Documents for the Record – 2/29/2024

Majority

- February 27, 2024 - Statement from ALS Association
- February 27, 2024 - Statement from American Academy of Pediatrics
- February 27, 2024 - Statement from the Center for a Humane Economy, Animal Wellness Action, and Animal Wellness Foundation
- February 27, 2024 - Statement from the Creutzfeldt-Jakob Disease Foundation
- February 28, 2024 - Article from Mr. Simpson
- February 28, 2024 - Statement from EveryLife Foundation for Rare Diseases
- February 28, 2024 - Statement from Mr. Seifert
- February 28, 2024 - Statement from Ms. Lowe
- February 28, 2024 - Statement from Patient Advocacy Organization Coalition on H.R. 1092
- February 28, 2024 - Statement from the AARP
- February 28, 2024 - Statement from the American Society of Health-System Pharmacists (ASHP)
- February 28, 2024 - Statement from the Muscular Dystrophy Association
- February 28, 2024 - Statement from the National Organization for Rare Disorders (NORD)
- February 28, 2024 - Statement from the Save Rare Treatments Task Force
- February 29, 2024 - Statement from the American Association of Tissue Banks
- February 29, 2024 - Statement from the American Society of Hematology
- February 29, 2024 - Statement from the Sickle Cell Disease Partnership
- February 29, 2024 - Statement from Parents of Children with Nephropathic Cystinosis
- February 29, 2024 - Statement from the Society of Thoracic Surgeons
- February 29, 2024 - Statement from the Alliance for Regenerative Medicine
- February 29, 2024 - Statement from the Children's Hospital Association
- February 29, 2024 - Statement from NMDP
- February 29, 2024 - Documents submitted by Rep. Miller-Meeks
    - February 29, 2024 - Statement from Patients Rising
    - February 29, 2024 - Statement from Leukemia & Lymphoma Society
    - February 29, 2024 - Statement from a Coalition of Children's Health and Wellbeing Organizations on H.R. 4758

Minority

- February 2019 - Health Affairs article, "Impact Of The Priority Review Voucher Program On Drug Development For Rare Pediatric Diseases"
- January 2020 - GAO report, "FDA's Priority Review Voucher Programs"

- January 2021 - Clinical and Translational Science article, “Priority Review Vouchers: GAO Report Provides Scant Evidence of Success”
- February 29, 2024 - Statement from Rep. Sarbanes
    - February 29, 2024 - Statement from David Mitchell, Patients for Affordable Drugs Now
- February 29, 2024 - Statement from Families USA
- February 29, 2024 - Statement from the National Multiple Sclerosis Society
- February 29, 2024 - Statement from the Children’s Cancer Cause
- February 29, 2024 - Document submitted by Rep. Schrier
    - February 29, 2024 - Statement from Patients & Providers for Medical Nutrition Equity
- February 29, 2024 - Documents submitted by Ranking Member Eshoo
    - December 4, 2023 - One-pager on the Innovation in Pediatric Drugs Act of 2023
    - December 21, 2023 - Letter from CBO on Additional Information About Drug Price Negotiation and CBO’s Simulation Model of Drug Development
    - February 25, 2024 - Orphanet Journal of Rare Diseases article, “Analysis of the first ten years of FDA’s rare pediatric disease priority review voucher program: designations, diseases, and drug development”
- February 29, 2024 - Document submitted by Rep. Matsui
    - February 29, 2024 - Statement from a Coalition in Support of the PROTECT Rare Act

February 27, 2024

The Honorable Jan Schakowsky
U.S. House of Representatives
2408 Rayburn HOB
Washington, DC 20515

The Honorable Brian Fitzpatrick
U.S. House of Representatives
271 Cannon HOB
Washington, DC 20515

Dear Congresswoman Schakowsky and Congressman Fitzpatrick,

On behalf of the approximately 30,000 people currently living with amyotrophic lateral sclerosis (ALS), their friends and families, and everyone who has been touched by this disease, The ALS Association is pleased to endorse H.R.5663 the ALS Better Care Act, which will increase access to multidisciplinary care clinics for people living with ALS.

ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. Over the course of the disease, people lose the ability to move, speak, and eventually breathe. On average, it takes about a year before an ALS diagnosis is made. The disease is always fatal, usually within five years of diagnosis. There currently is no cure.

Multidisciplinary care is considered the optimal standard for ALS care, it extends and improves the lives of people living with ALS. These clinics provide an array of healthcare services in one visit which reduces the physical, emotional, and financial stress of visiting numerous healthcare providers, and allows individuals living with ALS to spend more of their limited time with loved ones. Care at ALS clinics also addresses the needs of the family members, many who are primary caregivers.

The ALS Better Care Act is urgently needed to increase access to multidisciplinary care clinics. Right now, where a person lives and what financial resources they have determines whether they will be able to receive this life extending and life improving care. Unfortunately, current Medicare reimbursement rates make it nearly impossible to open new clinics and increase existing clinic capacity. This is because the current reimbursement does not cover the cost of the specialized multidisciplinary ALS care that people living with ALS need. In fact, many ALS clinics rely on donations to cover their costs. The ALS Better Care Act would create a $800 supplemental payment to cover costs that Medicare does not pay for at ALS clinics.

The ALS Association is committed to doing everything we can to increase equitable access to our network of certified multidisciplinary ALS clinics across the country. We are hopeful that Congress will partner with us and the entire ALS community to achieve this goal. We look forward to working with you on this and any future legislation that extends and improves the quality of life for people living with ALS and helps make ALS livable until we cure it.

Thank you for your time and consideration of this critical piece of legislation. If you have any questions, please contact our Director of Congressional Affairs, Denise Bailin at denise.bailin@als.org.

Sincerely,

Calaneet Balas
President and Chief Executive Officer

Testimony for the Record of Benjamin D. Hoffman, MD, FAAP
On Behalf of the American Academy of Pediatrics
Before the U.S. House of Representatives Committee on Energy and Commerce
Subcommittee on Health
"Legislative Proposals to Support Patients with Rare Diseases"
February 29, 2024

Chairman Guthrie, Ranking Member Eshoo, and Subcommittee Members, thank you for the opportunity to submit written testimony for today's hearing on the need to improve therapies and medical care for children with rare diseases and children with complex health care needs. My name is Dr. Benjamin D. Hoffman. I am a pediatrician and the president of the American Academy of Pediatrics (AAP), a non-profit professional organization of 67,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety and well-being of infants, children, adolescents, and young adults.

INNOVATION IN PEDIATRIC DRUGS ACT

The AAP strongly supports the bipartisan Innovation in Pediatric Drugs Act (H.R. 6664), introduced by Rep. Anna Eshoo and Rep. Michael McCaul. This legislation makes long-overdue improvements to the pediatric drug laws: the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

Together, BPCA and PREA have revolutionized medicines for children. Drugs used to be seldom studied in children. But children are not just little adults. Drugs work differently in children because of their unique biology and because diseases are often different in children compared to adults. Without studying drugs specifically in children, health care providers are left without information on whether drugs actually work in children, whether they are safe for children, and what the appropriate pediatric dosages are.

BPCA and PREA have fundamentally changed the pediatric drug development landscape. These laws have resulted in over 1,000 drug labels changed with new pediatric information.[1]

PREA is a requirement, first enacted by Congress in 2003, that requires certain new drugs to be studied in children. BPCA offers an incentive of six months of marketing exclusivity for drugs that are studied in children at the request of FDA. Pediatric exclusivity was first enacted in 1997. BPCA also authorizes a program at the National Institutes of Health (NIH) to fund the pediatric study of older, off-patent drugs that BPCA's incentive and PREA's requirements are unable to reach.

The Innovation in Pediatric Drugs Act would do three critical things: increase the number of rare disease drugs studied in children, ensure that required PREA studies actually get completed, and give the NIH BPCA program its first funding increase in 22 years.

[1] https://www.fda.gov/media/161414/download

Ensuring Drugs for Rare Diseases are Studied in Children

There are close to 7,000 rare diseases without a treatment, and the vast majority of orphan diseases affect children. However, FDA generally cannot require that drugs for rare diseases be studied in children. PREA currently exempts most orphan drugs—drugs used to treat diseases impacting less than 200,000 people—from pediatric study requirements.

This exemption provision dates back to when PREA was first authorized in 2003, a time when the orphan drug development landscape was very different and orphan drugs made up a small fraction of total FDA drug approvals. In 2003, for instance, only 25% of novel drug approvals were orphan drugs.[2] Today, the majority of drugs approved are orphan drugs. Last year, 28 of 55 (51%) novel drugs approved by FDA's Center for Drug Evaluation and Research (CDER) were orphan drugs, meaning that more than half of CDER drugs approved in 2020 were exempt from pediatric study requirements.[3]

In 2017, Congress amended the PREA orphan drug exemption to allow studies for oncology orphan drugs. That year, Congress also required FDA to evaluate the pediatric research gaps that have resulted from the PREA orphan exemption. This report was published in 2019 and showed that 36% of pediatric-relevant orphan drugs approved since 1999 lack some or all pediatric data (23% have no pediatric information and an additional 13% are missing some pediatric information).[4] In the conclusion to its report, FDA said that "there is a public health need for additional pediatric information in labeling for over one-third of approved orphan indications that are relevant in the pediatric population. FDA supports ensuring that information to support labeling is obtained for all appropriate pediatric age groups."[5]

According to the FDA report, orphan drugs for the following non-cancer diseases and conditions that impact children were approved with *no pediatric labeling at all* as a result of the PREA orphan exemption: pulmonary arterial hypertension, pulmonary multi-drug resistant tuberculosis, organ rejection in patients receiving kidney transplants, epilepsy, hypercalcemia in patients with primary hyperparathyroidism, multiple sclerosis, iron overload due to thalassemia syndromes, primary hyperkalemic periodic paralysis, Gaucher disease, aplastic anemia, Graft versus Host disease, angioedema, end stage renal disease, invasive aspergillosis, zygomycosis, carcinoid syndrome, human cytomegalovirus viremia, short bowel syndrome, homozygous familial hypercholesterolemia, growth hormone deficiency, endogenous Cushing's syndrome, Fabry Disease, primary biliary cirrhosis, hyperphenylalaninemia, hepatic encephalopathy, thromboembolic pulmonary hypertension, Wegener's granulomatosis, microscopic polyangiitis, immune thrombocytopenic purpura, Zollinger-Ellison syndrome, pancreatic exocrine dysfunction, non-24-hour sleep-wake disorder, autosomal dominant polycystic kidney disease, and von Willebrand disease.

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[2] https://www.ahip.org/wp-content/uploads/IB_OrphanDrugs-1004.pdf

[3] https://www.fda.gov/news-events/fda-voices/fda-approves-many-new-drugs-2023-will-benefit-patients-and-consumers

[4] https://www.fda.gov/media/130060/download

[5] https://www.fda.gov/media/130060/download

In addition, the report shows that orphan drugs for the following non-cancer diseases/conditions that impact children were approved with *no pediatric labeling for certain necessary age groups* as a result of the PREA orphan exemption: Pompe disease, Tourette's disorder, Chagas disease, Dravet syndrome, Fabry's disease, neuronal ceroid lipofuscinosis type 2, nephropathic cystinosis, Duchenne muscular dystrophy, angioedema, homozygous familial hypercholesterolemia, chronic drooling in patients with neurologic conditions, Hunter Syndrome, cystic fibrosis, hepatitis C, metabolic disorders secondary to lipodystrophy, leishmaniasis, onchocerciasis volvulus, tyrosinemia type 1, narcolepsy, pediatric hyperparathyroidism, malaria, Gaucher disease, amebiasis, and giardiasis.

The Innovation in Pediatric Drugs Act would strike the orphan drug exemption in PREA and require FDA to publish guidance for industry on the application of PREA to orphan drugs. It is important to note that if orphan drugs were subject to PREA, it is not the case that all orphan drugs would automatically be required to be studied in children. FDA would make case-by-case determinations for each drug and would use its authority to offer full and partial waivers of PREA requirements when orphan drugs treat diseases that do not occur in children or if studies would not be possible to conduct.

Equal Accountability for Pediatric Study Requirements

PREA studies are required by law, but too many drug companies have completed their pediatric studies late or have ignored their PREA obligations altogether. PREA is technically a premarket requirement, but due dates for PREA studies are typically and appropriately deferred by FDA until a date after the approval of the drug for adults. These deferred PREA studies become postmarket requirements, but FDA has no effective enforcement tools to ensure that these studies get completed.

While FDA has the authority to declare a drug misbranded for failure to complete PREA requirements, FDA has never done this and likely never will. Declaring a drug misbranded would result in the complete removal of a drug from the market, making it inaccessible to both adults and children. It is not appropriate to restrict drug access to one set of patients in order to ensure that a drug is appropriately studied for another set of patients.

Congress has previously attempted to address the problem of drug companies not completing studies required by PREA. In 2012, Congress amended PREA to set up a new process at FDA for extending PREA deadlines when there is good cause to do so (such as difficulty enrolling enough pediatric patients in trials despite making reasonable efforts) and issuing public non-compliance letters when FDA finds there is not good cause for delay. Unfortunately, these changes have not created the accountability necessary to ensure studies get done.

In 2022, a decade after Congress instituted the PREA non-compliance letters, the AAP conducted an analysis of those publicly available letters. The analysis at the time showed that 123 non-compliance letters had been issued by FDA. Unfortunately, only 41 (33%) of these instances of non-compliance had been resolved. That left 82 (67%) instances of non-compliance unresolved with studies still late. The average late study was 4.4 years late. Twenty-one studies were between 5-10 years late, 7 studies were between 10-15 years late, and 3 studies were more than 15 years late.

FDA requirements for postmarket studies in adults can be effectively enforced, but FDA requirements for postmarket studies in children cannot. FDA can require, as a condition of approval, postmarket approval studies of drugs for adults. If a company fails to complete those studies, FDA can penalize the company through the imposition of a fine. FDA can also penalize companies for not completing studies required under a Risk Evaluation and Mitigation Strategy. Unfortunately, the statute currently maintains a double standard because pediatric research requirements cannot be similarly enforced.

The Innovation in Pediatric Drugs Act would allow the FDA to issue civil monetary penalties for PREA non-compliance . FDA would retain the ability to extend PREA deadlines when there is good cause to do so, so companies acting in good faith to get their studies completed would not be subject to fines.

Increasing Funding for the NIH BPCA Program

In 2002, the Best Pharmaceuticals for Children Act authorized a program at the NIH to study older, generic drugs that the BPCA exclusivity incentive—and subsequently the PREA requirements—were unable to reach since the drugs are long-since off-patent. By funding the Pediatric Trials Network (PTN) to do pediatric studies on these drugs that have been used in children for decades without sufficient data, the BPCA NIH program fills an essential gap in pediatric drug research. This program has resulted in 18 drug labels and 2 device labels changed with important new pediatric information. Nine additional drugs are awaiting label changes after data has been submitted to the FDA by the PTN. The program has also completed studies on 12 additional drugs for which data will be submitted to FDA this year or next. All told, the BPCA NIH program has studied or is currently studying over 100 different drugs in children. The PTN has also studied 30 drugs in breast milk to determine infant drug exposure. Finally, the BPCA NIH program also helps fund training in pediatric pharmacology so that there are sufficient experts able to conduct drug studies in children.

The BPCA NIH program has been flat-funded at $25 million since its original authorization in 2002. While the current statute authorizes $25 million in appropriations for the program, the program has never been appropriated dedicated dollars. Rather, NIH funds this program by asking its institutes and centers to contribute money to it each year.

Drug studies are expensive and while the program is an efficient use of scare resources, the $25 million funding level is insufficient to meet the current needs. When accounting for biomedical research inflation, the purchasing power of the program in 2022 was only about half of what it was in 2002.[6]

The low level of funding also significantly restricts the type of studies that are able to be conducted through this program. To date, the BPCA program has only been able to fund less expensive Phase I and Phase II studies to evaluate safety and pharamacokinetics (drug absorption, distribution, metabolism, and excretion). BPCA currently lacks the funding necessary to do Phase 3 studies that could show drug efficacy in children when efficacy cannot be extrapolated from adults.

In many instances, the NIH BPCA program was unable to pursue needed Phase 3 studies given funding limitations. One example is antipsychotic drugs for children. Over 1 percent of children are

[6] https://officeofbudget.od.nih.gov/gbipriceindexes.html

prescribed antipsychotic drugs, but FDA-approved labeling is lacking for many of these therapies. PTN studied two antipsychotic drugs in children, aripiprazole and risperidone, but was unable to conduct Phase 3 studies to better understand the true risk of adverse events and the long-term effects of the drugs on children. Another example is a therapy for infants with congenital heart disease, which affects 40,000 infants per year and can be fatal without intervention. PTN studied digoxin, which is used to reduce infant mortality between heart surgeries, but it was unable to conduct a Phase 3 study that could have demonstrated effectiveness.

The Innovation in Pediatric Drugs Act would increase the authorization of the BPCA NIH program to $50 million in order to make the funding for this program more commensurate with the need.

ACCELERATING KIDS ACCESS TO CARE ACT

The AAP also strongly supports the bipartisan Accelerating Kids' Access to Care Act (H.R. 4758), introduced by Rep. Lori Trahan and Rep. Mariannette Miller-Meeks. It is vital that all children and adolescents can receive the health care they need, when they need it. For those with complex medical conditions, any delays in access to the specialized care they need can be detrimental to their health. Unfortunately, many children enrolled in Medicaid and CHIP experience just these delays and barriers when the care that they need isn't available in their home state.

While federal regulations outline ways children should be eligible for care from out-of-state providers under Medicaid's EPSDT benefit, many barriers still exist for pediatricians when attempting to coordinate care across state lines. Today, children enrolled in Medicaid who need care outside their home states often experience delays and fragmentation because some state Medicaid programs require out-of-state providers to be screened and enrolled into their program even if the provider is already enrolled and in good standing with their home state Medicaid program and in Medicare. This process of enrolling in multiple Medicaid programs consumes valuable time and resources, increases program costs and most importantly delays children's access to needed care.

As stated in its name, the Accelerating Kids' Access to Care Act would help ensure that children enrolled in Medicaid and the Children's Health Insurance Program (CHIP) can receive timely health care without facing unnecessary barriers simply based on where they live.

Thank you for prioritizing issues that are important to child health. We look forward to working with the committee to secure swift passage of this important legislation.

Testimony of

Zaher Nahle, Tamara Drake, and Wayne Pacelle

The Center for a Humane Economy, Animal Wellness Action, and Animal Wellness Foundation,

Before the Subcommittee on House Committee on Energy and Commerce

Thursday, February 29, 2024

"Legislative Proposals to Support Patients with Rare Diseases"

This testimony highlights key facts related to the FDA Modernization Act 3.0 (H.R. 7248) and expresses our enthusiastic support for this bill. We describe the benefits conferred by the proposed legislation and the urgent need for it at this time, especially in the context of the FDA Modernization Act 2.0 (FDAMA 2.0) becoming U.S. law in late 2022. As the honorable committee members explore legislative proposals to support patients with Rare Diseases, we hope that this information provides additional clarity and aid deliberation.

Summary of Features and Benefits of the FDA Modernization Act 3.0 (H.R. 7248)

The enactment of H.R. 7248 directly benefits patients with rare, serious, and life-threating diseases. At its core, the bill delineates a path to improve the crushing failure rate in drug development (95%) by leveraging innovative and reliable technologies. It reduces fiscal waste caused by the indefensible spending on poor-predictive-value models (like animal models) in favor of better New Approach Methodologies (NAMs). Finally, the bill facilitates the consolidation of disparate, fragmented resources at the FDA towards improving transparency and bolstering regulatory approvals, including time, efficiency, and output.

A hallmark of H.R. 7248 is its feasibility as a budget-neutral investment, requiring no new funds. Instead, the enactment of the bill will allow more efficient use of existing resources at the FDA, given the relief it creates to existing programs such as the oversized and demanding 'Animal model qualification program.' According to the FDA, "…significant delay in our DDT [Drug Development Tool] qualification reviews at CDER [is] due to an overall increase in the DDT Qualification Program workload (…)" The agency has been forthcoming about inefficiencies in regulatory review, as described. Briefly, when qualified NAMs exist to guide the drug development process, the need by drug developers to seek qualifications for animal models shrinks. Qualifying NAMs can radically reduce the backlog of the Animal model qualification program over time and as such add value to the FDA and sponsors alike.

Currently, over 7,000 rare diseases affect between 25-35 million Americans—and 95% of those diseases have FDA-approved drugs. The poor reliability of animal models compounds sky-high R&D costs to disincentivize investment in this area. In addition, most new-generation therapies (e.g., cell therapy, immunotherapy) are very human specific by design, hence their promise. They cannot and should not be recapitulated in other species. For Rare Diseases in particular, the innovative 21st-century methods stipulated in the FDAMA 3.0 (and FDAMA 2.0) are among the most promising frontiers. Examples include the use of organ chips to understand Barth Syndrome, 3D models (organoids) of the midbrain for characterizing NGLY1 deficiency (a rare neurological disease), and artificial intelligence (AI) tools in developing treatments for Fragile-X syndrome.

An Urgent Need for FDAMA 3.0 (H.R. 7248) in the Aftermath of FDAMA 2.0

On Dec. 29, 2022, the FDA Modernization Act 2.0 (FDAMA 2.0) became law as Sec. 3209 of the Consolidated Appropriations Act, 2023. FDAMA 2.0 made animal testing of investigational new drugs (INDs) optional by expanding the definition of "nonclinical test" to include modern 21st century methods or NAMs like cell-based assays, organ chips, organoids, computer modeling, and bioprinting. The goal was both to make drug testing more humane and to speed drug development. According to the National Center for Advancing Translational Sciences (NCATS), one of the centers within the NIH, the animals-only regime has led to a 95% failure rate for new drugs,[1] which wastes precious time for patients.

Regrettably, more than a year after FDAMA 2.0 was signed into law, little to no change has been created by the agency to practically translate such major development into meaningful practice. For instance, FDA has yet to demonstrate a sincere rulemaking effort to conform policy to the statute. This is causing marked regulatory confusion. In addition, the agency has ignored inquiries from nine lawmakers in the Senate who raised serious concerns and demanded explanations for such inaction through a letter addressed to FDA commissioner. Rulemaking is a critical step in implementing enacted U.S. laws, especially in complex health related matters. In turn, compliance with the law by federal agencies is not optional or discretionary.

The refractoriness by the Agency stands in stark contrast to the expectations, let alone excitement, that ensued following the signing of the new law in late December 2022. Since then, more than 460 worldwide publications, including news articles, commentaries, scientific reviews, and primary papers have been published, underscoring the transformative nature of the FDAMA 2.0 and its mighty importance. Naturally, many stakeholders assumed that the FDA would rush to embrace the new reforms which are aiming, first and foremost, at improving the safety and efficacy of the drug development process, a core responsibility of the agency.

[1] National Institutes of Health, National Center for Advancing Translational Sciences (NCATS), "New Therapeutic Uses": https://ncats.nih.gov/research/research-activities/ntu. Accessed 28 Jan. 2024. Additionally, federal regulations already recognize that "animal reproduction studies are not always predictive of human response." *See* 21 C.F.R. §201.80(f)(6)(i)(b).

The current paradigm of drug development yields a crushing 90-95% failure in clinical trials of the very experimental drugs that advanced based on animal testing. Such failure to act not only causes precious delays in critical drugs reaching the market but also squanders money, efforts, talent and hopes for effective treatments and life-saving cures for millions. Continuing down the path of the existing drug discovery paradigm is nothing short of perpetuating a futile cycle and is highly irresponsible.

A Clear Path for Qualification of NAMs as Proposed is Vital for Progress

A critical aspect in the regulatory review of experimental drugs is the qualification program of methods, measures, and materials, collectively termed Drug Development Tools (DTTs). According to the FDA "Having qualified DDTs that can be used by many sponsors helps optimize drug development and evaluation." On qualification, the FDA provides the following definition: "Qualification is a conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review. Once qualified, DDTs will be publicly available to be used in any drug development program for the qualified context of use. Additionally, the qualified DDT generally can be included in IND, NDA, or BLA submissions without needing FDA to reconsider and reconfirm its suitability."

