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# SUPPORTING DRUG INNOVATION AND FAIR PRICES FOR PATIENTS WITH RARE DISEASES: WHY CONGRESS SHOULD NOT UNDERMINE THE INFLATON REDUCTION ACT, SHOULD LET THE PRIORITY REVIEW VOUCHER PROGRAM SUNSET, AND SHOULD FIX THE *CATALYST* LOOPHOLE

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**Energy & Commerce Committee Subcommittee on Health**
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**Summary of major points**

- Patients with rare diseases face numerous challenges in the health care system, including finding knowledgeable providers and accessing affordable treatments.

- The 1983 Orphan Drug Act and the 2022 Inflation Reduction Act contain provisions intended to support patients with rare diseases.
    - The **Orphan Drug Act** established a set of regulatory and financial incentives for drugs approved by the FDA for rare diseases. While approvals for such drugs have increased in recent years, this growth is primarily attributable to (a) NIH-funded research in government and academic laboratories, which has catalyzed a transformation in our understanding of the biochemical bases of rare diseases, (b) the FDA's regulatory flexibility leading to more predictable preapproval periods for drugs that treat rare diseases, and (c) the potential for these drugs to become top-selling products.
    - The **Inflation Reduction Act (IRA)** created a process by which Medicare will negotiate the price of top-selling drugs nearing the ends of their market exclusivity periods to help promote the accessibility of those drugs for all patients, including those with rare diseases. The IRA excludes drugs approved for only a single rare disease ("sole orphan drugs").

- Three of the bills today should not be advanced by this subcommittee:
    - The *ORPHAN Cures Act* (H.R. 5539) expands the IRA exemption to products approved for multiple rare diseases ("multiorphan drugs"), but these drugs already generate substantial revenue. It also delays the start of negotiation until after a non-rare approval occurs, but this would create an opportunity for gaming by the industry that will hurt patients.
    - The *MINI Act* (H.R. 5547) delays IRA negotiations from 7 to 11 years for "advanced drug products," but this category is vague and the drugs likely to qualify for negotiation are already top-selling drugs for which delay will subject patients to unnecessarily high prices for longer periods of time, without substantially affecting private incentives to invest in the products.
    - The *Creating Hope Reauthorization Act* (H.R. 7384) would reauthorize the rare pediatric disease priority review voucher, but there is no rigorous evidence that the voucher works to bring new drugs into clinical testing, and it disrupts the FDA's calibrated drug review process. The rare pediatric disease priority review voucher should be left to sunset.

- One of the bills today should be advanced by this subcommittee:
    - The *RARE Act* (H.R. 7383) fixes a loophole in the Orphan Drug Act created by a federal court that would allow manufacturers to prevent timely competitors into rare disease drug markets, diminishing the prospect of patient-benefitting price competition and stability of supply.

- The Inflation Reduction Act need not reduce incentives for drug innovation for rare diseases, which often emerges from publicly funded research by the NIH. In the long term, the IRA is likely to actually improve patient-centered innovation by increasing manufacturers' incentives to invest in new drugs that offer meaningfully improved outcomes to patients, including those with rare diseases.

- If Congress is open to amending the Orphan Drug Act or the IRA, it might consider additional proposals that align the incentives and policies in those bills with the needs of patients who have rare diseases, including: (a) eliminating the sole-orphan exclusion and (b) authorizing Medicare to set up an independent body to evaluate the benefits of all new drugs for rare diseases (and non-rare diseases) at the time of approval to determine what sort of additional benefits they offer to patients.

**Subcommittee Chair Guthrie, Subcommittee Ranking Member Eshoo, Chair Rodgers, Ranking Member Pallone, and Members of the Subcommittee on Health:**

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and a Professor of Medicine at Harvard Medical School, in the Division of Pharmacoepidemiology and Pharmacoeconomics of the Department of Medicine at Brigham and Women's Hospital in Boston, one of the main Harvard teaching hospitals. Within the Division, I lead the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research center that studies the intersections between prescription drug affordability and use, laws and regulations related to medications, and the development and cost of drugs. PORTAL is one of the largest non-industry-funded research centers in the country that focuses on pharmaceutical use, law, and economics. In 2020, I was elected to the National Academy of Medicine.

I am honored to talk to you today about several new bills that this subcommittee is considering relating to patients with rare diseases. I will start by discussing the issue of care for patients with rare diseases. I will then discuss the specific provisions addressed in the suite of proposed bills and explain how they are likely to affect care for patients with rare diseases. Finally, I will propose a few additional items that the subcommittee should consider to promote availability of and access to new treatments for patients with rare diseases.[1]

## I. A Review of Key Issues Related to Therapeutic Options for Patients with Rare Diseases

Patients with rare diseases can face daunting medical challenges. By some counts, there are 10,000 known rare diseases affecting 30-40 million people in the US, only about 5% of which have FDA-approved treatments.[2] In a series of focus groups I led with patients suffering from rare diseases, we heard how each person learned to live with a condition with few or no treatment options and that is poorly understood by family members, clinicians, medical researchers, and the broader community. Patients with rare diseases and their families became actively involved in their own care and often also in promoting the interests of other patients. Patients with rare diseases have difficulties in finding knowledgeable medical care, experience isolation and lack of support, and bear substantial financial and social burdens in their care. Patients making decisions about medical care often have to weigh the high cost of drug treatment and the limited experience in the medical community of using the drug.[3]

In response to challenges faced by patients with rare diseases, Congress, the FDA, the National Institutes of Health (NIH), and other government entities have initiated several programs intended to benefit the rare disease community. Two of the most notable examples of rare disease-focused policymaking are at the center of today's hearing: the 1983 Orphan Drug Act and the 2022 Inflation Reduction Act.

