passage, the ODA and accompanying scientific advancements have been successful at increasing the number of treatments available for patients with rare diseases, but tremendous unmet need remains. As a society, we must prioritize ongoing innovation and drug development for rare diseases—particularly those with no available treatments today. Treatments for ultra-rare conditions have been particularly elusive, as current market dynamics make it challenging for manufacturers to bring these products to market. Progress will require new incentives and partnership approaches to stimulate investment in drug development for ultra-rare conditions.

At the same time, there are widespread concerns about perceived weakening of evidence standards for orphan drug regulatory approval and the long-term sustainability of orphan drug pricing as the number of orphan drugs continues to increase. Orphan products launch at persistently high prices that are neither scaled to clinical benefit at launch nor that decrease when additional indications are obtained. To ensure that patients enjoy broad access to future innovation, policymakers and health care industry leaders must consider solutions to focus incentives for innovation and improve affordability of rare disease treatments. This paper presents an analysis of the potential benefits and risks of a range of policy reforms that would improve evidence generation, target, and potentially increase incentives to drugs for ultra-rare conditions, and regulate orphan drug pricing directly or indirectly in a way that would improve affordability without undermining future investment and innovation. For those stakeholders and policymakers who see the current market ecosystem as functioning perfectly, no policy reform is likely to appear desirable. But for policymakers more broadly we have presented an analysis of potential policy reforms that would create a new landscape for orphan drug development, coverage, pricing, and payment. Policymakers and stakeholders will need to consider carefully whether these policy reforms would be able to retain the special incentives needed to ensure continued investment in orphan drugs while creating a better balance between the joint goals of broad innovation and affordability. Views will differ, however, one thing is certain: continued innovation will only prove sustainable and helpful to patients if the costs of the overall effort of innovation can be better managed, both for individual patients and for health systems and society.

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Appendix A. 2021 ICER Policy Summit Attendees

Representatives from the following companies and organizations attended ICER's 2021 Policy Summit, which was held from December 8-10, 2021 in Phoenix, Arizona:

- AbbVie
- Alnylam Pharmaceuticals
- America's Health Insurance Plans (AHIP)
- Anthem
- AstraZeneca
- Blue Shield of California
- Boehringer-Ingelheim
- Canadian Organization for Rare Disorders (CORD)
- CVS Health
- Envolve Pharmacy Solutions
- Express Scripts
- Genentech/Roche
- GlaxoSmithKline
- Health Care Service Corporation (HCSC)
- Humana
- Kaiser Permanente
- LEO Pharma
- Mallinckrodt Pharmaceuticals
- Merck
- National Organization for Rare Disorders (NORD)
- National Pharmaceutical Council (NPC)
- Novartis
- Pfizer
- Point32Health
- Premera Blue Cross
- Prime Therapeutics
- Regeneron Pharmaceuticals
- Sanofi
- Sun Life Financial
- uniQure
- UnitedHealthcare