As such, a qualification program for NAMs is vital to incorporate the use of such tools in the current paradigm of drug development. Currently, the FDA has three established qualification programs. In addition to the above-mentioned 'animal model qualification program', the biomarkers program and the clinical outcome assessments program constitute the other two. Unfortunately, FDA programs that qualify NAMs are cursory, ineffective, and lack transparency.

The FDAMA 3.0 urges the FDA to leverage and consolidate disparate resources to establish a qualification process for NAMs. Indeed, the agency has a unique opportunity to capitalize on the resources, lessons learned, and interagency efforts, including existing networks focused on NAMs (e.g., ICCVAM) as well as resources appropriated through pilot programs.

For instance, the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program has been in existence now for several years. It was established as a result of a congressional inquiry by the Office of Government Accountability (GAO, report date 2019) with the intent to improve interagency cooperation in this emerging domain. A pilot program, as the name implies, is exploratory. It is neither intended nor expected to be open-ended.

It is also safe to assume that what the FDA stipulated in the pilot phase of ISTAND anticipating accepting "2-4 submissions in the ISTAND pilot program each year with a triage and selection process that focuses on public health impact and feasibility of implementation" is incompatible with the spirit of innovation in a competitive capital market. The applications solicited and processed by the FDA on NAMs must count in the hundreds, not "2-4 submissions."

The NAMs qualification effort stipulated in FDAMA 3.0 is a logical next step to consolidate resources, eliminate redundancy, and reduce fiscal waste among well-intended but scattered

pilots aiming at advancing innovative Science and Technology approaches. Its realization will establish a tractable effort, akin to the other three FDA qualification programs, with the full transparency, accountability, and oversights that such federally established programs entail.

Executing Public Policy is not Optional and Requires Modest Efforts from the FDA

Amending regulations to conform to a statute passed by Congress is a routine task for any agency, regardless of whether a statutory deadline is imposed. The FDA has had a longstanding public commitment to the "3 Rs": 1) reducing the number of animals used in research, 2) replacing animal methods where superior ones are available, and 3) refining techniques to minimize animals' pain and distress. This is why FDAMA 2.0 did not mandate a preference for nonanimal testing methods; that preference already exists in agency policy. This is also why Congress did not consider it necessary to impose a deadline for rulemaking.

Changing the regulations, as a legal and technical drafting exercise, will require limited investments of time and resources. It has now been 14 months and FDA hasn't commenced that effort. When it comes to an agency rewriting regulations, this is as simple as it gets, and the work product was handed off to the key agency personnel months ago.

Dozens of regulations continue to call for animal tests without offering drug sponsors any other option. The plain language of FDAMA 2.0 was straightforward and not complex, opening the drug approval process to 21st-century human-biology-based screening methods. In this case, the revisions that FDA must make to its regulations for drug sponsors are also very straightforward. We itemized the conflicting regulations in Exhibit A.

The FDAMA 3.0 (H.R. 7248) is Feasible with No Burden to the Agency or Appropriations

- *No new infrastructure is needed at the Agency beyond existing resources*. In fact, no capital investments or infrastructure development are required given the largely review and assessment nature of this qualification effort - a scholarly exercise, first and foremost. Assessment and evaluation of standards is the core expertise of the agency and its qualified staff. In-house talent at the FDA (e.g., toxicology experts) or trusted outside reviewers are routinely solicited to review applications and serve on special emphasis panels at the FDA as needed. Experts evaluate applications based on FDA-qualified models and applicable standards. Such intellectual and largely academic activities represent the bulk of what is needed for the implementation of non-animal testing qualification efforts. Expertise and talent at the agency and its ecosystem are already existent, if not abundant.

The FDA Modernization Act 3.0 (H.R. 7248) will create value by requiring:

  - FDA to publish a final rule to implement FDAMA 2.0.
  - HHS to establish a process to qualify nonanimal methods that either improve predictivity for safety and effectiveness or reduce development time.

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- a public meeting and comment period, followed by guidance on the non-animal qualification process.
- FDA to submit an annual report analyzing the success of the qualification process with an estimate of how many animals it saves.

- *No new functions or responsibilities expected from the Agency beyond its current mandate.* The onus is on applicants seeking regulatory approvals to make convincing arguments and present in their applications the sufficient data gathered from relevant testing models. It is the sponsor's responsibility, not that of the FDA, to support the safety and efficacy of an experimental drug proposed. The role of the FDA is to qualify methods rendered permissible by law that are innovative and might offer equal or better value to existing schemes. In this context, the FDA acts as an objective judge of the work of others. The FDA's role and function in the case of non-animal testing qualification effort stipulated in FDAMA 3.0 is - not unlike - its routine and daily activities within the other FDA-established qualification programs (namely, the Animal model qualification program, the Biomarker Qualification program, and the Clinical Outcome Assessment Qualification program).

To Improve Drug Development, Congress Must Take Action to Implement FDA Modernization

H.R. 7248 is a public health bill, focusing on the implementation of the FDA Modernization Act 2.0 to address the problems with the current drug development model.

- Animal tests, in large part, are not predictive of the human response to drugs, with 90 to 95 percent of drugs and vaccines found safe in animal tests failing during human clinical trials.
- Most diseases have no treatment available. Adverse drug reactions are the fourth highest cause of death in the U.S. Use of human biology-based test methods would better predict how humans will respond to drugs in clinical trials.
- In addition to falsely identifying a toxic drug as "safe," animal tests can falsely label a potentially useful therapeutic agent as toxic. Thus, of the many thousands of drugs that have failed in animal tests, some might have worked in humans.
- The reduction in the number of false negatives (FN-drugs that are toxic but predicted by animal tests to be safe) directly increases consumer safety. Decreasing the rate of false positives (FP-drugs that are safe but predicted to be toxic) has a direct effect on productivity and allows the marketing of products that would otherwise have been filtered out. The effect of allowing for safer products (low FN rate) and more marketable products from the discovery process (low FP rate) means increased business profit.
- A recent Phase 2b human clinical trial of Johnson & Johnson's HIV/AIDS vaccine failed because of lack of efficacy. Animal data had shown 90% efficacy.[2] This is consistent with the 30+ year effort to develop a HIV/AIDS vaccine. The animal data show promise, but the vaccines do not work in humans.

[2] J &J's HIV vaccine fails phase 2b, extending long wait for an effective jab, Fierce Biotech, August 31, 2021 https://www.fiercebiotech.com/biotech/j-j-s-hiv-vaccine-fails-phase-2b-extending-long-wait-for-effective-jab and https://www.statnews.com/2021/08/31/first-efficacy-trial-of-johnson-johnsons-hiv-vaccine-fails

- On September 2, 2021, FDA's Cellular, Tissue, and Gene Therapies Advisory Committee said animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors. There have been "severe" adverse events in AAV vector clinical trials, including instances of acute liver and kidney failure in children. One third of the 500 children under the age of 2 treated with Zolgensma had at least once adverse event of hepatoxicity.[3]
- Studies show that while toxicity in animals may also be present in humans these tests are not consistent or reliable and provide nearly no insight into the possibility or likelihood of toxicity or the absence of toxicity in humans.[4]
- In one protocol, researchers studied six drugs to determine which of the 78 adverse effects that occurred in humans would occur in dogs or rats. Effects that are undetectable in animals (e.g., headaches) were not considered. Less than half (46%) of the remaining side effects were.
- detected in the animals - slightly less than the expected results from flipping a coin. In other words, animal tests were wrong 54% of the time.[5]
- Another study of drug registration files was conducted to determine whether post-marketing serious adverse reactions to small molecule drugs could have been detected based on animal data. Of 93 serious adverse reactions related to 43 small molecule drugs, only 19% were identified in animal studies as a true positive outcome.[6]

Aside from the little relevance to humans, animal data is very costly to generate:

- The cost for developing a single new drug may be from $1 - $6 billion, and the average timeline of development of a potential drug and vaccine from the lab to market is 10—15 years.
- Estimates suggest that, relative to *in vitro* models, animal testing is 1.5 to 30 times more expensive.[7]

[3] Animal models have limitations for safety assessment of gene therapies: FDA adcomm, Regulatory Focus, September 2, 2021. https://www.raps.org/news-and-articles/news-articles/2021/9/fda-adcomm-points-to-limitations-of-animal-studies?utm_source=MagnetMail&utm_medium=Email%20&utm_campaign=RF%20Today%20%7C%202%20September%202021

[4] Bailey, J., Thew, M., Balls, M., An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety, *Alternatives to Laboratory Animals,* 2013, 41(5), pp. 335-350., Bailey J, Thew M, Balls M., An analysis of the use of animal models in predicting human toxicology and drug safety. *Alternatives to Laboratory Animals*, 2014;42:189–99., Bailey, J., Thew, M., Balls, M., Predicting Human Drug Toxicity and Safety Via Animal Tests: Can Any One Species Predict Drug Toxicity in Any Other, and Do Monkeys Help? Alternatives to Laboratory Animals, 2015, 43 (6), pp,393-403.

[5] Clin Pharmacol Ther 1962; pp665-672 https://doi.org/10.1002/cpt196235665

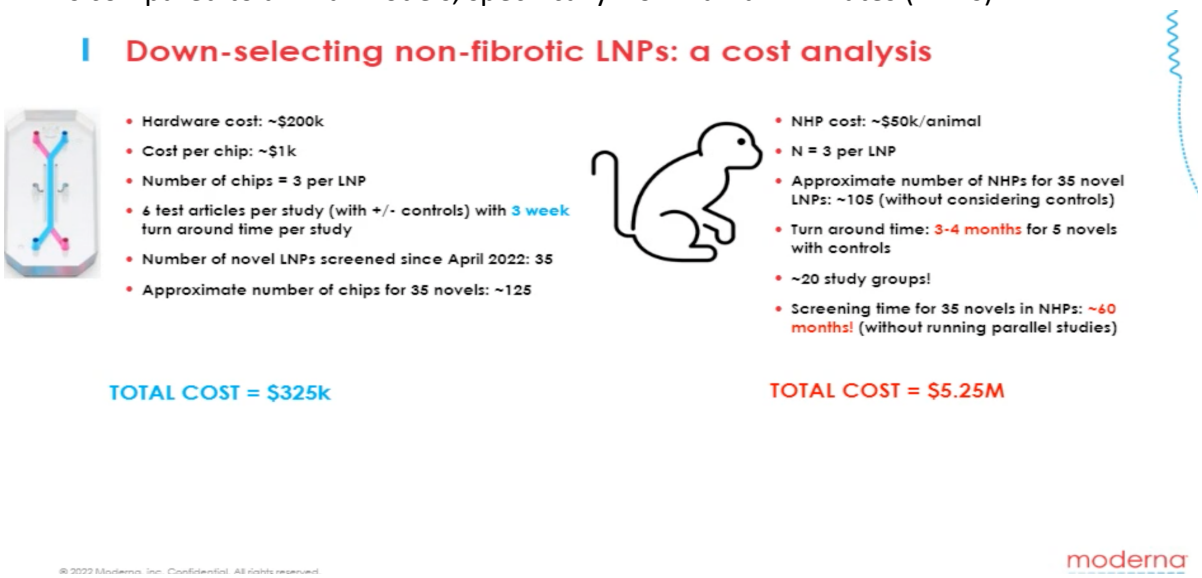
[6] Van Meer, P,J., Kooijiman, M., Gispen-de Wied, CC., Moors, E.H., Schellekens, H. The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited, *Regulatory Toxicology and Pharmacology*, 2012, 64 (3), pp. 345-349

[7] Rodent testing in cancer therapeutics adds an estimated 4 to 5 years to drug development and costs $2 to $4 million. Compared with the costs of in vitro testing, **animal tests range from 1.5× to >30× as expensive.** Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach? https://www.sciencedirect.com/science/article/pii/S2452302X1930316X

- The Emulate study (see next section), included an economic evaluation indicating routine use of the Emulate Liver-Chip to identify liver toxicity risk in small-molecule drug development could generate approximately $3 billion per year by driving an increase in research and development productivity. Regulatory acceptance of NAMs would provide drug sponsors more options for testing the safety and efficacy of drugs to improve clinical trial attrition rates, cut time to market in half, and substantially reduce R & D costs which could cut drug prices fivefold.[8]

<u>Human Relevant Models are Key to Improving the Drug Development Process</u>

- Analysis from the company Moderna in 2023 shows a significant economic benefit for using NAMs compared to animal models, specifically Non-Human Primates (NHPs). [9]



- In a recent study,[10] researchers assessed the performance of 780 human Liver-Chips across a blinded set of 27 known hepatotoxic and non-toxic drugs. In line with the IQ MPS guidelines, the tested drugs included seven matched pairs that demonstrate the chip's ability to distinguish toxic drugs from their less-toxic structural analogs. **Furthermore, the study demonstrated that the Emulate Liver-Chip was able to correctly identify 87% of the tested drugs that caused drug-induced liver injury in patients despite passing through animal testing**. At the same time, the Liver-Chip did not falsely flag any drugs as toxic, supporting its

[8] Marx, U., Andersson, T. B., Bahinski, A. et al. (2016). Biology-inspired microphysiological system approach to solve the prediction dilemma and substance testing. *ALTEX* 33, 272- 321. doi:10.14573/altex.1603161

[9] https://emulatebio-1.wistia.com/medias/fqblwxqfdq?hstc=68085326.27f8e5da2651d3dbeaf1e049d64894c3.1700521025313.1700521025313.1700521025313.1&hssc=68085326.1.1700521025313&hsfp=1723886671&submissionGuid=a73526a2-7ad0-468c-ad1e-187f664f887f at 12:32. "Down-selecting non-fibrotic LNPs: a cost analysis OOC (organ on chip) Liver chip" Moderna

[10] Ewart, L., Apostolou, A., Briggs, S.A. *et al.* Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. *Commun Med* **2**, 154 (2022). https://doi.org/10.1038/s43856-022-00209-1, https://www.nature.com/articles/s43856-022-00209-1

use in toxicology screening workflows. In comparison, published data for 3D hepatic spheroids shows a sensitivity rate of 42% and a specificity rate of 67% for the same drug set.

Additional Background on Prior Petitions and Earlier Responses From the FDA

- *For Nealy a Decade, FDA Has Stonewalled Legal Petitions Seeking Agency Support for Regulatory Updates to Clarify that Nonanimal Tests Are Permitted in Nonclinical Trials:*

Fifteen years ago, FDA received a thoroughly presented citizen petition specifically requesting a regulatory change to allow the use of data from non-animal methods. Three years later in response, FDA said it would issue draft guidance, but later moved decided not to do so. Nine years ago, another citizen petition seeking discretion to use such data was filed in 2015. While FDA provided two "interim responses," FDA has not yet provided a substantive response as required by 21 CFR 10.20(f).

- *Modification of Regulations Petition Related to Animal Testing – FDA-2015-P-2820- July 2015:*

In July 2015, the Center for Responsible Science, with a series of other co-petitioners[11] requested that FDA modify existing regulations in Title 21 of the Code of Federal Regulations (CFR) that govern requirements for investigational new drug (IND) applications, investigational device exemptions (IDE), and new drug applications (NDAs).

Specifically, petitioners requested that Commissioner of the FDA amend certain regulations to establish and clarify that FDA will accept data from scientifically recognized modern and emerging test methods to support a drug or device investigational application. The requested amendments would broaden options in nonclinical testing and will not require one type of testing over another. This clear signal would move product development forward by bringing written policy up to date with stated policy and science, and by paving the way for industry to develop and use emerging, superior technologies. Nearly nine years later, FDA has not provided a substantive response.

Conclusion

We are on the verge of the next phase of modern drug development made possible by powerful innovations. In this regard, the U.S. Congress has a vital role to play through enacting discerning legislation like the FDA Modernization Act 3.0 to make this possible and usher in the new era of human-relevant biomedical discoveries.

The significant value of this legislation to the public and patients in the Rare Disease community comes in the form of reducing the failure rate in translating scientific findings from the lab to the clinic. That includes not mislabeling a toxic or ineffective drug as safe or effective, not mislabeling

[11] Asterand Bioscience, AxoSim, Empiriko, Friends of Cancer Research, Hurel Corp, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek Corporation, National Organization for Rare Disorders, Safer Medicines Trust, United Spinal Association, 3D Biomatrix, Inc.)

a safe or effective drug as harmful or ineffective, and not enabling human-irrelevant models to continue to be the paradigm for our national drug discovery process and the development of modern medicines, especially in the presence of technology-driven alternatives. Decades of animal testing proved to be misleading, distracting, and utterly unwise investments.

We hope that the committee will favorably report H.R. 7248 with amendments agreed upon by the bill's authors.

Respectfully,

Wayne Pacelle is President of Animal Wellness Action and the Center for a Humane Economy.

Tamara Drake is Director of Research and Regulatory Policy for the Center for a Humane Economy

Zaher Nahle, PhD MPA is the Senior Scientific Advisor for Animal Wellness Action and the Center for a Humane Economy

611 Pennsylvania Ave. S.E. #136 | Washington, D.C. 20003

The FDA Modernization Act 3.0

(H.R. 7248)

The FDA Modernization Act 2.0 (FDAMA 2.0) was enacted into law as Sec. 3209 of the Consolidated Appropriations Act, 2023, which President Biden signed on Dec. 29, 2022. FDAMA 2.0 lifted a mandate in the Federal Food, Drug, and Cosmetic Act (FDCA) that required animal testing of investigational new drugs (INDs) to establish safety and efficacy prior to clinical trials in humans.

FDAMA 2.0 did not ban animal testing, but it offered drug sponsors the option to use 21st century alternatives such as cell-based assays, organ chips, computer modeling, and bioprinting. The goal was not only to make drug testing more humane, speed drug development by reducing the attrition rate, since non-animal methods are typically superior predictors of human responses to drugs. An astonishing 90-95% of drugs that pass animal tests go on to fail in human clinical trials, wasting precious time for patients.

Over 7,000 rare diseases affect between 25-35 million Americans—and 95% of those diseases have no cure. Rare-disease patients stand to benefit substantially by the acceptance of non-animal methods because the poor reliability of animal models compounds high R&D costs to disincentivize investment in this area. The innovative 21st century methods outlined in FDAMA 2.0 are among the most promising frontiers in understanding rare diseases: organ chips for Barth Syndrome, 3D models (organoids) of the midbrain for NGLY1 deficiency (a rare neurological disease), and artificial intelligence (AI) in developing treatments for Fragile-X syndrome. As a 2022 article noted of Fragile-X, "[t]his is a disease for which there were no mouse models. A different approach was needed, and the patients-on-a-chip model, combined with AI, seemed to be the best solution."

The Problem

To date, the FDA has not updated its regulations to conform with the law Congress passed in 2022. Dozens of FDA regulations continue to call for animal tests without offering drug sponsors any other option. FDA programs that qualify non-animal test methods are cursory, ineffective, and lack transparency.

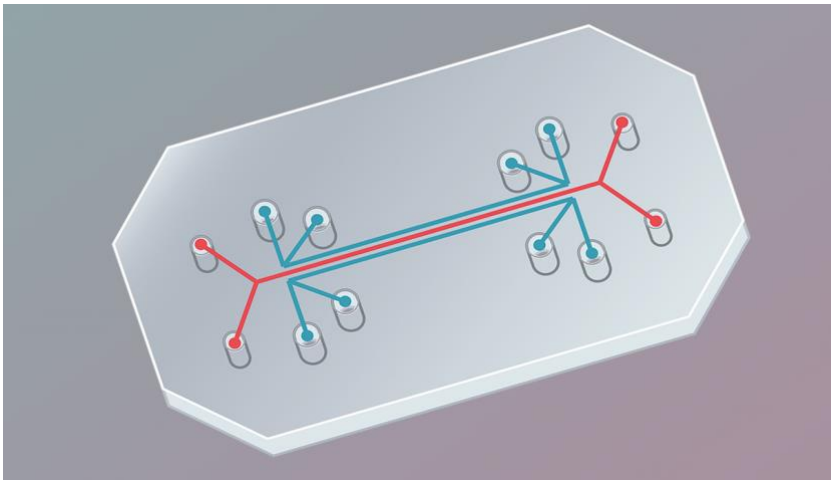
The Solution

To effectuate the will of Congress, the FDA Modernization Act 3.0 would:

- Require the FDA to publish a final rule to fully implement FDAMA 2.0.
- Require the HHS Secretary to establish a process to qualify test methods to reduce or

replace animal tests. The new methods must either 1) improve test predictivity for safety and efficacy or 2) reduce development time for drugs and/or biologics.

- Require the HHS Secretary to hold a public meeting of stakeholders to solicit input about the qualification process for non-animal methods. After this public meeting, the FDA must propose guidance, provide a comment period, and finalize the guidance within a year of comments closing.
- Require the FDA to publish an annual report on its website analyzing the success of the qualification process, including an estimate of the number of animals saved by it.



[1] National Institutes of Health, National Center for Advancing Translational Sciences (NCATS), "New Therapeutic Uses": https://ncats.nih.gov/research/research-activities/ntu. Accessed 28 Jan. 2024. Additionally, federal regulations already recognize that "animal reproduction studies are not always predictive of human response." *See* 21 C.F.R. §201.80(f)(6)(i)(b).

[1] Ed Miseta, "Needed: An AI Revolution in the Rare Disease Space," *Clinical Leader*, 11 Nov. 2022: https://www.clinicalleader.com/doc/needed-an-ai-revolution-in-the-rare-disease-space-0001

[1] *See* 21 C.F.R. §§ 312.22(c), 312.23(a)(3)(iv), 312.23(a)(5)(ii), 312.23(a)(5)(iii), 312.23(a)(8), 312.23(a)(8)(i), 312.23(a)(8)(ii), 312.23(a)(10)(i), 312.23(a)(10)(ii), 312.33(a)(6), 312.82(a), 312.88, 312.160, 314.50(d)(2), 314.50(d)(2)(iv), 314.50(d)(5)(i), 314.50(d)(5)(vi)(a), 314.50(d)(5)(vi)(b), 314.93(e)(2), 315.6(d), 330.10(a)(2), 610.35(d), 812.2(c), 812.5(c), 812.27(a), 812.35(a)(3)(iii), 860.5(f), and 860.7(d)(2). For uniformity and consistency, the following regulations should also be updated: 21 C.F.R. §§ 3.7, 10.20, 14.95, 16.1, 50.24, 58.3, 201.56, 201.57, 201.1, 312.32, 312.160, 314.81, 314.200, 314.430, 316.20, 330.14, 343.80, and 361.1. Definitions sections in the following regulations also must be harmonized with Sec. 3209 of the *Consolidated Appropriations Act, 2023*, P.L. 117-328, 136 Stat. 5822 (2022): 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, and 860.3.

United States Senate
WASHINGTON, DC 20510

16 November 2023

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

We write to you about the investigational new drug development work of the FDA in the wake of the enactment of the FDA Modernization Act 2.0.

That legislation, which Congress passed and the President signed into law at the end of 2022 with uncommon unanimity, removes FDA's mandate for animal testing of all new drug candidates and allows an applicant for new drug market approval to use methods other than animal testing to establish a drug's safety and effectiveness. During one of your appearances before the U.S. Senate Committee on Health, Education, Labor, and Pensions, you spoke favorably about the shift toward human-based biology, noting that alternative methods may include cell-based assays, organ chips and micro-physiological systems, computer modeling, bioprinting, and a growing variety of other New Approach Methodologies (NAMs).

As you are aware, agency regulations are promulgated in accordance and conformity with Congress's statutory language and intent. Yet in the aftermath of the enactment of the FDA Modernization Act 2.0, the FDA's regulations related to animal testing no longer fully conform with applicable law. For example, federal regulations governing submission of Investigational New Drug (IND) applications require that amendments to an IND "should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate."[1] Further, regulations governing the IND Investigator's Brochure call for a summary of "pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans."[2] These and other regulatory provisions no longer reflect the full scope of the governing statute and should therefore be updated as expeditiously as possible.