The Orphan Drug Act established certain regulatory and financial incentives for drugs approved by the FDA for rare diseases, including a tax break for research focused on rare diseases and a guaranteed 7-year exclusivity period during which time the FDA is prevented from approving a drug with the same active ingredient for the same disease. A "drug for a rare disease" was originally defined as one in which a limited patient market could otherwise prevent recovery of the investment made to develop a given product (the statute was later amended to include diseases with a prevalence of fewer than 1 in 200,000 US patients when drug companies generally refused to provide financial information to the FDA necessary to earn the designation under the original definition). The goal of these incentives was to help provide

[1] For providing research and drafting support for this statement, I would like to acknowledge the assistance of Alexander C. Egilman, Helen Mooney, Anushka Bhaskar, Liam Bendicksen, Ian Liu, Matthew Martin, and William Feldman.

[2] https://ncats.nih.gov/news-events/news/rare-disease-day-at-NIH-2023-putting-hope-into-action

[3] Kesselheim AS, McGraw S, Thompson L, O'Keefe K, Gagne JJ. Development and use of new therapeutics for rare diseases: views from patients, caregivers, and advocates. The Patient: Patient-Centered Outcomes Research 2015;8(1):75-84.

encouragement for drug manufacturers to enter the rare disease market, since the small number of patients taking these drugs might not provide enough revenue to ensure a return on investment.

Since 1983, the number of rare disease drugs approved by the FDA has grown substantially. By 2023, 51% of the FDA's new drug approvals had an Orphan Drug Act designation.[4] Although some have taken these trends to conclude that the Orphan Drug Act's incentives were successful, in actuality, studies show that the tax breaks amount to a relatively small value and the 7-year exclusivity period is often eclipsed by the thicket of 20-year patents that brand-name drug manufacturers routinely build around their products.[5] In a recent cohort of drugs facing generic or biosimilar competition, we found that drugs for rare diseases had a median market exclusivity length of about 13.7 years, with about a quarter enjoying 17 years or more.[6]

In fact, the rapid acceleration in drug development for rare disease drugs over the past 40 years has been more attributable to other important changes in the therapeutic market. First, NIH-funded research in government and academic laboratories has helped catalyze a transformation in our understanding of the biochemical bases of rare disease, which has helped scientists and physicians identify genetic and enzyme deficiencies that cause rare diseases and design drugs with mechanisms that can treat these deficiencies. Many of the most transformative drugs and treatment pathways identified over the past few decades relate to rare diseases.[7] Second, the FDA has exercised maximal regulatory flexibility around drugs for rare diseases, such that it now routinely accepts shorter, smaller, and less-rigorously designed pivotal trials to support the approval of drugs for rare diseases than for non-rare disorders.[8] Many drugs for rare diseases also fall into one of the FDA's various expedited development pathways, such as accelerated approval, in which the FDA will grant drug approval based on changes to highly preliminary "surrogate measures" (e.g., laboratory tests). Use of surrogate measures allows for clinical trials that are less expensive than studies measuring clinical outcomes and can yield positive findings even when the actual clinical effect of the drug is unknown. Thus, the path to regulatory approval for rare disease drugs has gotten shorter, cheaper, and more predictable than drugs for more common conditions.

Finally, drug manufacturers have learned that developing drugs for rare diseases is quite profitable. Drugs for rare diseases often make blockbuster revenues: in a 2023 study published in JAMA, we found that drugs initially approved for an Orphan Drug Act-designated condition were just as lucrative for their manufacturers as drugs developed for more common conditions: among 315 drugs marketed from 2008 to 2015, median 5-year net sales were $719 million for drugs initially approved with Orphan Drug Act designations and $812 million for other drugs.[9] In addition, drugs treating rare diseases are more consistently covered by Medicare and private insurers,[10] which under the Affordable Care Act, must provide minimum essential coverage including at least one drug in every class. When drugs for rare diseases are just as revenue-generating as drugs for more common conditions, but can be developed based on publicly-funded discoveries and given substantial regulatory advantages, the market for drugs to treat these diseases will be robust.

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[4] https://www.fda.gov/media/175253/download?attachment

[5] Sarpatwari A, Beall R, Abdurrob A, He M, Kesselheim AS. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. Health Affairs 2018;37(5):732-737.

[6] Rome BN, Lee CC, Kesselheim AS. Market exclusivity length for drugs with new generic or biosimilar competition, 2012-2018. Clinical Pharmacology and Therapeutics 2021;109(2):367-371.

[7] Kesselheim AS, Tan YT, Avorn J. The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. Health Affairs 2015;34:286-294.

[8] Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA 2011;305:2320-2326.

[9] Tu SS, Nagar S, Kesselheim AS, Lu Z, Rome BN. Five-year sales for newly marketed prescription drugs with and without initial Orphan Drug Act designation. JAMA 2023;329(18):1607-1608.

[10] They may have prior authorization or other utilization management requirements due to their massive prices.

Despite these trends in drug innovation, one barrier above all threatens to undermine access to therapy for patients with rare diseases—their price. In 2007, the median launch price of a new drug was about $2,000 in annual (or total) treatment costs; by 2021, the median launch price surpassed $180,000. Drugs for rare diseases are among the highest-priced drugs in the world, with prices for recent gene therapies set at as much as $4 million for a single treatment. Drug prices in the US are far higher than they are elsewhere in the world because we allow manufacturers to set whatever price they want for their products and then to raise that price over time without restriction. In the context of unprecedented increases in brand-name drug prices, the IRA was passed to give Medicare the ability for the first time to negotiate a fair price for a small number of top-selling drugs with over $200 million per year in Medicare spending, with negotiations to begin 7 years (or 11 years, for biologics) after FDA approval and the negotiated price to take effect 9 years after approval (13 years for biologics). IRA negotiation was intended to help achieve fair prices—rather than the exorbitant, manufacturer-set prices established in the years after launch—for patients taking top-selling drugs, when those drugs had already made billions of dollars in manufacturer revenue and might have been approaching the end of their exclusivity periods. Since surveys indicate that as many as 30% of patients struggle with high drug costs, fairer prices can increase medication adherence.[11] Cost-related medication non-adherence is exacerbated for patients with rare diseases, who must face the highest-priced drugs in the market. Lower prices can also increase access to drugs by helping reduce the utilization management requirements set up by insurance companies to manage their highest-priced products.