The above examples are just a sampling of a larger set of inconsistencies between the amended statute and FDA regulations. We therefore write to ask what specific steps the FDA is taking to update its animal testing regulations, and what its timeline is for implementation of a revised regulatory framework. Please respond with this information within 30 days of the date of this letter.

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[1] *See* 21 C.F.R. § 312.22(c).

[2] *See* 21 C.F.R. 312.23(a)(5)(ii).

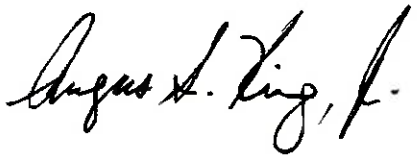
Thank you for your attention to this important matter.

Sincerely,

Rand Paul, M.D.
United States Senator

Cory Booker
United States Senator

Mike Braun
United States Senator



Angus King
United States Senator

Roger Marshall, M.D.
United States Senator

Tim Kaine
United States Senator

John Kennedy
United States Senator

Ben Ray Luján
United States Senator

Eric S. Schmitt
United States Senator

Exhibit A Regulation Updates

To conform with the updates to the Federal Food Drug and Cosmetics Act, the following regulatory text must be issued and placed under the definition sections of 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, 860.3:

Nonclinical test defined
"Nonclinical test" means a test conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following:

(1) Cell-based assays.
(2) Organ chips and microphysiological systems.
(3) Computer modeling.
(4) Other nonhuman or human biology-based test methods, such as bioprinting.
(5) Animal tests.

1. 21 C.F.R. § 312.22(c) (General Principles for IND Submissions)

Proposed: *The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of ~~animal~~ nonclinical toxicology studies or other human studies as appropriate. . . .*

2. 21 C.F.R. § 312.23(a)(3)(iv) ((IND Content and Format)

Proposed: *A brief description of the overall plan for investigating the drug product for the following year. The plan should include . . . . (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data ~~in animals~~ from nonclinical or prior studies in humans with the drug or related drugs.*

3. 21 C.F.R. § 312.23(a)(5)(ii) (IND Investigator's Brochure)

Proposed: *A summary of the pharmacological and toxicological effects of the drug in ~~animals~~ nonclinical tests and, to the extent known, in humans.*

4. 21 C.F.R. § 312.23(a)(5)(iii) (Investigator's Brochure)

Proposed: *A summary of the pharmacokinetics and biological disposition of the drug in ~~animals~~ nonclinical tests and, if known, in humans.*

5. 21 C.F.R. § 312.23(a)(8) (IND Pharmacology and Toxicology Information)

Proposed: *Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving ~~laboratory animals or in vitro~~ nonclinical tests, on the basis of which the sponsor has concluded that it is reasonably safe to*

conduct the proposed clinical investigations. The kind, duration, and scope of ~~animal and other tests~~ nonclinical tests required varies with the duration and nature of the proposed clinical investigations. . . .

6. 21 C.F.R. § 312.23(a)(8)(i) (Pharmacology and Drug Disposition)

Proposed: *Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in ~~animals~~ nonclinical tests, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.*

7. 21 C.F.R. § 312.23(a)(8)(ii) (Toxicology)

Proposed: *Toxicology. (a) An integrated summary of the toxicological effects of the drug in ~~animals and in vitro~~ nonclinical tests. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; ~~preclinical~~ tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.*

8. 21 C.F.R. § 312.23(a)(10)(i) (Drug Dependence and Abuse Potential)

Proposed: *Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in ~~test animals~~ nonclinical tests.*

9. 21 C.F.R. § 312.23(a)(10)(ii) (Radioactive Drugs)

Proposed: *Radioactive drugs. If the drug is a radioactive drug, sufficient data from ~~animal~~ nonclinical or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. . . .*

10. 21 C.F.R. § 312.33(a)(6) (Content of Annual Reports)

Proposed: *A list of the ~~preclinical~~ nonclinical studies ~~(including animal studies)~~ completed or in progress during the past year and a summary of the major ~~preclinical~~ nonclinical findings.*

11. 21 C.F.R. § 312.82(a) (Early Consultation)

Proposed: *Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of ~~animal~~ nonclinical studies needed to initiate human testing. . . .*

12. 21 C.F.R. § 312.88 (Safeguards for Patient Safety)

Proposed: *All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. . . . These safeguards further include the review of ~~animal~~ nonclinical studies prior to initial human testing (¤ 312.23) . . . .*

13. 21 C.F.R. § 312.160 (Drugs for Investigational Use in ~~Laboratory Research Animals on In Vitro Tests~~ in Nonclinical Tests).

Proposed: *Drugs for investigational use in ~~laboratory research animals or in vitro~~ nonclinical tests. . . . A person may ship a drug intended solely for ~~tests in vitro or in animals used only for laboratory research purposes~~ nonclinical tests if it is labeled as follows:*
CAUTION: Contains a new drug for investigational use only in ~~laboratory research animals or for tests in vitro~~ nonclinical tests.. Not for use in humans. . . . (2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for nonclinical testing ~~tests in vitro or in animals used only for laboratory research.~~

14. 21 C.F.R. § 314.50(d)(2) (NDA Technical Sections)

Proposed: *Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, ~~animal and in vitro~~ nonclinical studies with drug . . . .*

15. 21 C.F.R. § 314.50(d)(2)(iv) (NDA Non-Clinical Sections)

Proposed: *Any nonclinical studies of the absorption, distribution, metabolism, and excretion of the drug ~~in animals~~.*

16. 21 C.F.R. § 314.50(d)(5)(i) (Clinical Data Section)

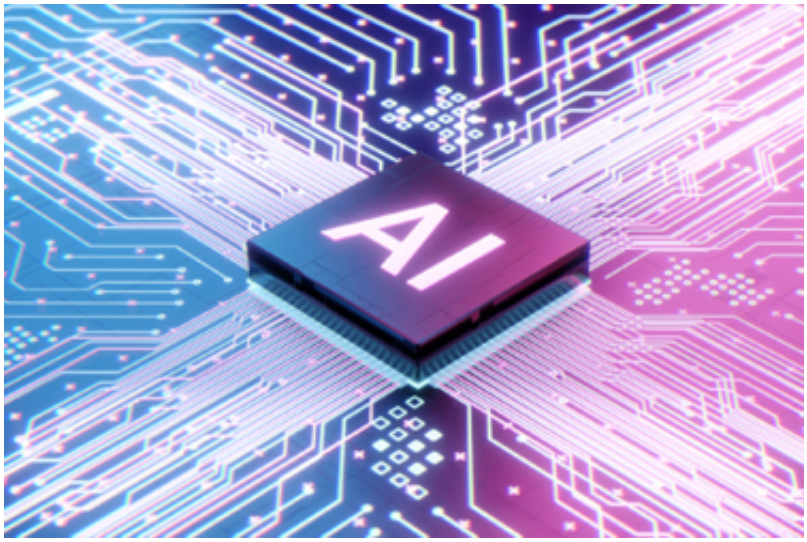
Proposed: *A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the ~~animal~~ nonclinical pharmacology and toxicology data.*

17. 21 C.F.R. § 314.50(d)(5)(vi)(a) (Clinical Data Section)

Proposed: *(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent ~~animal~~ nonclinical data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations . . . .*

Needed: An AI Revolution In The Rare Disease Space

By Ed Miseta, Chief Editor, Clinical Leader



Quris is involved in the rare disease space. The company has developed a treatment for Fragile-X Syndrome, the most common inherited cause of autism and intellectual disabilities worldwide. Isaac Bentwich M.D., the founder and CEO of Quris, believes the rare disease space, in general, is a difficult one to navigate. Fragile-X Syndrome itself has many challenges, and he notes Novartis and Roche have both failed in attempts to develop a drug for it. Bentwich believes the biggest challenge companies face is financial.

"Right now, the tools available to pharma, and the approach they use, make it exceedingly difficult, if not impossible, to develop rare disease drugs," he says. "The economics of drug development tell a good part of the story. It costs $2.5 billion and 12 to 18 years, on average, to develop a new drug. In the rare disease space, where there is a smaller number of patients, those numbers are simply unsustainable."

Bentwich notes there are many rare diseases and a patient population of 300 million worldwide, but the cost of developing a treatment for any *single* rare disease is what is not financially sustainable. Sadly, even when a drug in development fails to gain regulatory approval, there is still an average cost of $1 billion to the sponsor company. That means any drug gaining approval must generate enough revenue to pay for all the failures as well.

"One of the biggest challenges faced by the industry is knowing which drugs will be successful in human beings and clinical trials," states Bentwich. "If a company experiences 5 or 10 failures before developing a successful drug, the cost of those failures drives the cost of drug development even higher. If the industry had the ability to take only successful drugs through the drug development and clinical testing process, development costs could be reduced."

An Economic Conundrum

To better illustrate the conundrum, Bentwich uses a real estate example. If you wanted a skyscraper, you would find an architect to build it for you. Suppose that architect agrees to build 10 skyscrapers that you must pay for, and nine of the buildings are guaranteed to collapse. Your challenge would be to collect enough rent on the 10th building to pay for the cost of that building and the nine others. Alternatively, if you knew which building would not collapse, you could simply have that one built and skip the others. Bentwich believes the current economics in the drug development space are similar. It is simply untenable for pharma to keep spending money to develop drugs that will fail. Companies need to determine which of 10 potential treatments will be safe and effective in humans.

"This conundrum is one of the reasons why pharma companies will gravitate towards blockbuster drugs," he says. "It is the easiest way for them to cover

the costs of drug development. It is also the reason many companies prefer to avoid the rare disease and ultra-rare disease space altogether."

There are several reasons why a new drug might fail in clinical trials. One of the biggest issues faced by the industry is animal testing, which Bentwich notes does not accurately predict the safety of a drug in humans. He points to the FDA Modernization Act recently approved by unanimous vote by Senate, and now on its way to be signed into law, expected before year-end, as acknowledgement that animal studies are not a good predictor of success in humans. The Act will remove the requirement for sponsor companies to evaluate treatments on animals before administering them to humans.

In the rare disease space, there are not a lot of patients. This results in many studies being more expensive global trials. For many rare diseases, researchers also do not have access to a natural history of the disease. Combine those factors together, and you have a situation that is more difficult than the challenges faced in other therapeutic areas. Bentwich believes the solution to this problem is artificial intelligence (AI).

AI Can Determine Winners

Ideally, we would want to know, before a trial begins, if a treatment will be safe and effective in humans. In addition to the expense, Bentwich believes it is inhumane to put patients through a trial for a treatment that will not gain regulatory approval. AI is a technology that can help researchers determine which molecules are likely to end in failure. To illustrate, Bentwich gives the following example.

"If you wanted to create an AI machine that discerns cats from dogs, how would you go about it?" he asks. "You can take 500 cats and 500 dogs and run them through a scan that looks at different properties of these animals. The scan could look at the fur, tail, head, teeth, and paws of a group of

animals. You scan 500 cats and look at those factors, and then scan 500 dogs and look at the same factors. By the time animal number 1001 is scanned, the AI will be able to tell you whether it is a dog or a cat."

A technology known as Bio-AI uses patients-on-a-chip, which allows researchers to view miniaturized human tissues and organs on small chips that are less than a millimeter in size. Those researchers can then apply known drugs to those chips, rather than evaluating them on mice, and train the AI to recognize the difference. That is the essence of what Quris is trying to do.

"We are combining three disciplines: patients-on-a-chip, stem cell genomic diversity, and AI," says Bentwich. "This will allow us to determine which drugs will be safe in the human body. We can run the test on many different patients on a chip and train the AI, like the dog/cat example. If we show the AI 500 drugs that are safe in humans and 500 drugs that are not, when we show it drug number 1001, the AI will be able to tell us if that drug will be safe in humans."

Quris was able to look at 1,036 drugs that FDA has classified over the years by their level of toxicity to the liver. These drugs went through invitro testing, animal testing, and clinical trials and seemed fine, yet some were still found to be toxic in humans.

"Those 1,036 drugs are our dogs and cats," says Bentwich. "We know which are toxic and which are not. We run them on our platform, all the mini patients-on-a-chip, and let the AI study them. When an unknown drug comes along, we run it through the same platform and ask if it looks more like the toxic drugs or the non-toxic ones. We believe this approach will be the next generation of addressing rare disease drug development."

A New Solution Is Needed

Although Quris started out as a drug development company, Bentwich notes he was intrigued about how drugs are developed, especially in the rare disease space. The conundrum in that space became clear to him and he knew there had to be a better way of determining which treatments would be safe in humans. That problem led to the development of a technology solution.

The platform the company is using was developed entirely inhouse, and one that he says was developed out of necessity. He uses the company's development of Fragile-X as an example. This is a disease for which there were no mouse models. A different approach was needed, and the patients-on-a-chip model, combined with AI, seemed to be the best solution.

The AI expertise needed already existed inhouse. Bentwich is a medical doctor by training but has spent many years working on AI and other technology solutions for the life sciences industry. To develop the capabilities, Quris brought in technology experts from different domains including miniaturized biology engineering and machine learning to develop this capability.

Other pharma companies may also be interested in using the technology to predict the success or failure of their own drugs. Bentwich notes Quris will make it available to other pharma and biotech firms to maximize the impact of the technology. "We will make it available to any companies that have an interest," he adds. "We believe the impact of this technology will be felt around the wo

iXCells Biotechnologies Announces Grand Opening and 2024 Rare Disease Month Workshop

Thu, Feb 1, 2024

New 30,000 SF San Diego, California facility adds substantial capacity to sustain future growth.

SAN DIEGO, February 01, 2024--(BUSINESS WIRE)--iXCells Biotechnologies USA, Inc. ("iXCells"), a cell technology company providing innovative cell products and preclinical drug development services to the global academic, biotech, pharmaceutical, and rare disease communities today announced the grand opening celebration of its new San Diego headquarters and Rare Disease Month Workshop.

A ribbon-cutting ceremony scheduled February 8th at 9am marks a milestone in the company's growth, the grand opening of its new facility located at 10100 Willow Creek Road. This special event will be attended by invited guests, employees, leading industry scientists, entrepreneurs from the rare disease community, and San Diego's honorable Mayor, Todd Gloria.

The company's new 30,000 SF facility supports increasing market demand for disease relevant cell-based models and assay systems, such as iPSC derived cells, primary cells, 2 and 3-D cell culture models, organoids, and AI-ML based approaches. The pharmaceutical industry is increasingly shifting away from in-vivo animal models towards alternative cell-based systems since the FDA Modernization Act 2.0 signed into law December 29, 2022, now allows

organizations to submit non-animal data using such alternative technologies to demonstrate the safety and efficacy of investigational drugs prior to conducting clinical trials.

iXCells Biotechnologies continues to play a leadership role in providing CRO services and fostering industry collaboration and innovation to support the rare disease community, spearheaded by its Co-Founder and President, Dr. Nianwei Lin. A rare disease is described as a life-threatening or chronically debilitating disease having low prevalence and is often genetically predisposed - for example, a disease affecting less than 200,000 people in U.S, fewer than 2,000 people in EU, and according to World Health Organization, fewer than 65 per 100,000. Currently there are more than 10,000 distinct types of rare genetic diseases, affecting 20 million people in the US and 400 million globally. Among these patients, 50% of them are children, and many of them won't live to see their 5^{th} birthday. Ninety five percent (95%) of rare diseases lack an FDA approved treatment.

This year's Rare Disease Workshop will include talks from rare disease patient foundation leaders, scientific presentations covering iPSC derived CNS models, antisense oligonucleotide (ASO) development, industry collaborations in the Nof1 ecosystem, roundtable discussions and networking.

The company's newly appointed CEO, Dr. Helge Bastian, said, "We're thrilled to be officially celebrating this important milestone with our valued customers and employees, industry leaders, Great Point Partners, and Mayor Gloria. iXCells is a shining example of what an organization can accomplish with dedicated employees and a fervent desire to provide innovative solutions to some of the industry's most challenging aspects of preclinical development."

San Diego Mayor, Todd Gloria, commented, "San Diego's life-sciences companies are on the vanguard of drug research and development. iXCells Biotechnologies' pursuit of groundbreaking scientific advancements toward cures for common, rare, and ultra-rare diseases is truly remarkable, and I am delighted to support the important work they do both locally and worldwide."

About iXCells Biotechnologies

Founded in 2014 and based in San Diego, CA, iXCells Biotechnologies is an innovative cell biology and cell technology company dedicated to providing preclinical drug discovery solutions with the focus on disease relevant cellular models enabling technologies and services to the academic, biotech and pharma communities to accelerate the pace of drug discovery. iXCells offers customers access to high quality primary and iPSC derived cells, custom iPSC services, functional bioassay development and drug

screening. To learn more about this innovative leader within the preclinical iPSC sector, visit .

Follow iXCells Biotechnologies on , , and on .

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Contacts

Wayne E. Vaz
Corporate Development & Commercial Operations

Statement for the Record from the Creutzfeldt-Jakob Disease Foundation
Energy and Commerce Committee
Health Subcommittee Hearing: "Legislative Proposals to Support Patients with Rare Diseases"
February 29, 2024

The Creutzfeldt-Jakob Disease Foundation (Foundation) commends the Committee for its focus on rare diseases and the patients, families, and communities across our country impacted by rare diseases every day. The Foundation appreciates the opportunity to share our insights regarding Creutzfeldt-Jakob Disease (CJD), a particularly devastating rare disease, as part of the Committee's consideration of legislative proposals to support rare disease patients, including the Committee's ongoing consideration of H.R. 619, the NAPA Reauthorization Act.

The Foundation's mission is to support patients and families in the effort to raise awareness and expand medical research and discoveries. CJD, is a rare, 100% fatal, degenerative brain disease that causes rapidly progressive dementia. CJD is transmissible and presently has no treatment or cure. Individuals with CJD often exhibit symptoms similar to other degenerative brain diseases like Alzheimer's Disease and Parkinson's, making diagnosis difficult. While there are approximately 500 new and definitively diagnosed cases of CJD in the United States each year, it is likely that additional cases are unreported or misdiagnosed. Like other rare diseases, every family and community affected by the loss of a CJD patient has a compelling story to tell about how their lives have been affected by this deadly condition.

CJD falls within a group of illnesses which are the result of misfolded proteins in the brain, called *prions*. There are three forms of CJD, but all occur when a normal protein in the brain misfolds, then causes other proteins around it to also misfold, unleashing a chain of misfolded proteins that seriously impairs brain function, ultimately causing severe brain deterioration and death. Approximately 1 in 6,200 deaths per year in the U.S. are attributable to prion disease.

While the CJD community faces the unique challenges shared by many in the rare disease space, there are many molecular and pathologic similarities between Alzheimer's Disease/Alzheimer's Disease-Related Dementias (ADRDs) and prion diseases. This connection was recently highlighted by the 2023 National Plan to Address Alzheimer's Disease with a goal to broaden the view of the basic biology between ADRDs and prion diseases noting that this integration could lead to scientific breakthroughs. These similarities provide hope to the prion disease patient community, including the CJD patient community. However, the current absence of CJD and other prion diseases from the category of "ADRD-related research" under the National Institutes of Health (NIH) impedes the ability for Congressionally-funded research opportunities to fully explore and leverage the connection between prion diseases, like CJD, and ADRDs for patients.

This results in missed opportunities for patients impacted by ADRDs and CJD, among other prion diseases, including rare disease patients.

More transparency into ADRD research funding is needed as ADRDs have already benefited from prion disease research and given the significant level of federal resources that support ADRD research. As the Committee works on legislation this Congress, we strongly urge you to consider the importance of this transparency for rare disease patients, especially CJD patients in the context of the reauthorization of H.R. 619, the National Alzheimer's Project Act reauthorization. As the Committee works on this bill, there is an important opportunity to require the Secretary of HHS to include a summary of the Secretary's process for identifying and updating what conditions constitute Alzheimer's Disease and Related Dementias as part of the annual report required under the bill. Including this additional information in the annual report will help ensure that federal research on ADRDs is in line with the most current understanding of how these diseases are connected at a molecular level as informed by recent scientific advances that stand to benefit many patients, including rare disease patients. Incorporating this information into HHS' annual report to Congress will also improve transparency on this front for ADRD patients, families, caregivers, the related research community, and Congress.

Thank you, again, for your work on behalf of all rare disease patients, including those impacted by prion diseases. The Foundation looks forward to working with the Committee on behalf of CJD patients. For any question regarding this statement, please contact CJDF's Executive Director, Debbie Yobs (debbie@cjdfoundation.org).

Thank you.

Sincerely,

Debbie Yobs

Debbie Yobs
President and Executive Director

The Future of Medicine Is Unfolding Before Us. Are We Nurturing It?

Credit...Kaitlin Brito

By Elizabeth Currid-Halkett

Dr. Currid-Halkett is a Guggenheim fellow and professor of public policy at the University of Southern California.

On Jan. 8, 2020, as I was parking my car, I got a long-awaited phone call from one of my son's doctors. She informed me that our 7-month-old son, Eliot, had Duchenne muscular dystrophy, a fatal neuromuscular disease.

I can still remember the way the Los Angeles winter sunlight hit the dashboard. I can see my neighbor walking up her steps with groceries, a leaf falling, oblivious to the devastation below. “Life changes in an instant,” Joan Didion wrote. “The ordinary instant.” Our son had a fatal illness. He would die before us.

D.M.D. prevents the production of dystrophin, a protein needed to protect and repair muscle cells. It is caused by a genetic mutation on the X chromosome, thus the disease almost exclusively affects boys (one in 3,300). Over time, children with D.M.D. lose muscle mass and thus the ability to do basic things like run and walk. Eventually they lose their ability to breathe, and they experience heart failure. There is no known cure. While existing treatments have helped extend the life span of sufferers, they mainly focus on managing symptoms.

In my search for answers for how to save my son, I contacted Dr. Jerry Mendell, a now-retired neurologist at Nationwide Children’s Hospital in Columbus, Ohio, who was running clinical trials for an experimental gene therapy he developed to enable dystrophin production in boys with D.M.D. The treatment, now known as Elevidys, offered the prospect of not merely managing symptoms, but slowing the disease’s progression or even stopping it in its tracks — and potentially, for the first time in the history of this terrible disease, allowing boys with D.M.D. a chance to thrive.

Since I had that first conversation with Dr. Mendell (also a senior adviser for Sarepta, the maker of Elevidys), clinical trials for the gene therapy have had their ups and downs, and some adverse effects have been reported. But in June 2023, based on a two-part clinical trial, the Food and Drug Administration granted accelerated approval for the treatment for 4- and 5-year-olds who do not have other disqualifying conditions. The F.D.A.’s approval was contingent on continuing trials showing evidence of improved motor function, which had not yet been established.

Before Eliot received his treatment, he had difficulty going up stairs. He complained about being tired after walking only a block or two, even on Halloween, when candy ought to have motivated him. Hopping on one foot, a milestone for a 4-year-old, was impossible.

On Aug. 29, he finally received the one-time infusion. Three weeks later, he was marching upstairs and able to jump over and over. After four weeks, he could hop on one foot. Six weeks after treatment, Eliot’s neurologist decided to re-administer the North Star Ambulatory Assessment, used to test boys with D.M.D. on skills like balance, jumping and getting up from the floor unassisted. In June, Eliot’s score was 22 out of 34. In the second week of October, it was a perfect 34 — that of a typically developing, healthy 4-year-old boy. Head in my hands, I wept with joy. This was science at its very best, close to a miracle.

But the goal to offer this possible future to more patients with D.M.D. is in jeopardy. Sarepta is seeking F.D.A. approval to treat boys over 5. Disagreements over the latest clinical trial’s results threaten to derail that outcome.

Moreover, what the F.D.A. decides to do next with Elevidys could set the tone for how it handles other emerging gene therapies for rare diseases. We can already see roadblocks that prevent more families from gaining access to these new treatments — from high costs and insurance challenges to dissent over how flexible regulators should be in interpreting clinical trial results and taking qualitative improvements into account. What is at stake with the debate around Elevidys is more than just the chance to give other boys with D.M.D. a more normal life. The challenges that we are witnessing with Elevidys are a harbinger of the fights we may see with gene therapies developed for other rare diseases.