Medicare negotiation was designed to arrive at a reasonable price based on factors such as the extent to which the drug addresses unmet medical need, development costs, production costs, and public funding of the key discoveries, with a ceiling set of 25% lower than the manufacturer's price for drugs 9-16 years after FDA approval. The IRA Medicare price negotiation was estimated to save the US government approximately $100 billion over the following decade. Negotiation for the first group of 10 drugs selected is currently underway; the CEO of AstraZeneca commented that the process has been "relatively encouraging."[12]

The IRA identified some categories of drugs that would be automatically excluded from negotiations, of which the one most relevant to today's hearing is "sole orphan" drugs. These are drugs that are designated and approved for a single rare disease. The idea was to exclude a small number drugs intended for only a very limited population of patients, and to let Medicare instead prioritize drugs used by many more patients. In a recent JAMA Internal Medicine study, we examined the 282 top-selling drugs with greater than $200 million in Medicare spending any year between 2012 and 2021.[13] Among these, 25 (9%) were sole orphan drugs. Notably, even this set of drugs for extremely limited patient populations are massively revenue-generating products. The median sole orphan drug from the years 2012-2021 had earned $11 *billion* in global revenues by 2023 with Medicare spending on these products increasing from $3.4 billion in 2012 to $10.0 billion in 2021. Thus, the current rare disease drug exclusion already potentially diverts billions of dollars in savings from Medicare by excluding these drugs from negotiation. Despite the sole-orphan exclusion, many drugs that have been approved by the FDA for rare diseases are potentially subject to Medicare negotiation if they reach top-selling status; in our JAMA Internal Medicine paper, we also found 70 lucrative drugs approved for multiple rare disease indications or for both rare and more common disease indications.

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[11] Kirzinger A, Montero A, Sparks G, Valdes I, Hamel L. Public opinion on prescription drugs and their prices. Kaiser Family Foundation. August 21, 2023. Available at: https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/

[12] https://www.statnews.com/2024/02/08/astrazeneca-medicare-drug-pricing/

[13] Vogel M, Zhao O, Feldman WB, Chandra A, Kesselheim AS, Rome BN. Cost of exempting sole orphan drugs from Medicare negotiation. JAMA Internal Medicine 2024;184(1):63-69.

In summary, although patients with rare diseases face important medical challenges and there is substantial unmet medical need relating to these diseases, pharmaceutical innovation for rare diseases has markedly increased over the last three decades. The IRA is likely to improve access to high-priced drugs by allowing Medicare to negotiate fair prices for a small number of top-selling drugs nearing the end of their market exclusivity periods. Although some of the smallest-market rare disease drugs are excluded from negotiation, patients taking drugs indicated for multiple rare diseases and those indicated for rare diseases as well as more common diseases are in line to benefit from the IRA-negotiation.

## II. Some Bills Being Considered by This Subcommittee at Our Hearing Support Rare Disease Drug Innovation, While Others Do Not

Today's hearing focuses on several bills intended to change the current set of laws and regulations governing innovation and the cost of drugs for rare diseases. As I will discuss below, some bills try to expand the exclusions for the IRA or delay the onset of negotiation. Because they will make rare disease drugs less affordable while not meaningfully shifting incentives for innovation, they should be rejected. Another bill closes a new loophole created by a federal appeals court that, if passed, would help prevent manufacturers of rare disease drugs from manipulating the market and preventing timely competition; it should be approved. A final bill that seeks to extend one of the priority review voucher programs, an unsuccessful regulatory incentive program covering certain kinds of rare disease innovation, should be rejected.

### A. H.R. 5539: Optimizing Research Progress Hope And New (ORPHAN) Cures Act

The *ORPHAN Cures Act* has two primary components: it changes one of the key exclusions for Medicare price negotiation under the Inflation Reduction Act (IRA) related to rare disease drugs and it changes the calculation of the time until a drug qualifies for Medicare price negotiation. This bill ***should not*** be advanced in this subcommittee because it unnecessarily undermines the IRA's criteria for drug price negotiation and does not offer a pathway for providing real incentives for meaningful rare disease drug innovation. I will discuss each of these two components of the bill in turn.

#### 1. *Expanding IRA exemption for "multiorphans"*

The *ORPHAN Cures Act* proposes to expand the "sole orphan" exclusion contained in the IRA to cover drugs FDA-approved for "one or more" rare disease indications, which we have called "multiorphans." In our JAMA Internal Medicine study, we found 20 additional top-selling multiorphan drugs approved from 2012-2021 for two or more different rare disease indications only, with no other indications for more common diseases. Thus, the *ORPHAN Cures Act* threatens to expand the scope of the rare disease exemption further to cover about twice as many top-selling products. Under the *ORPHAN Cures Act*, between the sole orphan and multiorphan drugs, almost 10% of Medicare spending would be completely off the table for price negotiation.

What justification could there be for reducing the scope of the Inflation Reduction Act in this way? Some may argue that under the current IRA framework, manufacturers of sole-orphan drugs may not pursue subsequent rare disease indications, preferring instead to stay within the exemption. However, there are multiple reasons to believe that this concern is overblown. First, multiorphan drugs qualifying for IRA negotiation are *extremely profitable*—potentially even more so than sole orphan drugs. In our JAMA Internal Medicine study, between 2012 and 2021, Medicare spent $108 billion dollars on the 20 multiorphans. The median multiorphan drug in our sample had $746 million in peak annual Medicare expenditures, far higher than the median sole orphan drug ($567 million). When weighing these massive revenues against the possibility that under the IRA, Medicare will seek to negotiate a fair price for the drug that could be as little as 25% of a reduction in the price that would take effect 9-13 years after FDA approval, a rational drug company would still likely seek to pursue a multiorphan strategy.