There's an opportunity to reduce those barriers now, while these treatments are still in their early phases. Every child afflicted with a life-threatening disease deserves the chance Eliot has been given.

The biggest obstacle to getting these treatments is cost. Gene therapies cost, on average, $1 million to $2 million. At $3.2 million per patient, Elevidys is the second-most-expensive drug in the world. Insurance companies would probably prefer not to foot the bill, and without full F.D.A. approval, insurance companies can refuse to cover these treatments by claiming they are medically unnecessary or experimental. Before Eliot's treatment began, my insurance company initially said it would cover the cost but then started stalling on coverage and questioning the urgency of Eliot's treatment. I was able to call Dana Goldman, the dean of the Sol Price School of Public Policy at the University of Southern California, where I work, to help me navigate the process. I was in the rare position to marshal resources and assistance to pressure my insurance company into covering Elevidys. Across the country, physicians are fighting denials and seeking appeals for their young patients.

Dr. Goldman has argued that one way to incentivize insurance companies to cover the high costs of treatments like gene therapies is to amortize how much the companies pay over time if the effectiveness of such treatments does not last (analogous to a pay-for-performance model). Another option is for pharmaceutical companies to offer a warranty that gives a prorated refund to the insurance company if a patient needs to return to prophylaxis treatment within a certain number of years. Costs are an especially frustrating problem for rare diseases like D.M.D., for which the extremely small patient population deters companies from investing money and resources to develop new treatments. Some experts believe the federal government ought to do more to directly complement research funding for rare diseases, as it has through the Orphan Drug Act for over four decades. The government could also defray the cost to consumers by offering subsidies directly to patients.

There's another big role the government can play to accelerate gene therapies besides intervening in costs, and that's to make the wheels of regulatory approval for these drugs less onerous. Flexibility doesn't have to come at the cost of safety. The F.D.A. acted swiftly to approve an antiretroviral drug for H.I.V. in the 1980s and the Covid vaccines in December 2020, saving millions of lives without putting people in harm's way.

But Elevidys is a case study in how the F.D.A. can get in its own way. D.M.D. patients 4 or 5 years old received access to the drug under fast-tracked approval, the first time a drug was approved under this new framework. But this was reportedly only because Peter Marks, the director of the F.D.A.'s Center for Biologics Evaluation and Research, disagreed with his own staff's rejection. Current concern over Elevidys's approval for boys over 5 focuses on the most recent clinical trial results, which showed older boys, whose muscular decline is further along, did not improve on motor function as measured by the North Star Ambulatory Assessment after treatment. However, as Sarepta has noted, they still saw gains in their ability to rise from the floor and walk 10 meters, indicating possible slowing of the disease that could significantly improve and extend their lives.

Detractors suggest this improvement is not enough to meet the bar for approval. This is a common problem for rare disease trials because they often consist of very few participants. In such cases, a narrow focus on numbers ignores the real quality-of-life benefits doctors, patients and their families see from these treatments. During the advisory committee meeting for Elevidys in May 2023, I listened to F.D.A. analysts express skepticism about the drug after they watched videos of boys treated with Elevidys swimming and riding bikes. These experts — given the highest responsibility to evaluate treatments on behalf of others' lives — seemed unable to see the forest for the trees as they focused on statistics versus real-life examples.

The F.D.A. can have a more flexible view of treatment efficacy without losing focus on safety. As with any drug, whether for migraines or asthma, there will be a spectrum of effectiveness. The same will be true of all gene therapies, and the F.D.A. should reconsider the metrics it uses to green-light these

treatments now, before it potentially leaves thousands of patients in the lurch, out of access to something lifesaving.

Gene therapy is the future of medicine. Our bureaucracy and insurance companies should not hinder patients from receiving pioneering treatments that could transform their lives. As parents, we are not asking for the moon. We just want our children to live.

Elizabeth Currid-Halkett is a Guggenheim fellow and professor of public policy at the University of Southern California.

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To the Editor:

Re "Why Can't More Children Get the Treatment That Saved My Son's Life?," by Elizabeth Currid-Halkett (Opinion guest essay, Feb. 24):

Our three children, ages 5 and 7, battle a rare, relentless and ultimately fatal disease called cystinosis. We recently found hope in the initial phase of a gene therapy clinical trial that was shown to be safe and yielded very promising results — a therapy that could one day save our children's lives. Our biggest fear is that it will not be accessible to them or others in desperate need.

Dr. Currid-Halkett beautifully articulated the fears of parents like us, who find hope in the promise of new therapies but face, as she said, "roadblocks that prevent more families from gaining access to these new treatments," including "dissent over how flexible regulators should be in interpreting clinical trial results and taking qualitative improvements into account."

She cites Dr. Peter Marks, the director of the F.D.A.'s Center for Biologics Evaluation and Research, for recently making a courageous call for the approval of Elevidys, a treatment for patients with Duchenne muscular dystrophy. We applaud Dr. Marks's wisdom and perspective. However, the F.D.A. reviewers' initial rejection is a cautionary tale of how patient access to lifesaving therapies could be impeded by a narrow interpretation of efficacy.

> We implore the F.D.A. to consider what Dr. Currid-Halkett calls "a more flexible view of treatment efficacy without losing focus on safety." Specifically, this lens should be applied to the way outcomes are measured, including quality of life improvements, to avoid denying lifesaving treatments to all patients in need.

For example, if a 1-year-old who receives a gene therapy treatment is cured of their disease and a 10-year-old who receives the same treatment isn't cured but is granted a longer, healthier life as a result, should we not make treatment available to both of them?

Every child with a life-threatening disease deserves a fighting chance. We hope the F.D.A. agrees. The lives of our three children depend on it.

Erin Finucane
Erin McCarthy
Carli Beckett Simpson

Statement from EveryLife Foundation for Rare Diseases

House Energy & Commerce Subcommittee on Health Hearing:
Legislative Proposals to Support Patients with Rare Diseases Oversight

February 28, 2024

Chairs Rodgers and Guthrie and Members of the Subcommittee:

On behalf of the EveryLife Foundation for Rare Diseases, we thank you for convening today's hearing exploring a wide array of bipartisan legislation with the common denominator being the needs of people and their families impacted by rare diseases and disorders. As the committee ably notes in its hearing notice, rare diseases are, collectively, very common impacting more than 30 million Americans and costing our nation $1 trillion or more each year when accounting for medical, non-medical, and indirect costs[1].

The EveryLife Foundation for Rare Diseases is a 501 (c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures. EveryLife's establishment of the Community Congress, a diverse coalition comprised of patient advocacy organizations, industry leaders, coalition groups, and other relevant stakeholders guides our policy efforts and provides advice and insight on important policy issues impacting the rare disease community.

We can think of no better way to mark Rare Disease Week than by holding a hearing focused on legislative proposals seeking to improve life for people impacted by rare diseases. More than 40 years ago, Congress took the bold step of enacting the Orphan Drug Act (ODA), a law that helped transform rare disease therapy development from a barren desert to a field of opportunity. Between 1983 and 2022, the ODA led to the approval of more than 882 drugs to

[1] Yang G, Cintina I, Pariser A, Oehlrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17:163

treat rare diseases, many of which would not have existed if not for the policies contained in this law[2].

While the rare disease community has achieved much in recent years, we are reminded daily of how much more progress is still needed, particularly since 95% of the 10,000 identified rare diseases lack any FDA-approved therapies[3,4]. The bills on the agenda for this hearing will look at an array of policies to address challenges in developing therapies for rare diseases as well as barriers rare disease patients face in accessing care and treatments, including the highly specialized and well-coordinated care needed for many serious diseases and disorders.

The National Economic Burden of Rare Disease Study estimated that in 2019 the overall annual economic impact of rare diseases in the United States exceeded $966 billion[5]. Of the total economic burden, the largest expenditures were indirect costs from productivity losses at $437 billion, direct medical costs at $418 billion, and non-medical and uncovered healthcare costs of $111 billion absorbed directly by families living with rare diseases[6]. Aside from absenteeism, inpatient care was the biggest expense, accounting for nearly 15% of the overall economic burden while prescription medication and administration costs accounted for about 10% and outpatient care for about 6%[7]. These findings highlight the necessity of focusing on policies that address rare disease need spanning the overall healthcare system[8].

Lowering the cost of health care is an important but nuanced goal of multiple legislative proposals under consideration at the hearing. As the Committee considers different policy options, it must recognize the unique complexities of rare disease drug development and the high unmet need faced by the more than 30 million Americans living with rare diseases.

Several of the bills on today's agenda are priorities of the EveryLife Foundation and represent critical steps forward in our collective effort to accelerate the development and availability of therapies for rare diseases. Specifically, we'd like to offer our support of the following bills:

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[2] Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis. 2023 Jun 23;18(1):163. doi: 10.1186/s13023-023-02790-7. PMID: 37353796; PMCID: PMC10290406.

[3] Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., Dawkins, H., Rath, A., Thaxon, C., Bocci, G., Joachimiak, M. P., Köhler, S., Robinson, P. N., Mungall, C., & Oprea, T. I. (2020). How many rare diseases are there? Nature Reviews Drug Discovery, 19(2), 77–78. https://doi.org/10.1038/d41573-019-00180-y

[4] Navarrete-Opazo, A. A., Singh, M., Tisdale, A., Cutillo, C. M., & Garrison, S. R. (2021). Can you hear us now? The impact of health-care utilization by rare disease patients in the United States. Genetics in Medicine, 23(11), Article 11. https://doi.org/10.1038/s41436-021-01241-7 and U.S. Food and Drug Administration. 2023, Search Orphan Drug Designations and Approvals.

[5] Yang G, Cintina I, Pariser A, Oehlrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17:163

[6] Ibid

[7] Ibid

[8] Ibid

H.R. 7384, the Creating Hope Reauthorization Act of 2024:

Without Congressional action, the Rare Pediatric Priority Review Voucher (PRV) Program will expire on September 30, 2024, leaving one less tool to bring treatments to a rare disease community in which only five percent of diseases have an FDA-approved treatment. It is imperative that we continue to advance solutions to treat these devastating diseases. Allowing the Rare Pediatric PRV program to expire would eliminate a powerful incentive for the development of treatments for the 70 percent of rare diseases that start in childhood[9]. Developing treatments for rare pediatric diseases is even more challenging due to very small populations, complexities involved in conducting clinical trials in children, the nature of many pediatric genetic diseases, and delays in diagnosis among other factors.

The PRV Program has enabled life-saving treatments to reach children with rare diseases faster without adding new costs to taxpayers. Since 2012, 49 Rare Pediatric PRVs have been issued, bringing treatments to about 40 distinct rare disease communities[10]. PRVs have been associated with an increased rate of progress throughout the clinical trial process, leading to product approvals to treat multiple rare diseases such as Progeria syndrome, Spinal Muscular Atrophy, Sickle Cell Disease, Rett syndrome, and other conditions that previously lacked any FDA-approved treatments. In at least one example, the existence of the Rare Pediatric PRV can be credited for ensuring the treatment was available in the pediatric population immediately upon first approval rather than having the treatment be first approved for an older subset of the population and then having to wait years for additional pediatric research to be conducted; years that many kids with rare diseases do not have.

The EveryLife Foundation enthusiastically supports the Creating Hope Reauthorization Act to ensure that this important piece of the rare disease development incentive puzzle remains intact for another four years.

H.R. 1092, the Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act:

Thanks to Congress' leadership in supporting policies that grew and formalized the role of patient-focused drug development (PFDD) over the last decade, patient perspectives and patient experience data have a bigger role in driving the direction and success of rare disease therapy development. While we are grateful for the success of the patient-focused drug development movement thus far, some barriers threaten to disrupt this progress, one of which is the uncertainty in HOW the FDA uses this data in their regulatory review process. A provision

[9] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165–73.

[10] The Federal Register. https://www.federalregister.gov/

in the 21st Century Cures Act ensured that the FDA would have to disclose WHEN patient experience data was submitted as part of the regulatory review package, but it stopped short of requiring transparency into how this information played a role in the FDA's evaluation of a therapy's benefits and risks. The transparency that the BENEFIT Act proposes will guide future efforts to collect patient experience data, ensuring efficient and effective approaches to data collection are deployed. Additionally, the bill will incorporate patient experience data as part of the FDA risk-benefit assessment, ensuring this important information is a full part of this assessment.

The BENEFIT Act is a simple, common-sense addition to an existing tool utilized by the FDA. Patient advocacy organizations and sponsors have embraced the role patient experience should play in therapy development, spending precious resources on data collection and analysis, qualitative research, and PFDD-related engagements. The BENEFIT Act will ensure these investments and the growth of PFDD are sustained in the long term.

H.R. 4758, the Accelerating Kids Access to Care Act:
Many within the rare community are required to travel out of state to receive the healthcare they need. An EveryLife Foundation study found that the average number of out-of-state trips for rare disease patients just to obtain a diagnosis was 2.4[11]. For kids with Medicaid or CHIP coverage, the long delays associated with obtaining approval to see specialists located outside of their home state can result in irreversible adverse health outcomes. One aspect of this approval, the process to screen and enroll out-of-state physicians as eligible providers in the children's home state, can be improved through the simple changes proposed in the Accelerating Kids Access to Care Act. This legislation will allow pediatric providers to enroll more efficiently in multiple state Medicaid programs for a five-year period, enabling faster access to specialized rare disease care not available in a patient's home state. Streamlining this process for children with rare diseases will help to ensure timely and appropriate treatment for our youngest patients.

H.R. 6094, the Providing Realistic Opportunity to Equal and Comparable Treatment for (PROTECT) Rare Act:
The lack of approved treatments for most rare diseases results in many within the rare disease community relying on off-label use of drugs approved for other conditions[12]. However, those treatments are rarely covered by insurance even though clinical guidelines and peer-reviewed

[11] Yang G, Cintina I, Pariser A, Oehlrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17:163
[12] Navarrete-Opazo, A. A., Singh, M., Tisdale, A., Cutillo, C. M., & Garrison, S. R. (2021). Can you hear us now? The impact of health-care utilization by rare disease patients in the United States. Genetics in Medicine, 23(11), Article 11. https://doi.org/10.1038/s41436-021-01241-7 and U.S. Food and Drug Administration. 2023, Search Orphan Drug Designations and Approvals.

evidence support the expert's opinion that the treatment could provide benefit to one or more of the symptoms of an individual's rare disease. The PROTECT Rare Act permits Medicare and Medicaid to use clinical guidelines and peer-reviewed literature to allow for coverage of rare disease treatments. It will also require private payers to create an expedited review pathway for formulary exception, reconsideration, and/or appeal of any denial of coverage for a drug or biological prescribed for a patient with a rare disorder.

H.R. 7383, the Retaining Access and Restoring Exclusivity (RARE) Act:
A 2021 court ruling determined that orphan drug exclusivity under the Orphan Drug Act grants a manufacturer exclusivity across an entire disease or condition, even if it has only had a drug approved for one population or indication. This was contrary to how the FDA has interpreted the Orphan Drug Act over the last several decades. This legislation would specify that the seven-year market exclusivity period for drugs for rare diseases or conditions (i.e., orphan drug exclusivity period) prohibits the approval of other drugs for the same approved use or indication with respect to the disease or condition rather than applying to all uses within the disease or condition. The proposal is aligned with how FDA has been issuing exclusivity since the ODA became law and would ensure that the FDA can continue to approve a drug that aims to serve different patient populations such as pediatric approval for a drug that has exclusivity based on an adult approval.

IRA Concerns
While we appreciate the Committee's commitment to discussing legislation focused on reforming various aspects of the Inflation Reduction Act, we urge you to consider an alternative approach supported by 170 patient organizations that prioritizes two technical changes in the short-term to help preserve the hope of the 95% of rare disease communities without disease-specific FDA approved treatment options, yet will not change the number of approved indications a product can have before becoming eligible for Medicare negotiation. Specifically, this approach would:

1) *Clarify that the number of orphan designations FDA grants a product has no effect on its eligibility for the IRA's orphan drug exclusion.*
2) *Maintain the purpose of the orphan drug exclusion by clarifying an orphan product becomes negotiation-eligible 7 or 11 years after it loses that exclusion.*

These simple changes will support continued incentives to invest in the research and development necessary to address the vast unmet medical need of the rare disease community while further research and consideration of the long-term policy needs occur.

Conclusion

In closing, the EveryLife Foundation for Rare Diseases thanks you again for convening this legislative hearing. We are grateful for your leadership and ongoing commitment to the health and well-being of the 30 million Americans with rare diseases. We stand ready to assist the committee as you continue the consideration and markup of these and other policies relevant to all impacted by rare diseases.

Statement for the Record by
Paul Seifert
Before the
House Energy and Commerce Health Subcommittee
Hearing on
Legislative Proposals to Support Patients with Rare Diseases
February 29, 2024

Chairwoman Rodgers, Chairman Guthrie, and Ranking Member Eshoo, and members of the Subcommittee, thank you for holding this timely hearing on this critical legislation. My name is Paul Seifert and I am a person with ALS.

ALS is a progressive neurodegenerative disease that attacks the motor nervous system. It leads to loss of muscle control, paralysis, loss of the ability to speak or eat. Every 90 minutes someone in the U.S. is diagnosed with ALS. Every 90 minutes someone in the U.S. dies from ALS. ALS is 100% fatal. There is no cure.

I was diagnosed with ALS in January of 2023 through a genetic test that revealed a mutation in the C9orf72 gene. It is an autosomal dominant condition which means my children have a 50-50 chance of inheriting this gene mutation.

So it is important to keep in mind that the bills today won't just benefit patients today, but those who may develop this disease in the years to come.

There are two bills I want to highlight in my testimony today. First is HR 5663, the ALS Better Care Act. This legislation is urgently needed to increase access to multidisciplinary care clinics. Too often where a person lives and what financial resources they have will determine

whether they will be able to receive this life extending and life improving care.

Unfortunately, current Medicare reimbursement rates make it nearly impossible to open new clinics and/or increase existing clinic capacity. This is because the current reimbursement does not cover the cost of the specialized multidisciplinary ALS care that people living with ALS need. In fact, many ALS clinics rely on donations to cover their costs. The ALS Better Care Act would create an $800 supplemental payment to cover costs that for which Medicare does not pay at ALS clinics.

The second bill is HR 1092, Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act. This legislation would give greater weight to patient experience data within risk-benefit framework. On too many occasions the Food and Drug Administration (FDA) gives far too little weight to the experiences of patients in the drug approval process. HR 1092 would give patient experiences the proper weight it deserves.

HR 1092 has broad support among many patient and rare disease groups.

Once again, I want to thank the Subcommittee for holding this hearing and I urge the Subcommittee to give these bills prompt consideration.

Paul Seifert is a member of the ALS Association Policy Committee, and the IAMALS Legislative Team.

February 29, 2024

The Honorable Cathy McMorris Rodgers
Chair
House Energy & Commerce Committee

The Honorable Frank Pallone
Ranking Member
House Energy & Commerce Committee

The Honorable Brett Guthrie
Chair
House Energy & Commerce
Subcommittee on Health

The Honorable Anna Eshoo
Ranking Member
House Energy & Commerce
Subcommittee on Health

RE: House Energy & Commerce's Health Subcommittee hearing, "*Legislative Proposals to Support Patients with Rare Diseases."*

Dear Chairs McMorris Rodgers, Guthrie, and Ranking Members Pallone and Eshoo:

As a mother of a beautiful son who is living with a rare disease, I thank you for holding today's important hearing. I am fully dedicated to providing around-the-clock care for my son, which does not come without its challenges. I applaud you for focusing the committee's attention on this important issue that impacts so many families across the nation. I stand ready to work with this committee on the development of meaningful policies to address children impacted by rare diseases, and their full-time caregivers.

My name is Hannah Lowe, a Houston resident, and the mother of Austin Corman, a bright and silly 4.5-year-old boy, who is living with the rare disease LMNA-related congenital muscular dystrophy (L-CMD). It is believed there are only about 200 children in the entire world with this fatal, muscle-wasting disease which is characterized by progressively weakening skeletal and cardiac muscles; however, there are likely many more undiagnosed due to the lack of genetic testing.

Children eventually succumb to respiratory illness or cardiac arrest, and while they are living, most will eventually need wheelchairs, respiratory support, feeding tubes, and orthopedic interventions. A key symptom of this disease is "head drop" in that children cannot hold up their heads, and some, like Austin, have never been able to sit independently. These are significant health issues for any person to deal with, much less a child, but we find the strength to continue to work through these difficult challenges to ensure Austin continues his fight.

Despite these physical barriers, children are cognitively typical with smart and witty personalities. We, as parents, despair that the majority of our children won't have the opportunity to grow up and live long and happy lives, with work, marriage and children of their own. We despair that schools, playgrounds and other public spaces are inaccessible for our children's medical and physical conditions. Caregivers are grateful to be able to be with our children; however, we are physically and mentally exhausted by the above-and-beyond care needs. For families with two parents, one parent often leaves their profession to be able to serve as the full-time caregiver to their children with these rare diseases.

We appreciate your proclaimed support of “research and fostering innovation…[to] continue to support finding treatments and cures that provide hope to patients in need.” I too believe this is a top priority.

To this end, there are many avenues of support for rare disease families towards treatments and cures:

1. Increased incentives for research scientists at every level to work on rare diseases. Currently, not enough scientists are working on rare diseases, which leaves tremendous gaps in how to best treat children like Austin. Better understanding these diseases, through research, may be a key component to finding treatments in the short and long term.

2. Grant and other funding opportunities for small, patient-led nonprofits that are leading cutting-edge research. Many funding opportunities are driven by friends and families to use their networks to raise resources to dedicate to a particular rare disease. As you can imagine, there are inherent limitations on grassroots fundraising efforts, that are valuable, but often fall short of the critical dollars needed to perform meaningful research. As parents of these children, we are knocking on every door, and engaging our friends and family in fundraising efforts, but more help is needed. Bake sales and charity races only go so far in generating much-needed resources.

3. Congress should pursue policies that allow people living with terminal and rare diseases to swiftly access experimental treatments. The current timelines for treatments are too long–from research and development to the government approval process. In Austin’s case, this timeline will not work with his timeline.

I am thankful to see the bipartisan bills the committee will consider at today’s hearing. I hope that families with children inflicted with rare diseases will continue to be part of our discussions and development of policy. Austin’s care is my primary responsibility, and I stand ready to meet with you, and members of your committee to discuss who we can partner with on policies to benefit our children, and the caregivers who love and care for them.

I hope you will use me as a resource as these discussions continue. Additionally, I hope you will be able to meet with Austin in the near future to hear his story and feel the same commitment we have to tackling rare diseases. Thank you for taking the time to hear my testimony.

Respectfully,

Hannah Lowe
Houston, Texas

February 29, 2024

The Honorable Roger Wicker
U.S. Senate
555 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Doris Matsui
House of Representatives
2311 Rayburn House Office Building
Washington, DC 20515

The Honorable Amy Klobuchar
U.S. Senate
425 Dirksen Senate Building
Washington, DC 20510

The Honorable Brad Wenstrup
House of Representatives
2419 Rayburn House Office Building
Washington, DC 20515

RE: Support for the BENEFIT Act of 2023 (H.R. 1092 and S. 526)

Dear Senators Wicker and Klobuchar and Representatives Matsui and Wenstrup:

Thank you for your tireless efforts to encourage development of and expand access to treatments and cures for patients, including those with rare diseases. On behalf of the undersigned patient advocacy organizations, we write in strong support of your legislation, the Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act of 2023 (H.R. 1092 and S. 526).

As you know, the 21st Century Cures Act (P.L. 114-255) included sections 3001 and 3002, the Patient-Focused Impact Assessment (PFIA), which has accelerated the field of patient-focused drug development (PFDD). FDA now has a number of programs and policies in place to gather and assess patient perspectives within the regulatory review process, and patient advocacy organizations have been deeply engaged with the FDA over the past several years to develop PFDD tools that produce scientifically valid patient experience information. Tremendous progress has been made over the past decade since the fifth Prescription Drug User Fee Act (PDUFA) was authorized, including with PFIA and other provisions of 21st Century Cures. Now is the time to take the next step in moving patient perspectives and experience forward by enacting the BENEFIT Act.