Second, manufacturers might still pursue subsequent rare disease indications for their FDA-approved rare disease drug if they believe that revenues from payors outside of Medicare would make up for any reduction in revenue from Medicare negotiation. It is of course ethically dubious for manufacturers to refuse to pursue potentially valid uses of their drug for fear of qualifying for IRA negotiation, which is intended to achieve a fair (not rock-bottom) price for their drugs 9-13 years after they are first FDA-approved. But assuming manufacturers in such a circumstance will prioritize profits over potential breakthroughs for patients with rare diseases with unmet needs, manufacturers could still conduct clinical trials for additional patient populations while foregoing FDA approval and rely on off-label use of their drugs, which are often reimbursed by payors particularly when they are supported by high-quality evidence.

Finally, given the important savings to government spending that will result from IRA negotiation, if this subcommittee was worried that sole orphan drugs would not be tested for other rare disease indications, Congress could provide additional funds to the NIH to pursue those additional indications. For example, in the case of pomalidomide, which was approved for multiple myeloma and then subsequently for Kaposi's sarcoma (2 different rare cancers), the Kaposi's sarcoma trial was sponsored and conducted by the National Cancer Institute. The government could use Section 1498, which permits government use of patent-protected products, to secure adequate supply of the drug at issue to conduct the trials without having to pay the manufacturer's excessively high price for the rare disease drug.

In addition to public funding of trials for rare disease drugs with unmet medical need, another possible policy choice would be to eliminate the Orphan Drug Act sole-orphan exemption altogether. The IRA already protects low-revenue drugs by excluding from negotiation any drug with Medicare sales below $200 million. If any drug – including one that treats a rare disease – exceeds this threshold, it is likely to have made its manufacturer many billions of dollars in revenue by the time of negotiation. In our JAMA Internal Medicine study, we found that for the 10 sole-orphan rare disease-designated drugs that could become eligible for price negotiation under the IRA in coming years, the actual and projected revenues ranged from $4 billion to $72 billion in the years before drugs would be old enough to face price negotiation under the current IRA framework. The sole orphan rare disease drug exemption could therefore be eliminated to obtain additional savings for patients and taxpayers and to eliminate any hypothetical disincentive for developing additional indications for these drugs.

2. *Delaying IRA negotiation until 7-11 years after approval of a non-rare disease indication*

The other major component of the *ORPHAN Cures Act* is that it changes the timing of Medicare drug price negotiation for drugs that have both rare disease and non-rare disease indications so that negotiation cannot start until at least 7-11 years after the FDA approval of the non-rare disease. Earlier approvals for rare diseases would not count towards that time interval.

This amendment to the IRA would have the effect of undermining the savings and patient benefits derived from Medicare drug price negotiation. According to our JAMA Internal Medicine analysis, among the top-selling drugs in our sample from 2012-2023 that would have qualified for IRA negotiation if it had been in effect, there were 13 drugs that had rare disease approvals prior to approvals for non-rare disease conditions—with a median of about 2 years (interquartile range: 1.2-7.3 years) between the rare disease approval and the subsequent non-rare disease approval, although the time differential was as high as 15.5 years in the case of epoetin alfa (Epogen) for anemia associated with end-stage renal disease.[14] The total spending on these 13 drugs just in Medicare from 2012-2021 *alone* was $75 billion. Delays in the timely negotiation of these drugs under the IRA would therefore considerably reduce expected savings.

B. H.R. 5547: Maintaining Investments in New Innovation (MINI) Act

[14] https://www.biopharmadive.com/news/amgen-enbrel-patent-thicket-monopoly-biosimilar/609042/

The *MINI Act* delays the start of Medicare drug price negotiations under the IRA from 7 to 11 years for small-molecule (non-biologic) drugs in a new category it creates called "advanced drug products," which are defined as any drug that "incorporates or utilizes a genetically targeted technology (as defined in section 529A(c)(2) of the Federal Food, Drug, and Cosmetic Act) that may result in the modulation (including suppression, up-regulation, or activation) of the function of a gene or its associated gene product.'' The Food, Drug, and Cosmetic Act definition of a "genetically targeted technology" is "technology comprising non-replicating nucleic acid or analogous compounds with a common or similar chemistry that is intended to treat one or more patient subgroups, including subgroups of patients with different mutations of a gene, with the same disease or condition, including a disease or condition due to other variants in the same gene." Because drugs meeting this description already generate substantial revenues and delaying Medicare price negotiation will have no effect on generating incentives for the discovery and development of these drugs, this bill simply undermines the IRA and reduces the expected benefits of it to patients and the health care system. It therefore ***should not*** be advanced in this subcommittee.

Since the IRA was enacted, critics from the drug industry have raised concern about the different time periods before they qualify for Medicare drug price negotiation: 7 years for small-molecule drugs and 11 years for biologic drugs (the prices then take effect 2 years later in each case). One argument is that the shorter protection for small molecule drugs will lead manufacturers to abandon small-molecule drug development in favor of biologic drugs. For example, an executive at Lilly argued that they would not have pursued a small-molecule drug to treat breast cancer without the additional 4 years of protection from negotiation that biologic drugs get.[15] But that drug was approved in 2017 and peak global revenue is expected to be around $3 billion per year at the end of 2029. If its market exclusivity continues until 2032 (15 years, which is around the median time) and assuming the IRA results in *zero* Medicare revenue starting in 2027 (which far exceeds what it is designed to do), the change in present value (or potential profits to be realized) in 2017 would decrease from $24 billion to $20 billion. It would be absurd for a pharmaceutical manufacturer to set aside small-molecule drug innovation that could lead to revenues at that level.

When considering the *MINI Act*, it is important to recognize the scope of revenues that the drugs subject to Medicare negotiation will have earned even after 9 years on the market. Among the first 10 drugs selected for price negotiation, 7 were small-molecule drugs (Eliquis, Farxiga, Imbruvica, Januvia, Jardiance, Xarelto, Entresto) and global revenues for these products in the first 9 full years after FDA approval ranged from approximately $15 billion to $57 billion *per drug*.[16] Take the hypothetical case of a drug company that has a choice between investing in two different technologies that are 5 years away from FDA approval: a genetically targeted small molecule technology vs. a biologic drug. First, the potential difference in revenue 14 vs 18 years in the future would have little impact on the investment decision. Second, if that drug company could look into a crystal ball and conclude that the genetically targeted small molecule technology would be subject to the IRA and a negotiated price would be implemented 9 years after approval, it would mean that the genetically targeted technology would be top-selling product, with at least $200 million in Medicare sales.

The statutory definition in the *MINI Act* is vague as to what kinds of drugs qualify as "advanced drug products." Even the concept of a "genetically targeted technology" does not necessarily limit its scope, since an advanced drug product may only "incorporate or utilize" the technology, so the universe of qualifying products could be large. In addition, "genetically targeted technology" as defined in the Food, Drug, and Cosmetic Act, includes "non-replicating nucleic acid or analogous compounds," and it is not clear

[15] Skovronsky DM. The IRA's nonsensical distinction between small- and large-molecule drugs. STAT News First Opinion. May 9, 2023. Available from: https://www.statnews.com/2023/05/09/ira-inflation-reduction-act-small-large-molecule-drugs/

[16] Results compiled through 2022 using global revenue data. Entresto only contributed 7.5 years of data and Jardiance 8.5 years. This is a conservative estimate, since the numbers are not adjusted for inflation.

where to find the limits of what counts as analogous compounds. Given how vague the statute is, it is hard to predict what sort of drugs would qualify, and if passed, the pharmaceutical industry would certainly petition CMS to adopt as broad a definition as possible. Would the exclusion cover products like the ivacaftor (Kalydeco), approved to treat a specific genetic mutation in a subset of patients with cystic fibrosis? Although it is clearly not a non-replicating nucleic acid, it targets a genetic mutation; ivacaftor and its follow-on products ivacaftor/lumacaftor (Orkambi) and ivacaftor/tezacaftor (Symdeco) address different genetic mutations in patients with cystic fibrosis. Kalydeco and Orkambi alone were estimated to have a net present value in 2013 of $33 billion.[17] A drug with the promise of such massive revenues offers sufficient incentives for development even with Medicare negotiation 9 years after approval (assuming there is greater than $200 million in ivacaftor product-related sales in Medicare). Instead, it would be better to negotiate a price to help ensure coverage of the drug in ways that could benefit patients with rare diseases, since Vertex's list prices for these products at greater than $250,000 per patient per year.

Because this bill is excessively vague and because there is no evidence that another exception needs to be added to the IRA Medicare drug price negotiation framework, this bill ***should not*** be advanced in subcommittee.

C. H.R. 7383: Retaining Access and Restoring Exclusivity (RARE) Act

The *RARE Act* does not address the IRA, but focuses on the Orphan Drug Act. It adjusts the language in the Orphan Drug Act relating to the 7-year market exclusivity provision. The Orphan Drug Act protects new drugs treating rare diseases from direct competition by blocking the FDA from approving other versions of the same active ingredient for the "same disease or condition" for 7 years. The *RARE Act* amends the language to "same approved use or indication within such rare disease or condition." This bill ***should*** be advanced in this subcommittee because it helps close an important loophole in the Orphan Drug Act that was created in 2021 by the Eleventh Circuit Court of Appeals.

The story behind the *RARE Act* is remarkable. A very rare neurologic condition called Lambert-Eaton Myasthenic Syndrome (LEMS) affecting only a few hundred patients in the US had been treated effectively with a non-FDA-approved chemical called 3,4-diaminopyridine (or amifampridine) since the 1970s. Physicians at Mayo Clinic in the 1980s and later at Duke University in the 1990s confirmed in controlled trials (supported by grants from the NIH and US Public Health Service) that the drug worked for LEMS with acceptable side effects. Jacobus, a small New Jersey-based drug company that synthesized the product, received an Orphan Drug Act designation for use of amifampridine in LEMS in 1990, but then chose to make the drug available *for free* to LEMS patients under the FDA's expanded access program rather than pursue regulatory approval, given the relative ease of synthesis and the small disease market.

By the 2000s, another company, BioMarin started developing its own version of amifampridine and received an Orphan Drug Act designation for LEMS in 2009. Catalyst Pharmaceuticals bought the drug's rights in 2012 and filed a new drug application with the FDA in 2015, receiving approval for its use in adults in 2018. Catalyst set a price of $375,000 per year of therapy of amifampridine.

Also, in 2018, Jacobus re-filed an NDA for its formulation of amifampridine, which the FDA subsequently approved for use in LEMS in children aged 6-16. Catalyst then sued, arguing that Jacobus' approval was blocked under the Orphan Drug Act's 7-year market exclusivity period. FDA responded that Jacobus's version did not infringe upon Catalyst's exclusivity because of the different population it aimed to treat. In *Catalyst Pharmaceuticals v. Becerra*, the Eleventh Circuit disagreed with the FDA, concluding that the phrase "same disease or condition" in the Orphan Drug Act precluded FDA's approval of Jacobus' version of amifampridine, because the two products contained the same active ingredient, and the disease

[17] Hollis A. Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi. Healthcare Policy 2019;15(1):70-80.

affected adults and children equally.[18] Thus, the FDA was found to unlawfully construe the pediatric and adult versions of a disease as different conditions for purposes of Orphan Drug Act exclusivity.[19]

The implications of the *Catalyst Pharmaceuticals* decision are important. Most significantly, the decision will make it harder for manufacturers producing generic or biosimilar versions of drugs with rare diseases to reach the market in a timely fashion. The availability of these alternatives can contribute to price competition that increases the accessibility of exceedingly expensive drugs for rare diseases. Under the *Catalyst Pharmaceuticals* framework, manufacturers may be able to use the Orphan Drug Act to delay entry of competition indefinitely. As another example, deferasirox (Exjade) is a treatment for chronic iron overload. Exjade was originally approved in 2005 for the rare disease indication of chronic iron overload due to blood transfusions in patients aged 2 and older. Orphan Drug Act exclusivity for this indication ended in 2012. Then, Exjade received approval in 2013 for a second Orphan Drug Act-designated indication (chronic iron overload in alpha-thalassemia). Under a *Catalyst Pharmaceuticals* framework, generic versions of deferasirox would likely not be able to be marketed for rare disease patients with the first indication alone (blood transfusions) until the Orphan Drug Act market exclusivity would end for the second indication, even if the drug patents had expired before that, because *Catalyst Pharmaceuticals* would likely require the FDA to consider "chronic iron overload" to be the "same disease" in both cases.