The BENEFIT Act would require FDA to include in the benefit-risk assessment framework of a new drug application how patient experience data was considered in the review process. Currently, FDA includes patient experience data in reviews, but does not indicate how such data impacted the drug approval. Providing this information to the public, and patient communities making significant investments in developing PFDD, builds on transparency from PFIA and will accelerate PFDD strategies more broadly.

The field of patient engagement in drug development continues to flourish thanks to the continued interest and focus by Congress. The BENEFIT Act will build upon this foundation and fill a gap by appropriately disclosing how this data is considered as part of FDA review of new therapies. The BENEFIT Act initially passed the Senate in 2017 but further action was deferred as the 21st Century Cures was being implemented.

Now is the time to take this critical step in building the PFDD environment by passing the BENEFIT Act. Thank you again for your leadership and we look forward to working with you to enact this legislation this Congress.

Sincerely,

AliveAndKickn
Alpha-1 Foundation
Alport Syndrome Foundation
ALS Association
American Brain Coalition
American Kidney Fund
Ara Parseghian Medical Research Fund
Barth Syndrome Foundation
Beyond Celiac
Coalition Duchenne
Congenital Hyperinsulinism International
CSNK2A1 Foundation
Cure CMD
Cure HHT
Cure Sanfilippo Foundation
Cure SMA
CureDuchenne
CureSHANK
Dravet Syndrome Foundation
EveryLife Foundation for Rare Diseases
FND Hope
FORCE: Facing Our Risk of Cancer Empowered
Foundation for Angelman Syndrome Therapeutics (FAST)
Foundation for Prader-Willi Research
Genetic Alliance
Hermansky-Pudlak Syndrome Network
Hope For Marian
International Pemphigus Pemphigoid Foundation
International WAGR Syndrome Association, IWSA
Jett Foundation
Kindness Over Muscular Dystrophy
Klippel-Trenaunay (K-T) Support Group
Little Hercules Foundation
Lupus Foundation of America
MLD Foundation
Mucolipidosis Type IV
Muscular Dystrophy Association
National Ataxia Foundation
National Health Council

National Kidney Foundation
National MPS Society
National MS Society
NBIA Disorders Association
Organic Acidemia Association
Parent Project Muscular Dystrophy
Phelan-McDermid Syndrome Foundation
PXE International
RASopathies Network
RUNX1 Research Program
Ryan’s Quest
Sophie's Neighborhood
Stickler Involved People
Sudden Arrhythmia Death Syndromes (SADS) Foundation
Susan G. Komen
SYNGAP1 Foundation
The Global Foundation for Peroxisomal Disorders
TSC Alliance
United Mitochondrial Disease Foundation
Usher 1F Collaborative
WISKOTT ALDRICH FOUNDATION
Zack Heger Foundation

AARP
STATEMENT FOR THE RECORD
for the

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITEE ON HEALTH
on

LEGISLATIVE PROPOSALS TO SUPPORT PATIENTS WITH RARE DISEASES

February 29, 2024
Washington, DC

For further information contact:
Gidget Benitez
Health Access and Affordability
Government Affairs
gbenitez@aarp.org

AARP, which advocates for the more than 100 million Americans age 50 and older, submits this statement for the record for the hearing of the House Energy and Commerce Subcommittee on Health, "Legislative Proposals to Support Patients with Rare Diseases." Recognizing that there are several bills to be discussed, our comments are focused on legislation impacting the Medicare Drug Price Negotiation Program, specifically H.R. 5539 and H.R. 5547.

AARP appreciates the opportunity to reiterate our strong support for empowering Medicare to finally negotiate for lower drug prices for the American people. Prescription drugs do not work if you cannot afford to take them. And American taxpayers cannot afford to continue paying the highest prices in the world for our drugs.

On average, Medicare beneficiaries take between four and five prescriptions per month. Meanwhile, most people on Medicare have relatively modest financial resources. The median annual income is just over $35,000, and one in ten have no savings or are in debt. They simply do not have the resources to continue to absorb the costs associated with high and growing prescription drug prices.

As a result, far too many are forced to choose between paying for their medication or paying for basic life essentials such as food, housing, or heat. Some older people skip doses, split doses, or forego filling their prescriptions altogether to make ends meet; such behavior can lead to worsening health conditions, hospitalizations, and even death. Other people sell everything they own and drain their resources because the price of their medication is beyond their reach.

Meanwhile, Medicare and its more than 65 million beneficiaries are now spending more than $250 billion annually on prescription drugs, and that amount is growing every year. American taxpayers cannot continue to foot this outrageous bill. It is long past time for Medicare to negotiate for better prices.

It is important to note that at present, not one single drug price has been fully negotiated by Medicare. And yet, predictably, drug companies are already claiming that this commonsense and long-overdue policy will somehow slow drug development. It is difficult to ascertain the basis for these threats. Six of the first ten drugs selected for Medicare to negotiate their prices have already earned more than $50 billion in global revenue since they first entered the market, significantly dwarfing the industry-provided estimate that it costs $2.6 billion to bring a drug to market. The Congressional Budget Office has also estimated that any impact on new drug development would be very small. In addition, numerous reports have found that big drug companies spend more money on stock buybacks, dividends, and executive compensation than they do on research and development. This is alongside multiple reports of drug companies confirming to investors that their revenues have continued to significantly increase.

AARP strongly supports innovation and America's leading role in discovering and bringing new medicines to market. The majority of that work occurs at early-stage companies that are funded by venture capital and hedge funds, not sales of existing products. This indicates that when Medicare negotiates to lower drug prices, it will not have a direct or meaningful impact on these innovative companies or their important work. Further, the process that Medicare is using to negotiate lower prices includes provisions that effectively reward drugs that offer greater clinical

benefits than their competitors, creating strong financial incentives for drug companies to develop more innovative drugs, not less.

There is no objective evidence to support arguments that Medicare negotiating lower drug prices will have a detrimental effect on patients or the drugs they need. Further, the law already includes protections for certain classes of drugs. For example, Medicare cannot negotiate for lower prices on drugs that have a single orphan drug designation, and the law also phases in drugs from small biotechnology companies. Notably, many of these drugs are already exempted from negotiation based solely on revenue. Only 6 percent of the novel orphan drugs solely approved for a rare disease between 1990 and 2022 were among the top-selling drugs worldwide in 2021 (i.e., annual global sales of more than $1 billion). The first 10 drugs selected by Medicare to negotiate for lower prices all had sales that exceeded $2.6 billion in a single year *based on Medicare spending alone*.

Recent drug company financial reporting and merger and acquisition behaviors are not indicative of an industry in financial distress. Efforts to undermine or restrict Medicare from negotiating for lower prices, such as those under consideration today, will hurt consumers and taxpayers.

By attempting to expand the scope of the exclusions for orphan drugs, legislation such as the Optimizing Research Progress Hope and New (ORPHAN) Cures Act (H.R. 5539) provides a backdoor opportunity for big drug companies to effectively continue charging desperate patients outrageous prices for drugs they sell in other countries for a fraction of the price. This can and does occur as companies stagger applications and designations to extend their monopoly on orphan drugs. Further, allowing changes to expand the scope of exclusions is directly anti-innovation, as it rewards drug manufacturers for not innovating. This will harm patients with rare diseases by allowing drug companies to continue to charge outrageously expensive prices while bringing no new orphan drugs to market.

Likewise, the law already provides protections and specific criteria when considering the eligibility of prescription drugs for price negotiation. Drug products must be on the market for at least nine years, have no generic available, and meet other criteria before becoming eligible for price negotiation. Biologics must be on the market for at least 13 years and meet other similar criteria. Therefore, legislation such as the Maintaining Investments in New Innovation (MINI) Act (H.R. 5547) that attempts to extend the length of time before a drug product becomes eligible for negotiation – including gene therapies – gives drug companies a longer period to charge extremely high prices and harm consumers.

The Medicare Drug Price Negotiation Program addresses a well-known obstacle to reducing high prescription drug prices by allowing Medicare to negotiate with drug companies. Any attempt to change or undermine Medicare's ability to negotiate will allow drug prices to continue to rise at unsustainable rates. At this early juncture, the only guaranteed beneficiary of such changes is the pharmaceutical industry – and families and taxpayers will suffer as a result.

Thank you for the chance to provide AARP's perspective on legislative proposals that would impact Medicare's ability to negotiate drug prices. We look forward to working with you to ensure that all Americans have access to lower drug prices and lifesaving medications.

February 29, 2024

The Honorable Chairman Brett Guthrie
House Energy and Commerce Committee
Health Subcommittee
2434 Rayburn House Office Building
Washington, DC 20515

The Honorable Ranking Member Anna Eshoo
House Energy and Commerce Committee
Health Subcommittee
272 Cannon House Office Building Office Building
Washington, DC 20515

Re: Energy and Commerce, Subcommittee on Health, hearing on "Legislative Proposals to Support Patients with Rare Diseases."

Dear Chair Guthrie and Ranking Member Eshoo:

Thank you for holding this important hearing on Rare Disease Day. The American Society of Health-System Pharmacists (ASHP) is the largest association of pharmacy professionals in the United Sates, representing 60,000 pharmacists, student pharmacists, and pharmacy technicians in all patient care settings, including hospitals, ambulatory clinics, and health system community pharmacies. Our members provide critical pharmacy services to Americans suffering from rare diseases.

In particular, ASHP would like to highlight its support for H.R. 4758, the Accelerating Kids Access to Care Act, sponsored by Representatives Lori Trahan and Mariannette Miller-Meeks. This legislation would make it easier for families to receive Medicaid coverage for out-of-state pediatric care for children suffering from complex conditions by allowing a provider to enroll in another state's Medicaid program. Providing this continuity in coverage permits patients, particularly those in rural and boarder states, to access the life-saving care they need. Pharmacists play a critical role in providing this care by collaborating with physicians to ensure patients receive and understand the pharmaceutical drugs used to treat rare diseases.

ASHP also supports H.R. 7436, the Antimicrobial Resistance Research Assessment Act, sponsored by Representative Morgan Griffith. Pharmacists have been at the forefront of antimicrobial stewardship for decades and have advocated for the appropriate use of these live-saving treatments. This legislation would provide additional valuable information on and coordination among federal efforts to address antimicrobial resistance, further protecting the effectiveness of these treatments.

ASHP thanks you for holding this hearing and looks forward to working with you on this and other legislation. If you have any questions or if ASHP can assist your office in any way, please contact Frank Kolb at fkolb@ashp.org.

Sincerely,

Tom Kraus
American Society of Health-System Pharmacists

February 28th, 2024

The Honorable Brett Guthrie, Chairman
House Energy and Commerce Committee
Subcommittee on Health
2434 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo, Ranking Member
House Energy and Commerce Committee
Subcommittee on Health
272 Cannon House Office Building
Washington, DC 20515

Dear Chairman Guthrie and Ranking Member Eshoo:

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Energy and Commerce Committee's Subcommittee on Health for convening an impactful hearing on access to care for those with rare diseases. We appreciate the opportunity to provide our viewpoints.

We are grateful for the subcommittee's commitment to improving access to therapies and care for those living with rare diseases. Many of the neuromuscular diseases MDA represents are progressive, and all are rare, meaning access to relatively few effective interventions is vital to allow members of the NMD community to live longer, more independent lives. We ask that members of the subcommittee remember these perspectives as they consider the bills before them today.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our community. MDA's mission is to empower the people we serve to live longer, more independent lives.

Below are the specific bills under consideration for which we ask Subcommittee members to support:

H.R. 1092, Better Empowerment Now to Enhance Framework and Improve Treatments (BENEFIT) Act: MDA is supportive of the BENEFIT Act as it holds the potential to increase the collection, submission, and Food and Drug Administration (FDA or Agency) consideration of patient experience data within neuromuscular disease clinical trials. Too often blunt and archaic functional endpoints are solely considered by the Agency when evaluating the safety and effectiveness of a new product. This legislation, which has advanced in previous Congresses, would require FDA to consider our community's viewpoints when evaluating the risk/benefit ratio of our community and report on what patient experience data was considered in the approval of a therapy.

MDA strongly supports both of these goals that would make clinical trials and the resulting FDA-approved therapy more patient friendly and better targeted to our community, and we ask Subcommittee members to support the legislation.

H.R. 4758, Accelerating Kids Access to Care Act: MDA stands in strong support of the Accelerating Kids Access to Care Act. The bill serves as a common-sense solution to the needs of the many children living with rare diseases who experience delays in receiving care caused by traveling out of state. Children account for, roughly, half of total Medicaid enrollment,[1] and nearly one third of those children have complex medical needs.[2] Unfortunately, there are often an incredibly limited number of clinicians who specialize in a given rare disease. Additionally, as the number of FDA approvals for novel gene therapies grows, and administration of these therapies is incredibly complex and specialized, traveling out of state is often necessary for appropriate care. A 2019 study by the National Organization for Rare Disorders (NORD) found that 39% of respondents traveled more than 60 miles to receive care, which often means crossing state lines and utilizing an out-of-state Medicaid agency or Managed Care Organization.[3]

Given that there is no federal pathway for out-of-state providers to be screened by a child's home Medicaid program, providers are often required to be screened *every* time they see that child. This process can cause delays in treatment, which, given the progressive nature of many NMDs, means the disease progression experienced while waiting for treatment cannot be reversed. MDA supports the Accelerating Kids Access to Care Act's creation of a voluntary pathway to expeditiously enroll providers in out-of-state plans when needed, all without interfering with state Medicaid plans' authority to authorize out-of-state care or negotiate payment.

We thank the Subcommittee for its consideration of this legislation and support is continued progress through the Committee.

H.R. 5547, Maintaining Investments in New Innovation (MINI) Act: We support Congress addressing this technical fix at the intersection of the 21st Century Cures Act and the Inflation Reduction Act (IRA), two bills with provisions that can be transformative for our community. In particular, the IRA used a 21st Century Cures Act definition of anti-sense oligonucleotides (ASOs) (among others) that result in these incredibly complex products being considered small molecule therapies under the IRA.

There are several FDA-approved ASOs for neuromuscular diseases, including Spinraza for spinal muscular atrophy (SMA), Qalsody for an ultra-rare form of hereditary ALS, and more. These are incredibly complex products that have much more in common with complex biologics and gene therapies than small molecules.

Consequently, we appreciate the Subcommittee's consideration of this legislation and support its continued progress through the Committee.

H.R. 5663, **ALS Better Care Act:** MDA stands in support of the ALS Better Care Act. Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease that is typically fatal within two to five years after diagnosis. Recognized as a Quality Care Measure as defined by the American Academy of Neurology, the optimal way to care for those living with ALS is through a multidisciplinary approach (e.g. an approach combining neurology, physical and occupational therapy, respiratory, and speech therapy, among other modalities). While this

approach leads to a longer and higher quality of life for those living with ALS, the delivery of this care remains a challenge.

Currently, only the treating physician can bill Medicare for reimbursement; this means that the treating institution eats the cost of the rest of the *vital* care provided by the multidisciplinary care team. This financial paradigm means that fewer hospital systems and providers are willing to take a multidisciplinary approach, which leads to longer wait times and farther to travel for those living with ALS seeking care.

If multidisciplinary care were reimbursed appropriately, not only would it result in lower preventable healthcare costs for patients who could avoid emergency room visits with better access to clinics, shorten wait times for care, and reduce disparities between rural and urban populations by incentivizing more clinics to open and provide a fuller range of services, but also it would allow clinics more time for research to improve multidisciplinary care and offer access to more clinical trials accelerating the timeline to a transformative treatment for ALS.

For these reasons and more, MDA strongly supports the ALS Better Care Act, and we look forward to further Committee consideration of the bill.

H.R. 7383, Retaining Access and Restoring Exclusivity (RARE): When Catalyst Pharmaceuticals successfully retained exclusivity for Firdapse, an FDA-approved treatment for Lambert-Eaton Myasthenic Syndrome (also a disease that falls under MDA's umbrella), a loophole was opened within the Orphan Drug Act that counters FDA's long-term interpretation and implementation of the statute.[4] Under this decision, the FDA must more strictly interpret the Orphan Drug Act's "same disease" definition, thus handcuffing FDA in designating and subsequently approving therapies for subpopulations of rare diseases.

MDA joins many in the rare disease community in believing that this decision not only counters the intent of the Orphan Drug Act, but also is counter to the interests of the public health of the rare disease community. Consequently, we support the RARE Act, and welcome the Subcommittee's attention to it.

H.R. 7384, Creating Hope Reauthorization Act of 2024: The Rare Pediatric Disease Priority Review Voucher (RPD PRV) program has been instrumental in encouraging therapeutic development in challenging pediatric neuromuscular diseases that otherwise may not receive biopharmaceutical attention. Already, several FDA-approved rare neuromuscular disease treatments have received a PRV upon approval, including treatments for Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA). Both these areas, as well as several other ultra-rare pediatric neuromuscular diseases, have seen increases in biopharmaceutical attention since the creation of the RPD PRV program.

MDA has also heard from several small biotechnology companies developing treatments for ultra-rare pediatric neuromuscular diseases that the presence of the voucher upon approval, which they can then sell, is a major incentive for the continued activity in the space. Otherwise, the incentives are still far too inadequate to outweigh the risks of development in ultra-rare

pediatric rare diseases where commercialization, even with high prices, will not be lucrative whatsoever.

We strongly urge the Committee to reauthorize the RPD PRV program prior to its expiration at the end of September, and we are grateful that the Subcommittee is considering this legislation within this hearing.

MDA is committed to ensuring that individuals with neuromuscular diseases and other rare diseases have access to safe and effective therapies and robust access to care. We appreciate this opportunity to provide the Subcommittee with the perspectives of the NMD community. For questions regarding MDA or the above comments, please contact either Paul Melmeyer, Vice President, Public Policy and Advocacy, at pmelmeyer@mdausa.org or Joel Cartner, Director of Access Policy, at jcartner@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Vice President, Public Policy and Advocacy
Muscular Dystrophy Association

Joel Cartner, Esq
Director, Access Policy
Muscular Dystrophy Association

February 28, 2024

The Honorable Brett Guthrie
Chair, Health Subcommittee
House Committee on Energy and Commerce
2434 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Health Subcommittee
House Committee on Energy and Commerce
272 Cannon House Office Building
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
Chair
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
House Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

Dear Chair Guthrie, Ranking Member Eshoo, Chair McMorris Rodgers and Ranking Member Pallone,

On behalf of the more than 30 million Americans living with one of the over 10,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the House Committee on Energy and Commerce's Health Subcommittee for holding a hearing on Rare Disease Day 2024 focused on legislation that could have an impact on the rare disease community NORD so proudly represents.

NORD is a unique federation of non-profit and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded over 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of affordable, comprehensive health care, including access to safe and effective therapies.

The ODA defines a rare disease as a disease or condition affecting fewer than 200,000 Americans.[1] Before the ODA was enacted in 1983, fewer than 40 drugs had been approved by the Food and Drug Administration (FDA) to treat rare diseases.[2] Thanks to the ODA, as of the end of 2022, more than 880 drugs have been approved to treat rare diseases[3] and rare disease therapies now consistently account for more than half of FDA approvals for new molecular entities.[4] Still, an estimated 95% of the more than 10,000 known rare diseases do not have an FDA approved treatment,[5] making continued investment in rare disease research and innovation critical to the rare disease community.

[1] *Rare diseases at FDA*. U.S. Food and Drug Administration. (2022, December 13). https://www.fda.gov/patients/rare-diseases-fda
[2] Orphan Drugs In The United States: An Examination of Patents and Orphan Drug Exclusivity (2021): available at https://rarediseases.org/wp-content/uploads/2022/10/NORD-Avalere-Report-2021_FNL-1.pdf; accessed 2/2024
[3] Fermaglich, L.J., Miller, K.L. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis 18, 163 (2023). https://doi.org/10.1186/s13023-023-02790-7
[4] *New drug therapy approvals 2023*. U.S. Food and Drug Administration. (2024, January). https://www.fda.gov/media/175253/download
[5] Fermaglich, L.J., Miller, K.L. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis 18, 163 (2023). https://doi.org/10.1186/s13023-023-02790-7

1779 MASSACHUSETTS AVENUE NW, SUITE 500
WASHINGTON, DC 20036
T 202-588-5700 ▪ F 202-588-5701

7 KENOSIA AVENUE
DANBURY, CT 06810
T 203-744-0100 ▪ F 203-263-9938

1900 CROWN COLONY DRIVE, SUITE 310
QUINCY, MA 02169
T 617-249-7300 ▪ F 617-249-7301

rarediseases.org ▪ orphan@rarediseases.org

Beyond a lack of FDA approved treatment options, many people living with a rare disease struggle to obtain an accurate diagnosis, access health care providers with expertise in their condition, and afford the often high out-of-pocket costs associated with their treatment and care. The medical needs of those living with a rare disease are complex, as are the policies necessary to enable rare disease patients to thrive. NORD is grateful to the Subcommittee for holding today's hearing examining some of these policy issues and urges Congress to work in a bipartisan manner, and with other key stakeholders including the FDA and Centers for Medicare and Medicaid Services (CMS) to strengthen rare disease drug development, improve affordable patient access to necessary diagnostics, care and treatment, and effectively address the significant unmet needs that exist within the rare disease community.[6]

A. NORD is proud to endorse the following five bills under consideration at today's hearing:

1. **The Retaining Access and Restoring Exclusivity (RARE) Act (H.R. 7383)**

Introduced by Representative Gus M. Bilirakis and Representative Doris O. Matsui, H.R. 7383, the Retaining Access and Restoring Exclusivity (RARE) Act would clarify the original intent of the ODA and codify the FDA's longstanding interpretation that orphan drug exclusivity is awarded based on FDA approved indications, not the much broader orphan designation.

The ODA provides critical incentives to encourage drug companies to undertake research and development of drugs for rare diseases, including research funding and tax credits for clinical testing expenses. Another key ODA incentive is orphan drug exclusivity – which bars FDA from approving another company's marketing application for the same drug to treat the same orphan indication for seven years after the first drug is approved. FDA has long interpreted this exclusivity to be limited to the specific approved indication for which the drug's safety and efficacy has been demonstrated, potentially allowing a different company to further develop the drug for a different population subgroup, such as children. By awarding market exclusivity only for the patient population for which a drug was studied and determined to be safe and effective, FDA aimed to "make sure pharmaceutical companies didn't get total market control for a drug after doing studies on only the 'smallest, easiest-to-study populations.'"[7]

Unfortunately, FDA's longstanding interpretation of this exclusivity was challenged in a recent court case and in November 2021, U.S. Court of Appeals for the 11th Circuit ruled that orphan drug exclusivity should be awarded based on the much broader orphan designation. NORD is deeply concerned that awarding orphan drug exclusivity based on orphan designation would provide exclusivity for a product whose uses have not been adequately substantiated by safety and efficacy data. The RARE Act would provide much-needed certainty about the scope of this important ODA incentive and ensure orphan drug exclusivity is awarded based on approved indications.

The RARE Act is supported by 78 patient organizations and NORD urges members of the Subcommittee to support swift passage of the RARE Act.

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[6] FDA. (2022, March 4). CDER continues to make rare diseases a priority with drug approvals. U.S. Food and Drug Administration. https://www.fda.gov/news-events/fda-voices/cder-continues-make-rare-diseases-priority-drug-approvals-andprogramming-speed-therapeutic

[7] Tribble, S. J. (2023, February 23). *A bitter battle over the "orphan drug" program leaves patients' pocketbooks at risk*. KFF Health News. https://kffhealthnews.org/news/article/a-bitter-battle-over-the-orphan-drug-program-leaves-patients-pocketbooks-at-risk/

2. The Creating Hope Reauthorization Act of 2024 (H.R.7384)

Introduced by Representative Michael T. McCaul, Representative Anna G. Eshoo, Representative Gus M. Bilirakis, Representative Nanette Diaz Barragan, Representative Lori Trahan and Representative Michael C. Burgess, H.R. 7384, the Creating Hope Reauthorization Act would reauthorize the Rare Pediatric Disease Priority Review Voucher program for four years, through September 30, 2028. As many as half of those living with a rare disease are children, and rare pediatric disease priority review vouchers (PRVs) offer a crucial incentive for companies to develop therapies for these particularly challenging to study patient populations. Reauthorizing this program before the September 30, 2024 deadline is vital to maintain the progress needed to address the significant unmet treatment needs that exist within the pediatric rare disease population.