Because *Catalyst Pharmaceuticals* inhibits timely generic or biosimilar competition for rare disease drugs, it should be overturned via the *RARE Act*. The Orphan Drug Act was never intended to provide a pathway for manufacturers to obtain perpetual market exclusivity. *Catalyst*'s overly broad interpretation of the current Orphan Drug Act language raises the specter that patients with rare diseases may never benefit from timely price-lowering competition for the drugs they depend upon, and that numerous rare disease drugs currently facing generic or biosimilar competition may have their competing versions removed from the market. It also increases the risk of shortages for patients with rare diseases, since availability of numerous manufacturers serving a market can help stabilize supply.

The FDA would likely support this bill, and this subcommittee should as well.[20] For all of these reasons, the subcommittee ***should*** advance the *RARE Act*.

D. H.R. 7384: Creating Hope Reauthorization Act of 2024

The *Creating Hope Reauthorization Act of 2024* does not directly relate to the IRA or the Orphan Drug Act. Rather, it extends the sunset provision of the Priority Review Voucher program for pediatric rare diseases for 4 years. This bill ***should not*** be advanced in this committee because there is no evidence that it incentivizes rare pediatric disease drug development. To the contrary, there is evidence that it undermines FDA regulation of all drugs, wastes taxpayer money, and specifically harms patients with rare tropical diseases.

To understand why this bill will not meaningfully help patients with rare pediatric diseases, it is first important to understand what the priority review voucher is.[21] Under the Prescription Drug User Fee Act (PDUFA), as revised in 2002, the FDA is supposed to decide on new drug applications within 10 months of receiving a full application. Drugs that appear to represent a "therapeutic advance" or meet an

[18] Catalyst Pharmaceuticals v. Becerra, 14 F.4th 1299 (11th Cir. 2021).

[19] Bendicksen L, Kesselheim AS, Daval CJR. FDA and *Chevron* deference: a case review. Food and Drug Law Journal 2023;78(4):371-390.

[20] Ed Silverman, *Despite court ruling, FDA will continue with its approach to approving orphan drug exclusivity*, STAT (Jan. 23, 2023), https://www.statnews.com/pharmalot/2023/01/23/fda-orphan-drug-rare-disease-catalyst-exclusivity/.

[21] The testimony in this section is based in part on testimony I previously gave to the House Energy and Commerce Committee when the rare pediatric disease priority review voucher was up for renewal in 2020. *See* Kesselheim AS. Congress Should Support Development of New Treatments for Pediatric Rare Diseases, But Not with Priority Review Vouchers. Hearing before the House Committee on Energy and Commerce Subcommittee on Health (Rep. Eshoo, Chairwoman). July 29, 2020. https://www.congress.gov/congressional-report/116th-congress/house-report/551/1

unmet medical need may qualify for priority review, which reduces the goal FDA review-time to 6 months. The FDA meets its review goals over 90% of the time, and approves over 80% of the applications it receives. In the modern era, about two-thirds of new drugs already qualify for priority review, even though many of them do not represent meaningful clinical advances. The remaining drugs qualifying for standard review are expected to have therapeutic qualities similar to those of already-marketed drugs, and to lack any sort of even hypothetical special innovation that would lead the FDA to agree to speed up the normal time frame of its review.[22]

In 2006, economists proposed that it would be valuable for pharmaceutical manufacturers sponsoring run-of-the-mill, non-priority review drugs to short-circuit the FDA's usual processes and have their non-innovative drugs reviewed on the priority review time frame.[23] Getting earlier entry into the market would allow manufacturers to start charging high launch prices sooner and earning revenues, some of which might bring in a billion dollars of revenue or more per year despite being non-innovative. (In other work, we found that, of the 50 top-selling drugs in Medicare, about half had limited added clinical benefit, accounting for $19.3 billion per year in estimated net spending.[24]) These revenues would be earned due in large part to taxpayer spending through government insurance programs such as Medicare and Medicaid, which cover drug costs for over 100 million people in the US. It could also allow them to enjoy a longer period of market exclusivity before their patents would expire and give way to price-lowering generic or biosimilar competition.

Thus, a plan was put in place to address a drug development problem: lack of new drugs for neglected tropical diseases. These tropical diseases are infectious diseases such as tuberculosis, dengue, leishmaniasis, and malaria that occur predominantly in resource-poor settings around the world but also affect small numbers of patients in the US, making them rare diseases under the Orphan Drug Act. Since these diseases occur primarily among immigrants and un- or under-insured patients in the US (as well as around the world in settings with underdeveloped health care systems that have limited ability to pay for drug treatments), the pharmaceutical industry has invested little in treatments for these conditions.[25] The plan was devised to grant new manufacturers of neglected tropical disease drugs priority review vouchers that they could use to accelerate the review of another, non-innovative standard-review drug, or sell to another manufacturer that had such a drug in its pipeline. The economists estimated that this earlier time to market could be worth up to $325 million per drug for a lucrative product of the company that bought this queue-jumping priority review voucher from the innovator company that brought the neglected tropical disease drug to market. The hope was that winning and then re-selling these vouchers could create a powerful economic incentive to draw companies into research that would lead to treatments for neglected tropical diseases.