Under the Rare Pediatric Disease PRV program, companies that develop novel therapies for rare pediatric diseases – defined as rare diseases that primarily impact children and lead to their most significant health impacts in this population - can be awarded a PRV.[8] The PRV can then be redeemed at a later date to obtain priority review for another new drug application (NDA) or biologic license application (BLA) that would otherwise not qualify for priority review. Alternatively, the PRV can be sold to generate additional financial resources for a drug sponsor that ideally would be used to invest in additional research and development into new or better therapies to treat rare diseases.

The PRV program has helped spur rare pediatric disease drug development. To date, close to 50 rare disease therapies across more than 30 different rare diseases have been awarded a PRV, including many diseases that are typically fatal before children reach adulthood. Additionally, more than half of the PRVs were awarded after 2019, the cut-off for the last Government Accountability Office (GAO) analysis into the effectiveness of the PRV program. Notably, in the first 10 years of the program, more than 550 drugs have received rare pediatric disease designations[9] with more than half of these designations, 241, awarded in 2020 alone, in large part driven by the prospect of the program sunsetting at the end of that year.[10] The significant workforce challenges this sudden spike in applications created at FDA emphasizes the need for a swift program reauthorization, far ahead of the current deadline.

NORD urges Congress to pass H.R. 7384, the Creating Hope Reauthorization Act well in advance of the September 30th deadline to maintain this important tool in ongoing efforts to address the significant unmet treatment needs that exist in the pediatric rare disease population.

3. Accelerating Kids' Access to Care Act (AKACA) (H.R. 4758)

Introduced by Representative Lori Trahan and Representative Mariannette Miller-Meeks, H.R. 4758, the Accelerating Kids' Access to Care Act would streamline the credentialing processes for out-of-state

[8] Office of the Commissioner. (n.d.-d). Rare pediatric disease (RPD) designation and voucher programs. U.S. Food and Drug Administration. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

[9] Mease C, Miller KL, Fermaglich LJ, Best J, Liu G, Torjusen E. Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development. Orphanet J Rare Dis. 2024 Feb 25;19(1):86. doi: 10.1186/s13023-024-03097-x. PMID: 38403586; PMCID: PMC10895788.

[10] Mease C, Miller KL, Fermaglich LJ, Best J, Liu G, Torjusen E. Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development. Orphanet J Rare Dis. 2024 Feb 25;19(1):86. doi: 10.1186/s13023-024-03097-x. PMID: 38403586; PMCID: PMC10895788.

providers by establishing a voluntary pathway for qualified providers to enroll in other states' Medicaid and CHIP programs. This limited pathway, only available to providers in good standing with their home state program or Medicare, would enable them to bypass redundant subsequent screenings, expeditiously enroll in another state Medicaid and CHIP program, and provide essential time-sensitive care to children when necessary. It is important to note that AKACA only pertains to provider screening and enrollment; it does not change the authority states have to authorize out-of-state care and negotiate payment with accepting providers.

Both Medicaid and CHIP are core sources of health care coverage for children, with children accounting for over 46% of total Medicaid enrollment,[11] and more than one-third of all children with special health needs are enrolled in Medicaid.[12] Furthermore, the parents of children living with rare diseases often struggle to access the specialized care needed to treat their child's condition, as the best treatment for these children sometimes requires significant travel. In fact, a 2019 NORD survey of rare disease patients and caregivers nationwide found that 39% of respondents traveled more than 60 miles to receive medical care, and 17% had moved (or were considering relocating) to be closer to care.[13]

For many rare disease patients, it is not uncommon that only one or two clinical centers in the entire country have specialists with the requisite expertise to treat their condition. When a child's medical needs cannot be met by providers in their home state, the State Medicaid Agency and/or Medicaid Managed Care Organization authorizes such care with an out-of-state provider. The out-of-state provider must then be screened and enrolled by the home state's Medicaid program. While current laws and regulations allow for the child's state to rely on provider screenings done by other states' Medicaid programs or by Medicare, unfortunately, there is no single federal pathway. This means providers are often screened and enrolled every time they are called upon to treat a child from a different state. This process can delay time-sensitive care by weeks or months, resulting in the potential for disease progression and higher health care costs.

AKACA is supported by 215 organizations and NORD urges the members of the Subcommittee to support this common-sense solution that streamline the enrollment process for health care providers, facilitating access to critical, time-sensitive treatment for patients, and reducing the risk of care disruption and subsequent negative health outcomes.

4. **Innovation for Pediatric Drugs Act (H.R. 6664)**

Introduced by Representative Michael T. McCaul and Representative Anna G. Eshoo, H.R. 6664, the Innovation for Pediatric Drugs Act aims to support the development of vital safety and efficacy information specific to the use of rare disease drugs in pediatric populations.

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[11] Centers for Medicare and Medicaid Services. October 2023 Medicaid and CHIP Enrollment Data Highlights. https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html. Accessed on February 27, 2024.

[12] MACPAC. March 2023. Medicaid Access in Brief: Children and Youth with Special Health Care Needs. https://www.macpac.gov/wp-content/uploads/2023/03/Medicaid-Access-in-Brief-Children-and-Youth-with-Special-Health-Care-Needs.pdf Accessed on February 27, 2024.

[13] NORD. 2020. Barriers and Facilitators to Rare Disease Diagnosis, Care and Treatment: 30-year Follow-up. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

Currently, the Pediatric Research Equality Act (PREA) exempts most orphan therapies from its pediatric study requirements. Of the more than 30 million individuals in the United States living with rare diseases,[14] as many as half are children, and they need – and deserve – access to therapies that have been proven to be safe and effective for them. At the same time, pediatric studies are particularly challenging for rare diseases and can be significantly more difficult to complete than for more common diseases.

According to a report released by the FDA in August 2019, "Pediatric Labeling of Orphan Drugs," almost 40 percent (127 of 348) of orphan indications approved from January 1999 – August 2018 that warranted pediatric labeling were incompletely labeled, with 81 having no pediatric information and 46 missing some pediatric information.[15] Although some progress has been made in recent years, significant gaps in labeling instructions for pediatric patients remain. Without adequate labeling data for children, health care providers and caregivers are put in the difficult position of guessing whether and how much of a drug to give to a pediatric patient, which can have dangerous consequences for children.

The Innovation in Pediatric Drugs Act would increase research funding authorized as part of the Best Pharmaceuticals for Children Act (BPCA) to help close data gaps around pediatric uses for approved drugs and strengthen FDA's ability to enforce post-market commitments around pediatric studies. In addition, the bill would end the blanket exemption of orphan drugs from pediatric studies normally required under PREA, while instructing FDA to promulgate guidance on when and how pediatric studies for rare disease drugs may be impossible or require modifications to the standard PREA requirements (i.e., deferrals and full or partial waivers).

NORD strongly supports the intent of the Innovation for Pediatric Drugs Act, but also recognizes that its success will hinge on the mandated guidance from FDA being clear, well-balanced, practical, and on a workable timeframe for the rare disease community. The current timeline for the guidance and implementation are not practical, but NORD is grateful to the bill sponsors for their willingness to revise the timelines outlined in the current version of H.R. 6664, as this will be essential to NORD's continued support for the bill.

5. **Providing Realistic Opportunity to Equal and Comparable Treatment for Rare (PROTECT Rare) Act (H.R. 6904)**

Introduced by Representative Doris O. Matsui, Representative Neal P. Dunn, Representative Mike Thompson, and Representative Mike Kelly, H.R. 6904, the PROTECT Rare Act would refine the resources used to determine health program or insurance coverage for therapies used to treat or manage a rare disease.

Off-label drug use occurs when a physician prescribes a product that the FDA has deemed to be safe and effective for a condition other than the one it is being prescribed to treat. The practice of prescribing off-label drugs is rather frequent, with estimates ranging between 20% and 30% of all prescriptions written

[14] U.S. Government Accountability. (2021, October 18). *Rare diseases Although Limited, available evidence suggests medical and other costs can be substantial*. Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial | U.S. GAO. https://www.gao.gov/products/gao-22-104235

[15] Department of Health and Human Services, Food and Drug Administration. Pediatric Labeling of Orphan Drugs Report to Congress. Table 5. https://www.fda.gov/media/130060/download

for off-label uses.[16,17] As mentioned previously, over 95% of known rare diseases do not have an FDA approved treatment and as a result, many rare disease patients must rely on off-label use of prescription drugs to manage their condition.

However, insurance coverage of off-label prescriptions varies widely. While some payers may agree to cover the off-label use of a product as long as the off-label use is listed in a drug's compendium (a collection of data regarding the use of the product in patients), others may not, which can create significant barriers to patients obtaining affordable, timely access to the prescribed treatment. The PROTECT Rare Act is an important step towards ensuring rare disease patients have access to the drugs they need by requiring Medicare, Medicaid, and private insurers to utilize peer-reviewed medical literature, including clinical guidelines, when making treatment coverage determinations.

NORD urges members of the Subcommittee to support the PROTECT Rare Act and urges its swift consideration by the Committee to support rare disease patient access to necessary treatment.

B. NORD would further urge the Subcommittee to consider the following at the hearing:

NORD recognizes that the Subcommittee will consider legislation that would make changes to the Inflation Reduction Act (IRA). NORD has **not** taken a position on any of these three IRA-related bills under consideration at the hearing, as NORD's current focus is working as part of a coalition of 170 patient advocacy groups advocating for two small, technical corrections to the IRA's orphan drug exclusion.

The IRA currently includes a limited exclusion for some rare disease therapies from the drug price negotiation program. Under current law, otherwise qualifying therapies that have been approved only for a single indication for a rare disease tied to a single orphan designation are excluded from the negotiation process. A company can lose the exclusion under current law by applying for, and being granted, additional orphan **designations**, or receiving **approval** for a second indication not tied to the initial designation. If a company receives approval for a second indication, the countdown, or "clock," for when the product loses its exclusion begins with the date of the **very first approval**, rather than the approval of the second indication that caused the product to lose its exclusion.

Starting with the passage of the Orphan Drug Act, Congressional leaders and Administrations have consistently worked in a bipartisan manner to encourage more research and development into rare disease treatments. Unfortunately, NORD is concerned that the IRA language specific to the orphan drug exclusion will discourage even the most basic rare disease research, putting at risk the progress made because the ODA's incentives have so effectively spurred rare disease drug development over the last four decades.

The two, small technical corrections being sought by 170 patient organizations would **not** change the number of approved indications an orphan product can obtain to remain eligible for the orphan exclusion, but would clarify:

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[16] AHRQ. September, 2015. Off-Label Drugs: What You Need to Know. https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html. Accessed February 27, 2024.

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

1. **The number of <u>designations</u> that a product receives is not tied to the exclusion from negotiation.** Orphan drug designations are a key part of the drug development processes for rare diseases, as they unlock crucial research incentives. Designations are granted early in the process and are based on a preliminary proof of concept. Designations *do not* grant the manufacturer the ability to market the product. Penalizing manufacturers for seeking additional designations risks disincentivizing research into additional rare diseases. Almost 6,800 designations have been granted, compared to just over 1,200 FDA approved indications. Existing law strikes a product's exclusion from the negotiation period as soon as a manufacturer seeks a secondary designation to research the drug for additional uses. NORD urges Congress to protect vital rare disease research by allowing manufacturers to leverage the full intent of the Orphan Drug Act and seek multiple designations while remaining exempt from negotiation until a product is FDA approved to treat a second rare disease.

2. **Protecting the exclusion "clock" for rare disease products.** Under current law, the drug price negotiation process **<u>cannot</u>** begin until a product has been on the market for 7 or 11 years, for small molecule drugs and biologics, respectively. However, for an orphan product that loses exclusion from drug price negotiation, the 7 or 11 year countdown begins with the approval date for the **very first indication**, even if the product loses its exclusion status many years later. NORD believes this unfairly penalizes rare disease drug developers by artificially reducing the exclusion period established by Congress. To fix this issue, NORD urges beginning the countdown "clock" for a previously excluded orphan product from the start date of the second approved orphan product.

A careful balance between continued innovation and affordable patient access to treatment and care is vital to the rare disease community. NORD is grateful for the Subcommittee's attention to these critical issues as part of today's hearing and looks forward to working with the Subcommittee to better support the rare disease community. Please do not hesitate to reach out to Heidi Ross at HRoss@rarediseases.org, Karin Hoelzer at KHoelzer@rarediseases.org, Hayley Mason at HMason@rarediseaess.org or Mason Barrett at MBarrett@rarediseases.org when NORD can be of assistance to the Subcommittee's important work.

Sincerely,

Heidi Ross, MPH
Vice President, Policy and Regulatory Affairs
National Organization for Rare Disorders

Karin Hoelzer, DVM, PhD
Director, Policy and Regulatory Affairs
National Organization for Rare Disorders

Hayley Mason, MPA
Policy Analyst
National Organization for Rare Disorders

Mason Barrett
Policy Analyst
National Organization for Rare Disorders

Save Rare Treatments

Feb. 29, 2024

Statement for the Record
House Energy and Commerce Committee, Health Subcommittee
Hearing "Legislative Proposals to Support Patients With Rare Diseases"

The Save Rare Treatments Task Force, a multi-sector public policy and advocacy task force, commends the members of the House Energy and Commerce Committee for holding a hearing on February 29, 2024 to examine important legislative proposals that would address key policy issues affecting the rare disease community, including H.R 5539, the *Optimizing Research Progress Hope and New (ORPHAN) Cures Act, introduced by Rep. John Joyce (R-PA) and Rep. Wiley Nickel (D-NC)*.[1]

Approximately 30 million Americans have a rare disease and about half of this number are children.[2] Yet, of the estimated 10,000 rare diseases, 95 percent lack an FDA-approved treatment. This means most Americans with a rare disease have *no treatment options* specific to their condition. Millions of Americans with a rare disease need continued research and development to make new treatments available. Every American with a rare disease deserves a treatment option for his or her disease.

This is why H.R 5539, the *Optimizing Research Progress Hope and New (ORPHAN) Cures Act* is such a critically important piece of bipartisan legislation. The legislation would correct the overly narrow orphan drug exclusion in the Medicare Drug Price Negotiation Program that excludes orphan drugs treating rare diseases from negotiation eligibility so long as they treat a single rare disease.

Unfortunately, this narrow exclusion discourages research and development of treatments for rare diseases and undermines longstanding bipartisan incentives for medical innovation in a manner that jeopardizes access to future treatments for persons living with rare diseases. To correct this problem, the bipartisan *ORPHAN Cures Act* ensures that products would remain excluded from negotiation so long as their FDA-approved uses are exclusively for rare diseases.

Before the *Orphan Drug Act of 1983*, there were fewer than 40 FDA-approved treatments for rare diseases. Today there are more than 550 treatments for more than 1,100 indications.[3] This progress underscores the need for Congress to preserve incentives for research and development of treatments for rare disease. At a time when the collective scientific understanding of human biology and genetics is rapidly expanding, it is critical that Congress advance the *ORPHAN Cures Act* to remove current barriers for research and development for rare disease.

The Task Force thanks Members of the Committee for the hearing exploring this important policy issue and looks forward to working with the Committee through the legislative process to ensure that our nation's health care is more inclusive, responsive, and supportive of the diverse needs of millions of Americans who have a rare disease.

[1] https://energycommerce.house.gov/events/health-subcommittee-hearing-legislative-proposals-to-support-patients-with-rare-diseases
[2] https://rarediseases.info.nih.gov/
[3] https://www.fda.gov/news-events/fda-voices/fda-continues-important-work-advance-medical-products-patients-rare-diseases.

American Association of Tissue Banks®

Testimony for the Record
House Committee on Energy and Commerce Health Subcommittee
"Legislative Proposals to Support Patients with Rare Diseases"
Thursday, February 29, 2024

Chairs Rodgers and Guthrie, Ranking Members Pallone and Eshoo, and members of the Subcommittee, thank you for holding this important hearing today, which includes H.R. 6705, the Effective Screening and Testing for Tuberculosis Act, and H.R. 7188, the Shandra Eisenga Human Cell and Tissue Product Safety Act. The American Association of Tissue Banks (AATB) and AATB Tissue Policy Group (TPG) are pleased to submit this statement for the record and hope the committee will consider AATB as a resource for future activities related to human tissues.

As you may know, in May 2021, a tuberculosis (TB) outbreak was linked to a contaminated viable allograft bone matrix product used in spinal surgery. While the investigation of the 2021 transmission events was ongoing, the AATB Physicians Council worked with an independent contractor to review the literature and the information available at the time. This culminated in an advisory Bulletin (AATB Bulletin 22- 2, published March 22, 2022) along with a companion document with more medical and scientific details.

In August 2022, a paper was published by Schwartz, et al with details of the investigation and findings. In September 2022, after review of details provided in the Schwartz et al manuscript, the Physicians Council formed a Working Group. This group has been meeting on an ongoing basis, at least twice a month, to carefully consider the Mycobacterium tuberculosis (MTB) science and medical literature and

develop more specific and binding requirements for AATB members regarding screening potential donors for MTB.

In July 2023, the same tissue processor announced another investigation of post-surgical MTB infections in two patients treated with viable allograft bone matrix products from a different single donor lot.

Due to the urgency of putting into place donor screening requirements regarding MTB for AATB members, in August 2023 the Physicians Council MTB Working Group deemed it necessary to publish current consensus donor screening requirements that represent the highest risks for tissue transplantation, particularly among products containing viable cells.

The new requirements, published in AATB Bulletin 23-6, will help improve donor screening processes and improve patient safety, but will only apply to AATB-accredited banks. Congress can take additional steps to improve the safety of human cell and tissue transplants.

H.R. 7188, the Shandra Eisenga Human Cell and Tissue Product Safety Act

The Shandra Eisenga Human Cell and Tissue Product Safety Act would provide the Department of Health and Human Services (HHS) with important authorities related to tissue products. First, the legislation would authorize a national, evidence-based public awareness campaign regarding the potential risks and benefits of human cell and tissue transplants. HHS would be required to consult with stakeholder experts regarding the campaign, and HHS may award grants to nonprofit organizations to carry out the initiative.

The legislation would also authorize civil penalties for violations of section 361 of the Public Health Services Act. This authority would help FDA bring rogue stem cell clinics and other "bad actors" into compliance with FDA regulations for human cell and tissue product manufacturers.

Finally, the bill would require HHS to initiate a review of existing regulations and guidance documents related to human cell and tissue products; and inspection rates of human cell and tissue product manufacturing facilities compared to blood and Source Plasma establishments. HHS would be required to issue updated guidance related to determining eligibility of donors of human cell and tissue products within 3 years of enactment of the legislation.

H.R. 6705, the Effective Screening and Testing for Tuberculosis Act

In general, the AATB and TPG are concerned that the Effective Screening and Testing for Tuberculosis Act emphasizes donor testing over donor screening. Donor screening is the review of the potential donor's relevant medical records, including lab results other than communicable disease testing, coroner/autopsy reports, and the donor history medical interview, for risk factors and clinical evidence of communicable diseases. Donor testing is the actual testing of a potential donor's serum or plasma for evidence of infection. It is ideal to have overlapping layers of safety to include both donor screening and testing, but there are significant limitations to any testing that can currently be performed, as will be discussed below. Therefore, donor screening is the most important component of donor-eligibility determinations to reduce the potential risk of TB transmission through transplanted human cells, tissues, and cellular and tissue-based products (HCT/Ps), as opposed to donor or product testing.

Regarding section 2, which would require HHS to establish an expedited development and priority review pathway for a new and innovative donor screening test with heightened sensitivity to effectively screen HCT/P product donors for evidence of active or latent tuberculosis infection, AATB is not aware of any entity currently developing a deceased tissue donor test for TB. The development of such a test could take years, and there may not be a test that can be developed that provides dependable results. However, AATB has no concerns with establishing an expedited review process for potentially new and innovative donor screening tests in this space.

It appears that Section 3 would require regulations be promulgated to require donor screening to include screening for active and latent TB, and to require "an establishment that performs donor testing to test for active and latent tuberculosis." AATB recommends either striking section 3 or revising it to focus solely on donor screening. It is also noted that rulemaking may not be necessary for FDA to achieve the goal of requiring donor screening for tuberculosis.

AATB Bulletin 23-6 was published with a frequently asked questions (FAQs) document that includes a section on testing. From that section:

> "There are no FDA licensed/cleared/approved tests for tuberculosis for deceased tissue donors. The 2 approved tests for clinical/diagnostic purposes are QuantiFERON-TB Gold Plus and T-SPOT TB test. These interferon gamma release assays (IGRA) rely on the ability of white blood cells to release interferon gamma in response to TB antigen, and therefore require living cells. As a result, testing must be completed in a very short timeframe that is not possible with deceased tissue donors. Furthermore, poor immune function will negatively impact the ability to obtain

positive test results. More information about IGRA testing can be found at https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm.

For the 2023 tuberculosis transmission event, the viable bone matrix tissue was tested for MTB using polymerase chain reaction (PCR) methodology."

Furthermore, those blood tests do not differentiate between latent or active TB, and a negative result cannot rule out that the presence of latent or active TB.

There are many limitations that come with testing the HCT/P for MTB, which can be accomplished either by performing culturing, or performing nucleic acid amplification testing (NAT) + culturing. Limitations include but are not limited to challenges in determining an appropriate sampling plan given TB is not evenly distributed within the body, the possibility of having to use so much of a tissue sample for testing that there is significantly diminished volume left to distribute for transplant, and the time that it takes for culture results to be available—up to 8 weeks. While NAT testing provides faster results, it is less sensitive than culture, and would need to be performed in addition to, not instead of, culture—which in turn, would require additional sample for testing. It is notable that the second transmission case happened in the context of product testing by NAT methodology. Both culture and NAT testing for *Mycobacterium tuberculosis* are challenging to perform, and require specialized expertise to do correctly. It is common to obtain a negative test result in the presence of MTB (or a "false negative") if the testing is not performed correctly, which would lead to a false sense of safety.

For these reasons, AATB believes that the focus should be on enhanced donor screening specific for TB, and not on donor testing.

Finally, the guidance referenced in section 4 is related to complying with requirements under 21 CFR Part 1271, subparts D and E, which has to do with manufacturing of HCT/Ps. The AATB and TPG think it would be more appropriate to instead direct the FDA to finish updating the Eligibility Determination for Donors of HCT/Ps Guidance for Industry, which hasn't been fully updated since 2007.

Thank you for taking these comments into consideration. The AATB and TPG stand ready and willing to assist in any way that you deem appropriate.

The American Association of Tissue Banks

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 120 accredited tissue banks and over 7,000 individual members. These banks recover tissue from more than 70,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

To learn more visit: www.aatb.org

AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

Statement for the Record on "Legislative Proposals to Support Patients with Rare Diseases"
February 29, 2024

The American Society of Hematology (ASH) commends the House Energy & Commerce's Health Subcommittee for holding a legislative hearing on the Sickle Cell Disease Comprehensive Care Act (H.R. 7432) and other rare disease legislation.

SCD is the most common inherited red blood cell disorder in the United States, affecting an estimated 100,000 people. According to the Centers for Disease Control and Prevention (CDC), SCD affects one out of every 365 Black or African American births and one out of every 16,300 Hispanic American births. Individuals with SCD suffer from acute pain episodes and chronic pain and may be affected by an array of other organ complications, which can cause disability or even death. A Centers for Medicare and Medicaid Services (CMS) report found that approximately 50% of individuals living with SCD in the United States are covered by Medicaid.

ASH has collaborated with members of Congress to educate policy makers on the issue of access to quality care for individuals with SCD, and to advocate for coverage of essential care services for those insured by Medicaid. ASH has a long record of advocating for previous versions of the Sickle Cell Disease Comprehensive Care Act and other sickle cell priorities as part of the Society's multi-faceted Sickle Cell Disease Initiative.