It hasn't worked out that way, on multiple levels. First, over the last 17 years, there is no controlled evidence that the neglected tropical disease priority review voucher program generated research and development leading to new treatments for neglected tropical diseases. In a study from PORTAL, we first identified products potentially eligible for a priority review voucher entering Phase 1 trials between 1 January 2000 and 31 December 2014 (7 years before and after the creation of the voucher).[26] We found that the trends in new Phase 1 trials for drugs with primary or secondary neglected tropical disease indications did not change (from 1.9% from 2000-2007 to 1.5% from 2008-2014). That is, the program

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[22] Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category—implications for patients. New England Journal of Medicine 2014;370:1252-1258.

[23] Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. Health Affairs 2006;25:313-324.

[24] Egilman AC, Rome BN, Kesselheim AS**.** Added therapeutic benefit of top-selling brand-name drugs in Medicare. JAMA 2023;329(15):1283-1289.

[25] Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. Lancet 2002;359: 2188-2194.

[26] Id.

did not increase the rate of companies starting clinical development of new neglected tropical disease drug products.[27]

Second, the voucher has turned out to be a nuisance to the FDA and threatened larger public health problems. In a report filed by the US Government Accountability Office, FDA officials raised concerns that the priority review program impaired the FDA's ability to define its public health priorities by hastening review of unremarkable products that would not otherwise merit an expedited timeline.[28] The agency also reported that, despite the additional user fee associated with using a voucher, the program strained the agency's resources since the FDA cannot quickly hire and train new staff with the necessary expertise.[29] Too-speedy FDA review in cases when expedited review is not essential may lead to bad regulatory decision-making, as demonstrated in a review published in the New England Journal of Medicine finding that drugs approved in the 2 months before their normal PDUFA deadlines were more likely to be withdrawn for safety reasons than drugs approved without such a looming deadline, or to have a major safety warning added to its labeling, and/or to have one or more dosage forms discontinued by the manufacturer.[30]

Although there was no controlled evidence at the time that the original priority review voucher was promoting research and development in neglected tropical diseases, Congress nonetheless extended the program in 2012 to allow priority review vouchers to be issued for rare pediatric diseases. Unfortunately, the pediatric rare disease priority review voucher did not succeed any better in promoting research and development in this field. In a study we published in Health Affairs in 2019, we found no change in the rate at which drugs eligible for a pediatric priority review voucher were introduced into clinical testing, compared to the rate of drugs for rare diseases affecting adults. [31] We also found no significant differences in the rate at which such pediatric drugs progressed from Phase II to Phase II and from Phase III to approval, although we did find a statistically significant effect on the timing of drugs moving from Phase I to Phase II.[32] We concluded that, since the program was not associated with a change in the number or rate of new drugs starting clinical testing, other policies may be needed to expand the pipeline of therapies for rare pediatric diseases.[33]

The expansion of the priority review voucher to pediatric rare diseases (and later to medical countermeasures in 2016) revealed new flaws in the priority review voucher concept. First, it became clear that the value of the voucher is highly dependent on the number of vouchers available in the market. That is, because there are limited supplies of potentially blockbuster standard-review drugs to which the voucher could apply, if there are too many vouchers on the market, the amount a drugmaker would be willing to pay for them would be diminished. Now that numerous vouchers have been issued since 2007, vouchers are consistently being sold on the market for approximately $80-110 million.[34]

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[27] Id.

[28] Government Accountability office (GAO-16-319). Rare diseases: too early to gauge effectiveness of FDA's pediatric voucher program. 2016.

[29] Id.

[30] Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. New England Journal of Medicine 2008:358(13):1354-1361.

[31] Hwang TJ, Bourgeois FT, Franklin JM, Kesselheim AS. Impact of the priority review voucher program on drug development for rare pediatric diseases. Health Affairs 2019;38(2):313-319.

[32] Id.

[33] Id.

[34] The most recent voucher was sold on February 6, 2024 for $103 million reportedly to "an undisclosed buyer." Brennan Z. Priority review voucher updates: Who's won PRVs, who's bought them, and how much they're selling for. Endpoints News. Available at: https://endpts.com/priority-review-voucher-updates-whos-won-prvs-whos-bought-them-and-how-much-theyre-selling-for/. *See also* Kesselheim AS. Encouraging drug development for neglected diseases — the trouble with FDA review vouchers. New England Journal of Medicine 2008;359:1981-1983.

The rare pediatric disease voucher also made clear that there is nothing in the voucher program that requires sponsors to make voucher-eligible therapies affordable to patients. High prices charged for products developed under the priority review voucher program contribute to limited access by patients for these therapies. For instance, the manufacturer of the gene therapy beremagene geperpavec, approved in 2023 for dystrophic epidermolysis bullosa, received a rare pediatric disease priority review voucher. At a price of $24,450 per 2.5 ml bottle, annual treatment costs for this condition could range from $300,000 to $600,000 per year depending on the extent of disease, with the expected lifetime costs at the low end of that pricing range of treating a patient being between $15 million and $22 million.[35] This issue has also come up for products granted tropical disease priority review vouchers, some of which their manufacturers price at alarmingly high levels.[36] More recent evidence suggests that rare pediatric diseases may not need a voucher anyway. In a review of recent rare pediatric disease drugs, we found that mean annual global revenues reached blockbuster status by their third year on the market.

Overall, the priority review voucher program was ill-conceived and in the 17 years since its creation, there has been no systematic, rigorous evidence that it has proven useful in achieving its goals—stimulating the generation of new treatments for tropical diseases, rare pediatric diseases, or medical countermeasures. Indeed, the studies cited in these comments demonstrate that it has had virtually no measurable impact on the emergence of new treatments, although the sale of such vouchers has been enormously lucrative to the companies that were awarded them. As the voucher program has expanded over that time, it has paradoxically undermined its own goals, as one of the economists who devised the voucher recently recognized, when he and a colleague concluded that "Congress should be cautious about expanding the voucher program, because increasing the number of vouchers sharply decreases the expected price" of each voucher issued.[37] At the same time, the voucher program has been criticized by the FDA for disrupting its public health-based process for prioritizing which drugs should get faster regulatory review and for putting an unnecessary strain on the agency's already-limited resources.

Since priority review voucher program has been a failure, the next step to correcting Congress's mistake in creating it would be to allow the rare pediatric disease priority review voucher to sunset and ***not to pass H.R. 7384***. A better pathway forward for Congress would be to consider more direct ways to encourage drug development for pediatric medical conditions. Greater up-front funding through the NIH or tax credits could be offered for research into certain rare pediatric diseases lacking adequate treatment. Because of the public's involvement in reducing the risks and costs of research and development, along with such investments should come commitments to make the drugs available at a reasonable price so that children with rare diseases can optimally benefit from useful new therapeutic options. This approach, not the rare pediatric disease priority review voucher, will get children with rare diseases the scientific discovery and clinical trials they need and the treatments they deserve.

## III. Additional Policy Proposals That Could Support Availability of and Access to Treatments for Rare Diseases

I have testified to this before, but it is worth saying again[38]: the Inflation Reduction Act need not reduce incentives for meaningful pharmaceutical innovation. Large pharmaceutical manufacturers invest

[35] Raymakers AJN, Kesselheim AS, Mostaghimi A, Feldman WB. Estimated Spending on Beremagene Geperpavec for Dystrophic Epidermolysis Bullosa. JAMA Dermatology 2024 Jan 31:e235857.

[36] Delaunay S, et al. Letter from Medicins Sans Frontieres, Drugs for New Diseases Initiative and TB Alliance to Hon. Tom Harkin and Hon. Lamar Alexander. July 30 2014. (on file with Dr. Kesselheim)

[37] Ridley DB and Regnier S. The commercial market for priority review vouchers. Health Affairs 2016;35(5):776-783.

[38] The testimony in this section is based in part on testimony I previously gave to the Senate HELP Committee relating to drug pricing. *See* Kesselheim AS. High drug prices in the US: what we can learn from other countries (and some US states). Hearing

only about 10-20% of their revenues in research and development, so providing exceedingly high profit margins to such manufacturers indefinitely does not directly translate to substantial investment in innovation. A considerable amount of work from our research group has documented how transformative drug innovation often emerges in large part from publicly funded research and development, even though this is rarely reflected in the pricing of the resulting drugs, or in commensurate "payback" to the funding agencies that made them possible. As long as Congress continues funding for the National Institutes of Health, then we can be assured that the next generation of important new therapeutics will be in the pipeline. Indeed, in December 2023, the Congressional Budget Office released a letter revealing that "the share of venture capital reaching pharmaceutical companies has been trending upward" since the IRA was enacted.[39] If concern arises about insufficient support to bring certain types or classes products through clinical testing and regulatory approval—such as "advanced drug products"—the recent evolution of Covid-19 treatments and vaccines has shown that public funding and partnerships with industry can help advance highly promising new treatments.

In the long term, the IRA is actually likely to improve meaningful innovation. The current system in which brand-name manufacturers are rewarded with high US prices for new drugs that have limited clinical advantages may even reduce the pressure for them to develop medications that truly add clinical value. It is notable that fewer than one-third of new drugs approved in the past decade were rated as providing high clinical value compared to existing alternatives, although this has not led to lower prices. If drug prices more adequately reflected the clinical benefits they offer to patients—which is one of the guiding principles leading CMS in its negotiation process—this would incentivize more meaningful pharmaceutical innovation, and there would be less investment in making trivial changes to existing products and more investment in addressing unmet medical needs. When Medicare exercises its negotiating ability to seek fair prices for drugs towards the end of their exclusivity periods, it incrementally increases the value of new drugs that offer improved outcomes to patients, creating a powerful incentive for manufacturers to invest their resources in bringing to market drugs that will achieve this price premium rather than continue to invest in protecting their years-old products from generic and biosimilar competition.

If Congress is open to amending the Orphan Drug Act or the IRA, it might consider additional proposals to better align the incentives and policies in those bills with the needs of patients suffering from rare diseases. First, as described above, rather than extending the rare disease drug exclusion to top-selling multiorphan products, Congress should consider eliminating the sole-orphan exclusion, since sole-orphan drugs that qualify for Medicare negotiation are top-selling products that need no additional protection to be financially attractive for manufacturers. Instead, Congress should be concerned about providing a pathway to help patients with rare diseases afford those products by subjecting them to negotiation, in the case of the IRA, after a reasonable time on the market. Second, instead of trying to extend negotiation-free periods for a murkily-defined set of "advanced drug products," Congress should authorize Medicare to start negotiation soon after approval to achieve fair prices based on their clinical benefits and value to patients. As an incremental step in that process, Congress might consider reducing the time until negotiation for biologic drugs from 11 years down to the 7-year period set for small molecule drugs. There is no need for biologic drugs to have so long of a negotiation-free period because biologic drugs do not necessarily take longer or cost more to develop than small molecule drugs.[40] Third,

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before the Senate Committee on Health, Education, Labor and Pensions (Sen. Sanders, Chairman). 23 March 2021. United States Congressional Record. Available on-line at: https://www.help.senate.gov/hearings/why-does-the-us-pay-the-highest-prices-in-the-world-for-prescription-drugs

[39] Swagel PL, Director, Congressional Budget Office. Letter to Hon. Jodey Arrington and Hon. Michael Burgess. *Re: Additional Information About Drug Price Negotiation and CBO's Simulation Model of Drug Development.* December 21, 2023.

[40] Beall RF, Hwang TJ, Kesselheim AS. Pre-market development times for biologic versus small-molecule drugs. Nature Biotechnology 2019;37(7):708-711.

Congress should authorize Medicare to set up an independent body that would evaluate the benefits of all new drugs for rare diseases (and non-rare diseases) at the time of approval to determine what sort of additional benefits they offer to patients. The panel could be empowered to provide rapid-turnaround evidence-based reports on new drugs' added clinical value, pricing, and any potential disparities in access. Its recommendations could be non-binding, but the body would be tasked with regularly issuing high-profile data-driven pronouncements on these issues. Patients with rare diseases, who often struggle to find physicians who can help them and drugs that work for them—and anyone who believes that marketplaces function best with more information—should support such an organization.