Representatives Michael Burgess (R-TX) and Danny Davis (R-IL) introduced H.R. 7432 to addresses a critical need for high quality comprehensive outpatient care for individuals living with SCD who are enrolled in Medicaid**.** The bill would enable State Medicaid programs to provide comprehensive, coordinated care through a health home model for individuals with SCD. The health home model is a proven care delivery model in Medicaid that has been widely used by states to improve quality, enhance care, and reduce unnecessary costs. Health homes for SCD will help to alleviate the many challenges and disparities in care that individuals with SCD have faced for far too long. This bill ensures a multi-faceted approach to care ensuring SCD patients have access to coordinated clinical, mental health, and ancillary services to address their physical, mental, and social needs.

ASH looks forward to continuing to work with Representatives Burgess and Davis, the Committee on Energy and Commerce, and other Members of Congress to advance and improve H.R. 7432 optimizing care for people living with SCD. While H.R. 7432 as drafted takes an important step towards providing comprehensive care to individuals living with SCD, ASH hopes to work with the bill sponsors and the Committee to ensure all individuals in a SCD health home have coverage for dental, vision, and non-emergency transportation services in addition to other comprehensive care services. By passing the Comprehensive Care Act with these revisions, Congress would take a necessary step to ensuring individuals with SCD in the United States have timely and sustained access to the high-quality, equitable, coordinated care and treatment.

If you have any questions, please contact Tracy Roades, ASH Senior Manager, Legislative Advocacy, at *troades@hematology.org*.

The American Society of Hematology (ASH) represents more than 18,000 physicians, researchers, and medical trainees committed to the study and treatment of blood and blood-related diseases, including SCD. In 2015, ASH launched a transformative, multi-faceted, patient-centric initiative to improve outcomes for individuals with SCD, both in the United States and globally, by bringing together stakeholders in the public and private sectors committed to significantly improving the state of SCD worldwide. Visit www.hematology.org/scd to learn more about ASH's efforts to make significant a difference in SCD access to care, research, and ultimately, cure.

February 29, 2024

Statement for the Record for the House Energy & Commerce Hearing on "Legislative Proposals to Support Patients with Rare Diseases"

The Sickle Cell Disease Partnership ("The Partnership") is a multi-sector collaboration of more than a dozen health care organizations working together to advance federal policies to improve the lives of Americans with Sickle Cell Disease (SCD). The Partnership commends the House Energy & Commerce's Health Subcommittee for holding a legislative hearing on rare disease legislative proposals and including H.R. 7432, the *Sickle Cell Disease Comprehensive Care Act* and other rare disease legislation.

SCD is a rare, genetic blood disorder that disproportionately impacts Black and Hispanic Americans.[1] SCD causes a myriad of debilitating acute and chronic health issues, severely impacting quality of life[2] and often leading to premature death.[3] Unfortunately, individuals with SCD in the United States continue to face severe gaps in accessing high-quality, equitable, and coordinated care and treatment.

Reps. Michael Burgess (R-TX) and Danny Davis (R-IL) introduced H.R. 7432 to improve access for individuals with SCD by enabling State Medicaid programs to provide comprehensive, coordinated care through a Health Home model to individuals with SCD. Health Homes are a proven care delivery model in Medicaid that have been used by states to improve quality, enhance care, and reduce unnecessary costs.[4] Incentivizing state Medicaid programs to create Health Homes to coordinate care for individuals with SCD will help to alleviate the disparities in care that individuals with SCD have faced for far too long.

In addition to the SCD-focused legislation, the Partnership also appreciates the Committee's consideration of the policy issues that Rep. Guthrie's legislation, H.R. ____, *Patient Access Act*, seeks to address related to the Anti-Kickback Statute. This draft legislation presents an opportunity to think about new ways to address certain social drivers of health that can be barriers for individuals with SCD receiving timely access to care.

The Partnership looks forward to working with Reps. Burgess and Davis, the Committee on Energy and Commerce, and other Members of Congress to advance and improve these important policies through the legislative process. While H.R. 7432, as drafted, takes an important step towards providing comprehensive care to individuals living with SCD, the Partnership hopes to work with the bill sponsors and the Committee to ensure all individuals in any SCD Health Home have coverage for dental, vision, and non-emergency transportation services in addition to other comprehensive care services. By advancing H.R. 7432, the *Sickle Cell Disease Comprehensive Care Act*, with these proposed changes, the Committee and Congress would take a necessary step to ensuring individuals with SCD in the United States have timely and sustained access to the high-quality, equitable, coordinated care and treatment that they deserve.

For questions, please contact josh.trent@leavittpartners.com or clay.alspach@leavittpartners.com.

[1] The Partnership is comprised of sickle cell disease patient and community organizations, healthcare providers who have experience caring for individuals with SCD, manufacturers, health plans, researchers, and others interested in improving the lives of patients living with SCD.
[2] https://www.cdc.gov/ncbddd/sicklecell/data.html#:~ text=SCD%20occurs%20among%20about%201,sickle%20cell%20trait%20(SCT).
[3] https://www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=SCD%20occurs%20among%20about%201,sickle%20cell%20trait%20(SCT).
[4] https://www.medicaid.gov/sites/default/files/2020-02/medicaidhomehealthstateplanoptionrtc.pdf

Statement for the Record
Of
Carli Simpson, Erin McCarthy, and Erin Finucane
United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health
Legislative Hearing on Proposals to Support Patients with Rare Diseases

February 29, 2024
Washington, DC

Chairman Guthrie, Vice Chair Bucshon, Ranking Member Eshoo, and Members of the Committee, We commend the Committee for taking the time and resources to hold this Rare Disease Day hearing to promote awareness and review and debate several bills under consideration regarding rare diseases.

We write to you as concerned parents of children with Nephropathic Cystinosis, a progressive multisystemic orphan disease that affects 1 in 100,000 - 200,000 live births in the United States. It affects every system within the body, typically starting with the kidneys via Fanconi syndrome, but also manifesting in the heart, thyroid, muscles, pancreas, eyes and central nervous system. The average life expectancy for those living with cystinosis is about 28 years, though many die sooner. We appreciate the opportunity to raise awareness through this platform.

Most importantly

We are concerned that the rareness and complexity of the disease may inadvertently lead to oversights or inaccurate assumptions about what is needed and reasonably expected in a therapy. As noted in a Feb. 19 New York Times column ("The Future of Medicine Is Unfolding Before Us. Are We Nurturing It?") and our response Letter to the Editor, published only this morning, ("Three Mothers' Plea to the F.D.A: Save Our Children,") there is ample reason for concern and attention to the risk that both companies and regulators could miss the mark when targeting certain outcomes for a trial and lose sight of some of its greatest promise.

As cystinosis eventually affects every system within the body, the longer our children must wait for promising treatments, the more physical, neurological, and social emotional turmoil it inflicts on all those afflicted by this terminal disease. Life with cystinosis is arduous, and whenever we experience a setback, it is devastating. We cannot overstate the urgency and gravity of the situation because we live it every single day. Historically we have felt powerless to halt the disease's progression, but now we have hope.

Disease severity and current treatment options

For the vast majority of cystinosis families, there is no break from the grueling daily medication schedules, doctor's appointments, hospitalizations, supplemental therapies, and dozens of other tasks that need to be completed just so our children can try to participate in some semblance of

everyday life. Many of us parents have given up careers to manage our children's daily care, as it is a full-time endeavor. Cystinosis is brutal and relentless and cannot be underestimated. Our community recently lost another friend with cystinosis who was only 20 years-old.

Patients with cystinosis are not only suffering from the cruel complications of the disease itself, but also the extreme side effects of the only current treatments available. The numerous side effects and interactions from many of the necessary medications are wide ranging and debilitating, which severely affects adherence to medical regimens and overall quality of life. For example, Cysteamine is a needed but noxious medication. Unfortunately, there is no other option.

However, between 2019 and 2022, hope arrived via the work of Dr. Stephanie Cherqui and her team at UC San Diego. Dr. Cherqui developed an experimental gene therapy that could be the cure for cystinosis. Thanks to five brave individuals who volunteered for Phase 1/2 of the clinical trial, there is proven safety and sufficient information and positive results to proceed to the final phase of the clinical trial. We would note here that, critically, none of this rather historical medical advancement would have been possible absent the more than $68 million which the Cystinosis Research Foundation raised – from families, friends, foundations, and even strangers willing to give of themselves to find a cure.[1] The community of those affected by this disease is not large, but its relative impact is massive.

To us, no greater test of the system could possibly be administered than to see whether such a promising treatment can now be delivered to the community that has endured and sacrificed so much – both voluntarily and involuntarily – to get this far. On Rare Disease Day, we hope that this exciting prospect for curing a deadly disease will gain attention and thought.

Concerns within the cystinosis community

We are most concerned that the Phase 3 trial could include overly narrow endpoints that ultimately exclude the overwhelming majority of the current cystinosis patient community from treatment when it becomes available. We are concerned that the rareness and complexity of the disease may inadvertently lead to oversights or inaccurate assumptions about what is needed and reasonably expected in a therapy. Indeed, the hearing memo denotes at least one scenario where current policy may disincentivize companies from researching more than one drug indication, such as those for rare diseases and children. Greater transparency and dialogue around this and related risks would be welcome, and any such issues should be acknowledged and resolved swiftly.

As we note above regarding the Feb. 19 New York Times column and our response, we reiterate our concern and ask for attention to the risk that either companies or regulators could fall short of the potential for a cure when limiting or even missing certain outcomes for a trial – and this would be a terrible shame and failure. Meaningful, early communication and collaboration with cystinosis families along with all the advocacy groups would ease concerns and only improve the treatment's chances of success.

[1] While we are active with and support the CRF, we are not speaking for or otherwise representing it or any formalized advocacy group here.

We remain hopeful about Novartis' work towards better treatments and a potential cure for cystinosis. To that end, we express the following recommendations which, at a public policy and commonsense level, we hope the Committee and the FDA will consider the following:

1. The timing, inclusion/exclusion criteria, clinical endpoints, and overall design of the Program should be as inclusive as possible to not exclude a certain age group from the trial or the availability of the gene therapy for treatment.
2. The timing and sequencing for access to the treatment or chance to participate in trials should be communicated as soon as possible and, if specific timelines are not knowable, an estimated range should be provided so that patient families can at least put thought and research into what may soon be major and difficult decisions.

3. Presuming that Phase 3 will be proving efficacy for the treatment or cure of cystinosis as opposed to other potential applications for the therapy, is it possible and appropriate to simultaneously be seeking applications for treating conditions other than cystinosis? If so, are there safeguards in place that ensure the original purpose of the trial – in which this community has placed its highest hopes – not be sidelined?

For many, especially those suffering advanced cystinosis with diminishing effectiveness of medications, the Program is our last and only chance. We are hopeful but anxious as we know that every day we wait has a devastating impact on our children's health. We believe all involved parties share the same mission - finding better treatments and a cure for cystinosis. We hope the Committee will take an interest in this and any situation where access to lifesaving or life-giving treatments for rare diseases may risk falling victim to misunderstanding or bureaucratic inflexibility. We are grateful to the Committee's attention to this matter and stand in solidarity with the rare disease community in hopes that these delicate policy issues receive thought, resources, and resolution.

Sincerely,

Carli Simpson; New Orleans, LA
Parents of Charlie, Age 5

Erin McCarthy; Chicago, IL
Parent of Aidan, Age 7

Erin Finucane; Philadelphia, PA
Parents of Sofie, Age 5

STS Headquarters
633 N Saint Clair St, Suite 2100
Chicago, IL 60611-3658
(312) 202-5800
sts@sts.org

Washington Office
20 F St NW, Suite 310 C
Washington, DC 20001-6702
(202) 787-1230
advocacy@sts.org

February 29, 2024

The Honorable Lori Trahan
United States House of Representatives
Washington, DC 20515

The Honorable Chuck Grassley
United States Senate
Washington, DC 20510

The Honorable Mariannette Miller-Meeks, MD
United States House of Representatives
Washington, DC 20515

The Honorable Michael Bennet
United States Senate
Washington, DC 20510

Dear Representatives Trahan and Miller-Meeks and Senators Grassley and Bennet,

On behalf of The Society of Thoracic Surgeons (STS), I would like to thank you for introducing H.R. 4758/S. 2372, the Accelerating Kids' Access to Care Act. This necessary legislation would help reduce the time it takes children covered by Medicaid or the Children's Health Insurance Program (CHIP) to access specialized care when providers in their home state cannot address their needs.

Founded in 1964, STS is a not-for-profit organization representing more than 7,700 surgeons, researchers, and allied healthcare professionals worldwide who are dedicated to ensuring the best possible outcomes for surgeries of the heart, lungs, and esophagus, as well as other surgical procedures within the chest.

Congenital and pediatric cardiothoracic surgeons treat children who live with complex medical needs such as congenital heart disease. Families of these children often struggle to access and coordinate specialized care and must travel out-of-state to seek necessary lifesaving treatment. When a child's medical needs cannot be met by providers in their home state, the State Medicaid Agency and/or Medicaid Managed Care Organization authorizes such care with an out-of-state provider which requires additional screenings and enrollment. Currently, there is no federal pathway to streamline this process which means providers are often required to be screened and enrolled every time they treat a child from out-of-state. This process can be onerous, redundant and cause significant delays in time-sensitive care.

Your legislation would streamline this process by establishing a voluntary pathway for qualified providers caring for children to enroll in other states' Medicaid or CHIP programs without burdensome paperwork or subsequent screenings. Your leadership on this issue will help ensure timely access to care for children and families with complex medical conditions.

Thank you once again for your commitment to this important issue. We look forward to working with you and your colleagues in this endeavor. Please contact Molly Peltzman, Associate Director of Health Policy, at mpeltzman@sts.org, or Derek Brandt, Vice President of Government Affairs, at dbrandt@sts.org, should you need additional information or clarification.

Sincerely,

Jennifer Romano, MD
President

February 28, 2024

The Honorable Cathy McMorris Rodgers
Chair, Committee on Energy and Commerce
United States House of Representatives
Washington, DC 20510

The Honorable Frank Pallone
Ranking Member, Committee on Energy and Commerce
United States House of Representatives
Washington, DC 20510

The Honorable Brett Guthrie
Chair, Committee on Energy and Commerce Health Subcommittee
United States House of Representatives
Washington, DC 20510

The Honorable Anna G. Eshoo
Ranking Member, Committee on Energy and Commerce Health Subcommittee
United States House of Representatives
Washington, DC 20510

Dear Chairs Rodgers and Guthrie and Ranking Members Pallone and Eshoo:

On behalf of the Alliance for Regenerative Medicine (ARM), which represents more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations, I commend the Energy and Commerce Health Subcommittee for holding a hearing to discuss "Legislative Proposals to Support Patients with Rare Diseases".

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. Because over 70% of rare disorders have genetic causes[i], cell and gene therapies (CGTs) are critical in targeting the root causes of these diseases rather than treating symptoms and have the potential to transform the lives of afflicted patients.

It is becoming increasingly clear that the promise of CGTs is bearing fruit for rare disease patients. Gene therapy seeks to modify or introduce genes into a patient's body with the goal of durably treating, preventing or potentially curing a disease. There are currently ten gene therapies approved for rare genetic diseases for conditions such as Duchenne muscular dystrophy, sickle cell disease and two forms of hemophilia. In 2024, three gene therapies for rare genetic diseases already have FDA decision dates while regulatory submissions are possible for an additional three. Cell therapy is the administration of viable, often purified cells into a patient's body to grow, replace, or repair damaged tissue. In 2024, the Food and Drug Administration (FDA) approved the first-ever adoptive cell therapy – for metastatic melanoma. There are also several pending FDA approval decisions on new cell therapies such as those for advanced synovial sarcoma, a rare type of cancer that attacks large joints, and for dystrophic epidermolysis bullosa, a rare skin condition that causes widespread blistering that can lead to vision loss or permanent scarring. However, despite these advances, more than 90 percent of the estimated 10,000+ rare diseases still have no FDA-approved products, and about half of those diseases affect children. Given the hope CGTs bring to patients, it is particularly important that these innovative

breakthroughs are met with a proactive and nimble legislative framework. ARM supports several of the legislative proposals noticed by the Subcommittee on Health and hopes to see timely action on the following:

Creating Hope Reauthorization Act of 2024 (H.R. 7384)
Because of the challenges in reaching a timely diagnosis and the corresponding clinical prognosis of rare diseases in the pediatric population, it is particularly important that biotechnology companies have the appropriate incentives and regulatory mechanisms to facilitate expeditious development of these products. The Rare Pediatric Disease Priority Review Voucher (PRV) program has stood as a key component in propelling product development for these populations.

To date, several CGT sponsors have received PRVs for therapeutics that treat a range of devastating pediatric diseases with high mortality and morbidity. The PRV program notably does not cost US taxpayers – but rather leverages market forces and regulatory flexibility to achieve the goal of accelerating the provision of medical advances to children who often have no other treatment options. Similarly, this program does not negatively affect the FDA's budgetary capabilities as companies that use vouchers must still pay the Agency's user fees. While the statute allows products late in the pipeline to be "grandfathered" into vouchers through 2026, any disruption to this program may have a significant negative impact on companies making decisions regarding their early-stage pipelines, which ultimately impacts access to future treatments for rare diseases. ARM has endorsed H.R. 7384 and urges Congress to swiftly reauthorize the Rare Pediatric Disease PRV Program.

Accelerating Kids Access to Care Act (H.R. 4758)
Medicaid beneficiaries face numerous challenges accessing CGTs, in part, because of the geographic limitation of highly specialized providers required to administer these innovative therapies. As an emerging field, the unique specialization necessary for the administration of CGTs requires biotechnology companies to contract directly with providers in a growing, but limited, number of states. Patients seeking CGT treatments, who in many cases tend to be critically ill with medically complex conditions, must travel beyond their home states to obtain these treatments and to receive necessary pre- and post-administration care.

Specialized providers seeking to treat nonresident Medicaid beneficiaries must become enrolled in, and credentialed by, the program in the patient's home state. Currently, since each state Medicaid program establishes and administers its own credentialing program, the rules and procedures for credentialing can vary from state to state, resulting in a patchwork of state-specific credentialing requirements. These requirements can be onerous, complex, and time-consuming. As a result, patients can face weeks- or months-long delays in receiving treatment while these issues are resolved.

STAT News recently reported on the experience of an infant, Sufyan, that has an ultra-rate genetic disorder residing in Texas who needed to receive CGT treatment in Minnesota and illustrates this problem: "At one point, it seemed as though every provider in Minnesota that might care for the child — and ultimately bill for the care provided — would have to be credentialed as a Texas Medicaid provider, including surgeons, brain specialists, ICU staff, and possibly dozens of other doctors and nurses. That process generally takes months, months that Sufyan may not have."

Because of their complex and burdensome requirements, certain providers qualified to administer CGTs may be reluctant to complete necessary credentialing procedures to allow the treatment of nonresident beneficiaries, creating avoidable barriers to care for medically complex patients seeking treatment with CGTs.

ARM has endorsed HR 4758 and believes it is a helpful first step in alleviating administrative delays for Medicaid patients. As drafted, the legislation only applies to patients under the age of eighteen. ARM recommends amending the legislation to include specialized providers who treat Medicaid patients of all ages. We also urge the Committee to implore the Centers for Medicaid and CHIP Services to take immediate action within their existing authority to streamline Medicaid provider credentialling.

Establishment of a safe harbor from the federal Anti-kickback Statute to permit organizations to provide travel and lodging assistance for patients who must travel to receive specialized care
Because of their unique pre-treatment and on-site manufacturing requirements, CGTs must be administered at highly specialized Centers of Excellence and thus, as a therapeutic modality, differ from other types of medical treatments. As a result, travel, lodging and related expenses, particularly those incurred for out-of-state travel, are often required and can be particularly burdensome for Medicaid patients in need of CGTs. This concern warrants a clear legislative framework that enables biotechnology companies to support patients, particularly in underserved populations, to benefit from innovations in regenerative medicine.

For example, the highest concentration of the population affected by sickle cell disease are in states such as Florida, Georgia, Alabama, Mississippi, Louisiana and South Carolina, however, despite the availability of two groundbreaking gene therapies that can offer relief for those who suffer from the most severe form of the disease, none of the aforementioned states have a sickle cell gene therapy treatment center authorized to administer this medication and patients are required to travel multiple times to seek care.[ii,iii]

ARM believes that creating a safe harbor to address travel and lodging assistance for patients eligible for CGT treatments can provide greater certainty to biotechnology companies and other entities seeking to reduce barriers and eliminates the need for the Department of Health and Human Services Office of Inspector General ("OIG") to issue individual advisory opinions. The OIG has already observed that travel, lodging and associated cost assistance provided to patients receiving CGTs would not cause overutilization of healthcare or steer patients to particular providers or therapies.[iv, v] We thank Congressman Guthrie for drafting legislation to establish a new safe harbor for travel and lodging assistance and urge the Committee to consider it's passage. ARM has also called for the establishment of an anti-kickback statute safe harbor to allow CGT companies to provide support for fertility preservation for patients who risk compromised fertility associated with the administration of certain CGTs.

Additionally, ARM is concerned that several of the changes to the Medicaid Drug Rebate Program (MDRP) that the Centers for Medicare and Medicaid Services (CMS) has proposed could undermine patients' access to CGTs and disincentivize the development of new rare disease treatments. We oppose CMS reinterpreting the definition of "covered outpatient drug" which would eliminate the

incentive for states to provide separate payment for CGTs outside of reimbursement for hospital services – a tactic that has helped improve patient access to innovative new therapies by protecting providers from unsustainable financial losses. We also oppose the proposed drug price verification survey which would require drug manufacturers to submit unprecedented amounts of new data and disproportionately targets CGTs given the upfront investment associated with a single administration product. The price verification survey ignores the long-term positive impact that CGTs are likely to have on patients' healthcare utilization and Medicaid spending. As currently proposed, there are no exemptions for products with an orphan drug or rare disease designation. Using the threat of public disclosure to coerce manufacturers into offering additional Medicaid rebates could threaten the commercial viability of CGTs for rare diseases and ultimately cause companies to abandon those programs leaving many rare disease patients with no hope. We urge members of this Committee to continue engaging with CMS to ensure implementation of the MDRP in a way that is consistent with its Congressional intent and protects beneficiaries' access to FDA-approved therapies.

ARM recommends that CMS collaborate with manufacturers and states on a voluntary basis to develop alternative methodologies for addressing the short-term cost of high-value CGTs that support, rather than threaten, patient access. The recently announced Cell and Gene Therapy Access Model which will launch for sickle cell disease patients next year may be one such example.

As evidenced by the many powerful testimonies of patients and their advocates heard throughout Rare Disease Week, rare diseases profoundly impact the quality of life of affected individuals and their families. The CGT sector holds great promise for transforming the landscape of rare disease treatment by offering the innovative, targeted, and potentially curative therapies these patients deserve. We thank you for your continued focus on improving the lives of those living with rare medical conditions, for some of whom CGTs may be the only treatment option.

ARM strives to be a resource for this Committee. We look forward to working with you to advance the aforementioned legislation and to develop additional policy solutions that bring safe and effective regenerative medicines to patients. Should you have any questions or concerns, feel free to contact me at ecischke@alliancerm.org.

Sincerely,

Erica Cischke, MPH
Vice President, Government Affairs
Alliance for Regenerative Medicine

[i] Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020). Available at: https://doi.org/10.1038/s41431-019-0508-0

[ii] Phillips S, Chen Y, Masese R, Noisette L, Jordan K, Jacobs S, et al. (2022) Perspectives Of Individuals With Sickle Cell Disease On Barriers To Care. PLoS ONE 17(3): e0265342. Available at: https://doi.org/ 10.1371/journal.pone.0265342

[iii] Feuerstein, A. (December 2023) In historic decision, FDA Approves A CRISPR-Based Medicine For Treatment Of Sickle Cell Disease. Available at: https://www.statnews.com/2023/12/08/fda-approves-casgevy-crispr-based-medicine-for-treatment-of-sickle-cell-disease/

[iv] Notice of Modification of Advisory Opinion 20-02, OIG (May 26, 2022) Available at: https://oig.hhs.gov/documents/advisory-opinions/1035/Modification-AO-20-02.pdf.

[v] Advisory Opinion No. 20-09, OIG (December 28, 2020) Available at: https://oig.hhs.gov/documents/advisoryopinions/772/AO-20-09.pdf.

Children's Hospital Association Statement for the Record

U.S. House Energy and Commerce, Subcommittee on Health Hearing "Legislative Proposals to Support Patients with Rare Diseases"

February 29, 2024

On behalf of the Children's Hospital Association (CHA), representing over 200 children's hospitals nationwide, we are grateful for the opportunity to submit this statement for the record for the Energy and Commerce Subcommittee on Health hearing titled "Legislative Proposals to Support Patients with Rare Diseases." We strongly support the advancement of legislative proposals to address critical gaps in pediatric medical research and treatment.

Children and families affected by rare diseases and other chronic or complex conditions often face barriers to accessing care that is timely and coordinated given the range of specialists and subspecialists that may be involved in their care and the regionalized nature of pediatric specialty care. It is not uncommon for children, particularly those with medical complexity or specialized health care needs, to travel out of their community, state, or region to receive the care that can only be provided at a children's hospital. For these children, the children's hospital is the focal point of care, as pediatric specialists are frequently needed to provide expertise in treating their rare and complex clinical conditions. In recognizing these immense challenges, we emphasize the importance of legislative solutions that address the barriers faced by children and families seeking specialized care, particularly those compelled to travel for treatment at children's hospitals.

CHA strongly supports the **Accelerating Kids' Access to Care Act (H.R. 4758)** sponsored by Reps. Trahan and Miller-Meeks and appreciates the committee including it in this hearing. The strongly bicameral, bipartisan bill will improve children's access to needed out-of-state care by streamlining the burdensome and time-consuming Medicaid provider screening and enrollment process. We look forward to continuing to work with the committee to advance.

Medicaid plays a pivotal role for children, providing coverage for about half of the nation's children, including three million children in military-connected families, and essential wrap-around care to many children with complex needs who have private insurance. Children on Medicaid often require out-of-state care, particularly those with medically complex conditions like cancer or other rare diseases treated in children's hospitals. Today, children on Medicaid needing care outside their home states often experience delays due to the cumbersome provider enrollment process. By facilitating and streamlining this enrollment, the bill ensures that pediatric patients with rare diseases have timely access to specialized care, irrespective of their location. We appreciate the commitment of the sponsors to improve the overall well-being of pediatric patients, including those served by children's hospitals across the country. We ask the committee to move this bill through the legislative process quickly to ensure children get the care they need when and where they need it.

Children are not little adults. They are constantly growing and developing, and their health care needs, the delivery system to meet those needs, and support systems (e.g., schools, childcare settings) are different from those of adults.

Pediatric care requires specialized medications, therapeutics, and equipment, as well as extra time, monitoring, and specially trained health care providers who are compassionate and understand kids of all ages and from all backgrounds. It is critical that pediatric-focused innovations for rare diseases, including childhood cancers, are developed, reimbursed, and available to meet children's unique needs.

Children's hospitals dedicate significant efforts to advancing knowledge and improving access to essential treatments for children facing childhood cancers and rare diseases through studies, trials, and innovations. Unfortunately, the promising outcomes of their work often face obstacles in becoming readily available bedside treatments, as manufacturers' and payers' policies can hinder children's access `to care. Recognizing the urgency, children's hospitals, as hubs for pediatric medical research, emphasize the need to address impediments and incentivize the development, study, dissemination, and accessibility of these crucial treatments for children with rare diseases. In appreciation of the subcommittee's steadfast commitment to addressing critical issues affecting the well-being of the nation's children and families, CHA also supports the following three bills slated for consideration during today's hearing:

H.R. 3433 – Give Kids A Chance Act: CHA enthusiastically supports H.R. 3433, Give Kids A Chance Act, sponsored by Reps. McCaul and Eshoo. This legislation grants the FDA the authority to guide drug companies in conducting targeted clinical trials for combinations of pediatric cancer treatments. Currently, most pediatric cancer trials focus on children with advanced cancer, and the FDA is limited to directing trials for one drug given by itself. However, one-drug treatments are very unlikely to help children with advanced cancers. In fact, almost all curative treatments for cancer in adults and children are with drug combinations. That is why it is so important to explore drug combinations in pediatric as well as adult patients. The bill marks a significant step in advancing pediatric oncology research, providing hope to children and families grappling with these devastating diseases. The sponsors' dedication to prioritizing research and development for pediatric cancer treatments is commendable and aligns seamlessly with our mission to enhance the overall well-being of children nationwide.

H.R. 6664 – Innovation in Pediatric Drugs Act: CHA supports H.R. 6664, Innovation in Pediatric Drugs Act, sponsored by Reps. Eshoo and McCaul. This legislation is pivotal, mandating the study of drugs for rare diseases in children when safe and appropriate and granting the FDA the authority to penalize non-compliance by drug companies. Additionally, it increases NIH funding for clinical trials through the Best Pharmaceuticals for Children Act. The comprehensive approach of this bill ensures that pediatric patients with rare diseases are not overlooked in drug development, promoting their well-being, and advancing medical knowledge in pediatric medicine. We appreciate the dedication of the sponsors to address critical gaps in pediatric health care and contribute to the improved health outcomes of children across the nation.

H.R. 7384 – Creating Hope Reauthorization Act: CHA proudly supports H.R. 7384, Creating Hope Reauthorization Act led by Reps. McCaul, Eshoo, Bilirakis, Barragán, Trahan, and Burgess. This bipartisan legislation extends the authority to issue priority review vouchers, providing crucial incentives for the development of treatments targeting rare pediatric diseases. Since this program's inception, these vouchers have played a pivotal role in accelerating pharmaceutical innovation and expediting the approval process for therapies that address the unique health care needs of children with rare diseases. By extending this authority until September 30, 2030, this legislation ensures a sustained commitment to advancing the treatment of rare pediatric medical conditions. We

commend the bipartisan efforts behind this bill, and as supporters of the original legislation, we urge the committee to advance the Creating Hope Reauthorization Act, which continues to contribute to advancements in pediatric rare disease treatments.

These bills collectively address crucial gaps in pediatric medical research and treatment, demonstrating a steadfast commitment to improving the accessibility of lifesaving health care for children. From streamlining Medicaid processes to enhancing pediatric cancer research and ensuring the study of rare disease drugs in children, each bill addresses unique challenges faced by pediatric patients. Moreover, the extension of priority review vouchers underscores a vital measure in incentivizing treatments for rare pediatric diseases, thereby contributing to advancements in pediatric rare disease treatments and the overall health outcomes of our nation's youngest citizens. As CHA stands in strong support of these legislative proposals, we are confident that the subcommittee's consideration will lead to positive outcomes for pediatric patients and their families. Thank you for your continued bipartisan efforts in championing policies that directly impact the health and well-being of children. CHA stands ready to collaborate with the subcommittee and other stakeholders to advance legislation that prioritizes child health, ensures access to quality care, promotes healthy development, and fosters an environment conducive to the overall happiness and prosperity of kids. Together, we actively contribute to shaping a brighter and healthier future for the children and families across our nation.

500 N 5th St
Minneapolis, MN
55401

1 (800) 627-7692
(763) 406-5800
nmdp.org

February 29, 2024

Dear Chairwoman McMorris Rodgers, Ranking Member Pallone, Chairman Guthrie, and Ranking Member Eshoo,

NMDP (formerly National Marrow Donor Program) is writing to express our support for the Accelerating Kids' Access to Care Act (H.R. 4758). Many of our patients in need of life-saving cell therapy are enrolled in Medicaid and need to travel to another state to receive care. This bill would alleviate a barrier many of our patients and providers encounter when faced with needing life-saving care.

For children diagnosed with life-threatening blood cancers like leukemia and lymphoma, or a blood disease like sickle cell, a cure exists. NMDP manages the world's most diverse bone marrow registry to provide potentially life-saving cell therapies for these children. However, pediatric patients on Medicaid are facing unnecessary barriers to getting their much-needed treatment out of state. We support this bill so that the type of insurance a child has isn't a barrier to seeking the care they need from a provider that might not be available in their home state.

One-fifth of pediatric bone marrow transplant patients receive their care out of state. Children with blood cancers and blood disease often need to travel out of state because they:

- Live in one of the 15 states that do not have a pediatric transplant center.
- Require specialized care from a specific provider or facility that may not be available in their home state.
- Have rare diseases and need access to the few specialists across the country who know how to treat their specific condition.
- Need to travel for clinical trials, which may be their best treatment option, but are not always offered in their home state.

Kids in need of a transplant and their parents already face many barriers to getting the treatment they need. By passing H.R. 4758, some of that burden can be removed, making it easier for patients to access care out of state and for providers to accept pediatric patients from other states. Where you live shouldn't prevent you from getting the right treatment at the right time in the right place.

Please pass the Accelerating Kids' Access to Care Act and help kids who need a bone marrow transplant get the care they need.

Sincerely,

Jessica Knutson
Director, Government Affairs
NMDP (formerly National Marrow Donor Program)

U.S. House of Representatives Committee on Energy and Commerce
Subcommittee on Health

Legislative Proposals To Support Patients With Rare Diseases
February 29, 2024

Statement for the Record

The Patient Senate at Patients Rising Urges the Energy and Commerce Health Subcommittee to Act for Rare Diseases Patients and Caregivers

Introduction:

Good morning, esteemed members of the Energy and Commerce Committee. The Patients Senate is a collection of chronic and rare disease patients, patient advocates and caregivers from across the country. We are volunteer leaders from Patients Rising's national patient advocacy network that seeks to put forward and pass patient-inspired health policy. Many of our patients have been touched by a rare disease and we are united by a shared struggle, facing unique challenges that are often talked about in Washington, DC, but not fully understood.

The Uniqueness of Rare Disease:

Imagine being diagnosed with a condition affecting only a handful of people nationwide. The fear, the isolation, the uncertainty – these are the hallmarks of living with a rare disease. Only 10% of these conditions have FDA-approved treatments, leaving many of us desperately searching for answers and clinging to hope for scientific advancements.

Stop the Political Food Fight:

Many of us turn to the federal government- the National Institute for Health (NIH), the Food & Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and Congress- for help or to seek change. Too often we are told by our elected officials and federal health agencies that they are listening to us, but that isn't our experience. Instead we witness a disheartening "political food fight" between politicians and monied healthcare special interests, leaving patients like us caught in the crossfire.

We were disappointed that a bill that would ban the Quality-Adjusted Life-Year (QALY) in federal health programs was called a Trojan Horse by some members of this committee. This framing led to the bill passing the House on a narrow party-line vote. If you believe banning the QALY is a Trojan Horse, then you are not listening to patients. Discrimination in healthcare is real. We experience it. These are tools used by payers used in Medicaid and the Veterans

Health Administration to restrict patient access and ration care for those in the greatest need of care. We urge you to move beyond these partisan squabbles and focus on what truly matters: our lives.

Our Urgent Needs:

- **Innovation Ecosystem:** We need a regulatory framework tailored to the unique challenges of rare diseases, fostering innovation and accelerating drug development.
- **Health Insurance:** Insurance companies must deliver on their promise of shielding patients from financial ruin caused by illness. This includes holding health insurers accountable for designing inclusive health benefits that offer comprehensive coverage for rare disease treatments.
- **Access to Healthcare Workers:** America is facing a serious shortage of healthcare workers. We must break the dam on the policies that are controlling the supply of healthcare workers and support creative solutions that will maximize the education and capabilities of all healthcare workers.

Supporting Legislation:

We commend the efforts reflected in several proposed bills before this committee:

- **H.R. 1092 (BENEFIT Act):** This act's focus on incorporating patient experience data in the approval process holds promise for more patient-centric treatments. Patients and caregivers are frustrated by FDA listening sessions and Patient-Focused Drug Development efforts because they often seem to be check-the-box exercises. Federal health agencies need to demonstrate that they are being responsive to the citizens they are designed to serve. That should include agencies, like the FDA, demonstrating how patient insights are being applied to regulatory decisions.

- **H.R. 7384 (Creating Hope Reauthorization Act):** Reauthorizing the Rare Pediatric Disease Priority Review Voucher Program incentivizes research and development for children with rare diseases. We must advance our scientific understanding of rare diseases and increase the commitment from industry to invest in potential treatments. For children with rare diseases, time is life and there is no time to wait. Medicine development incentives like the Rare Pediatric Disease Priority Review Voucher is a critical tool for industry, the FDA and patients.

- **H.R. 4758 (Accelerating Kids Access to Care Act):** Streamlining Medicaid cross-border credentialing can ensure children with rare diseases receive the specialized care they need. Just finding qualified specialists to care for rare disease patients is difficult enough, and the shortage of healthcare workers only makes that more difficult. Cross-border credentialing is a creative idea to help maximize the use of qualified healthcare providers.

Finally, many rare disease patients have to travel long distances on a regular basis just to receive the care they need. These costs that patients and their families should not have to pay

out of pocket. We are hopeful that the **Patient Access Act** will be introduced and gain bipartisan support so patient travel assistance programs can improve access and affordability for essential care.

Conclusion:

To the esteemed members of the Committee, please listen to our needs with open hearts and minds. We are real people fighting for our lives and the lives of our loved ones. By working together, we can create a healthcare system that truly serves the needs of the rare disease community and ensures that no one is left behind.

LEUKEMIA & LYMPHOMA SOCIETY®

February 26, 2024

The Honorable Cathy McMorris Rodgers
Chair
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Brett Guthrie
Chair
Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna G. Eshoo
Ranking Member
Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chair McMorris Rodgers, Ranking Member Pallone, Chair Guthrie, and Ranking Member Eshoo:

The Leukemia & Lymphoma Society (LLS) is proud to offer our endorsement of multiple bills under consideration in the Energy and Commerce Subcommittee on Health's hearing on "Legislative Proposals to Support Patients with Rare Diseases." These bills reflect the hard bipartisan work of the Committee to improve the lives of the millions of patients and families affected by rare diseases.

Accelerating Kids' Access to Care Act (H.R. 4758)
LLS works to ensure that blood cancer patients have sustainable access to quality, affordable, and coordinated healthcare, starting with access to meaningful coverage – that is, coverage that guarantees access, ensures quality, promotes affordability, and provides stability for patients. For decades, both Medicaid and the Children's Health Insurance Program (CHIP) have been core sources of health insurance coverage for children in the United States.

However, children with complex medical needs often require specialized care that is sometimes unavailable in their home state. As a result, children with life-threatening diagnoses such as leukemias and other pediatric cancers often must travel outside their home state to receive crucial specialty care. For children with blood cancer, this may also include time-sensitive specialty care due to a relapse in their cancer or refractory disease. Yet, for an out-of-state provider—or often an entire care team—to be approved to treat the child, a provider must undergo the screening and enrollment process in the child's home state Medicaid program, even though the provider has already been successfully screened and enrolled in their own state's program. This duplicative process causes burdensome, unnecessary delays in giving time-sensitive care and, unfortunately, in some cases, can cause a child's condition to worsen.

H.R. 4758, the Accelerating Kids' Access to Care Act (AKACA), would cut through this red tape by establishing a voluntary pathway for providers caring for children under twenty-one to enroll as providers in other states' Medicaid programs quickly while maintaining program integrity safeguards. This pathway would be available only to providers successfully enrolled in their own state's Medicaid program, allowing them to expeditiously step in to provide essential care to children when called upon. Providers must recertify for the pathway every five years, keeping program integrity central. AKACA

would facilitate access to critical, time-sensitive treatment for children with leukemia and other life-threatening or debilitating conditions and reduce the risk of care disruption and subsequent negative outcomes.

Innovation in Pediatric Drugs Act (H.R. 6664)
Regulators and researchers often approach kids as if they are tiny adults. Yet, the biology of kids and their cancers is typically distinct from that of adults and their disease. The Innovation in Pediatric Drugs Act of 2023 amends the Pediatric Research Equity Act (PREA) to remove exemptions that present significant research barriers for children with orphan diseases, including pediatric cancers. The vast majority of orphan diseases affect children, and most drugs approved are orphan drugs. Considering the smaller patient populations for pediatric cancers and orphan diseases, children do not see the same investment in new drugs as adults. Unfortunately, for new orphan drugs approved for adults, with the exception of certain oncology drugs, an exemption under PREA prevents the FDA from requiring those drugs to be studied in children. Further drug companies are required under PREA to study adult drug indications in children when children could benefit from pediatric studies. While current law allows FDA to assess civil monetary penalties for late post-market study requirements for adults, the orphan drug exemption under PREA forbids FDA from doing the same for children. Failure to give FDA the authority it needs to ensure PREA studies get completed will prevent children with rare and orphan diseases from accessing drugs that could be used to save their life.

Retaining Access and Restoring Exclusivity (RARE) Act (H.R. 7383)
The incentives provided by the Orphan Drug Act (ODA) have proven extremely successful by stimulating research and development of drugs for conditions that would otherwise be ignored. These incentives have proven especially critical for pediatric and other populations studied later in drug development. By studying rare diseases, researchers better understand the body's biochemical pathways and have discovered how genes interact with other factors to cause disease. This has driven innovation within many fields of medicine, including cancer therapy.[1] Unfortunately, an 11th Circuit Court of Appeals decision has threatened the longstanding Food and Drug Administration (FDA) interpretation of the ODA. The Retaining Access and Restoring Exclusivity (RARE) Act would codify FDA's longstanding interpretation of the ODA to ensure that the scope of the orphan drug exclusivity is clarified to apply only to the same approved use or indication within such rare disease or condition instead of the same disease or condition. If Congress fails to pass this legislation, the FDA could be forced to block approval of another drug that could treat pediatric patients due to broad exclusivity rights, even when the initially approved drug has no efficacy for children.

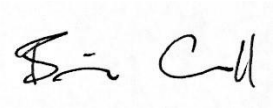
Creating Hope Reauthorization Act of 2024 (H.R. 7384)
The Creating Hope Act, initially passed in 2012 and reauthorized through 2024, expanded the FDA priority review voucher program to incentivize pharmaceutical manufacturers to invest in drugs with indications for rare pediatric diseases. The priority review voucher expanded under the Creating Hope Act incentivizes investment in pediatric treatments and has led to the development of new cures, like CAR T-cell therapy. Congress should reauthorize this important program to continue advancing the research that brings us closer to curing childhood cancers.

[1] National Organization for Rare Disorders, 5 Myths About Orphan Drugs and the Orphan Drug Act. https://rarediseases.org/advocate/rareinsights/5-myths-orphan-drugs-orphan-drug-act/

LEUKEMIA & LYMPHOMA SOCIETY®

We look forward to continuing to work together on these issues moving forward on behalf of the 1.6 million patients living with blood cancer in the U.S. Should you have any questions or need additional information, please contact Matt Marks, Director of Federal Affairs, at Matthew.Marks@lls.org.

Sincerely,



Brian Connell
Vice President, Federal Affairs
The Leukemia & Lymphoma Society

July 19, 2023

The Honorable Chuck Grassley
U.S. Senate
135 Hart Senate Office Building
Washington, DC 20510

The Honorable Michael Bennet
U.S. Senate
261 Russell Senate Office Building
Washington, DC 20510

The Honorable Lori Trahan
U.S. House Of Representatives
2439 Rayburn House Office Building
Washington, DC 20515

The Honorable Mariannette Miller-Meeks
U.S. House Of Representatives
1034 Longworth House Office Building
Washington, DC 20515

Dear Senator Grassley, Senator Bennet, Representative Trahan, and Representative Miller-Meeks:

Our 215 organizations are dedicated to improving the health and well-being of children – including children impacted by pediatric cancers, rare diseases, and complex medical conditions. We are pleased to offer our strong support of your legislation, the Accelerating Kids' Access to Care Act (HR 4758 / S 2372) (AKACA). Once enacted into law, this legislation will help reduce the time it currently takes children covered by Medicaid or the Children's Health Insurance Program (CHIP) to access specialized care when providers in their home state cannot address their care needs.

Both Medicaid and the CHIP are core sources of health insurance coverage for children, with children accounting for roughly 50% of total Medicaid enrollment[1] and more than one-third of all children with special health needs enrolled in Medicaid[2]. Families with children who live with complex medical needs such as cancer, pediatric brain tumors, sickle cell disease, congenital heart disease, and other rare diseases often struggle to access and coordinate the specialized care needed to treat their child's condition. Many times, the best treatment for these children requires out-of-state travel coupled with substantial coordination between the child's family and their care team. Particularly for patients with rare conditions and for novel gene therapy treatments, it is not uncommon for there to be only one or two clinical centers in the country with specialists who have the requisite expertise to treat their condition. A 2019 study of rare disease patients and caregivers across the US found that 39% of respondents traveled more than 60 miles to receive medical care, and 17% had moved (or considered relocating) to be closer to care.[3] For children with cancer, an initial diagnosis or relapse can require immediate and intensive treatment or clinical trials that may not be available in the child's home state.

When a child's medical needs cannot be met by providers in their home state, the State Medicaid Agency and/or Medicaid Managed Care Organization authorizes such care with an out-of-state provider. The out-of-state provider must then be screened and enrolled by the home state's Medicaid program. While current laws and regulations allow for the child's state to rely on provider screenings done by other state Medicaid programs or by Medicare, unfortunately, there is no single federal pathway. This means providers are often required to be screened and enrolled every time they are called upon to treat a child from out-of-state. This process can delay time-sensitive care by weeks or months. During this time, a child's condition can worsen, resulting in worse health outcomes and higher health care costs.

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[1] Medicaid & CHIP Enrollment Data Highlights, CMS, May 2021 (https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html)

[2] "Medicaid Access in Brief: Children and Youth with Special Health Care Needs." MACPAC, March 2023 (https://www.macpac.gov/wp-content/uploads/2023/03/Medicaid-Access-in-Brief-Children-and-Youth-with-Special-Health-Care-Needs.pdf)

[3] "Barriers and Facilitators to Rare Disease Diagnosis, Care and Treatment: 30-year Follow-up." National Organization for Rare Disorders, 2020 (https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

Your legislation would address this problem by establishing a voluntary pathway for qualified providers caring for children to enroll in other states' Medicaid or CHIP programs quickly. This limited pathway, only available to providers in good standing within their home state program or Medicare, would enable them to bypass subsequent screenings, expeditiously enroll in another state Medicaid program, and step in to provide essential time-sensitive care to children when necessary.

This legislation only pertains to provider screening and enrollment and does not change the authority states have to authorize out-of-state care and negotiate payment with accepting providers. It is a common-sense solution that will reduce burdens on health care providers, facilitate access to critical, time-sensitive treatment, and reduce the risk of care disruption and subsequent negative outcomes.

Thank you again for your leadership on behalf of all children with cancer, rare diseases, and other complex health conditions. We look forward to working with you to advance the AKACA. If you have any questions, please contact Matt Marks, Senior Manager of Federal Government Affairs with The Leukemia & Lymphoma Society, at matthew.marks@lls.org, Aimee Ossman, Vice President, Policy Analysis with the Children's Hospital Association, at aimee.ossman@childrenshospitals.org, or Mason Barrett, Policy Analyst with the National Organization for Rare Disorders, at mbarrett@rarediseases.org. Thank you for your consideration.

Sincerely,

Academy of Oncology Nurse & Patient Navigators
Aiden's Army
Akari Foundation
Along Comes Hope
Amanda Hope Rainbow Angels
American Academy of Allergy, Asthma & Immunology
American Academy of Pediatrics
American Association for Cancer Research
American Cancer Society Cancer Action Network
American Childhood Cancer Organization
American Heart Association
American Lung Association
American Partnership for Eosinophilic Disorders
American Society of Pediatric Hematology/Oncology
The Andrew McDonough B+ Foundation
Ann & Robert H. Lurie Children's Hospital of Chicago
Aplastic Anemia and MDS International Foundation
APS Foundation of America, Inc
Arms Wide Open Childhood Cancer Foundation
Arthritis Foundation
Association for Clinical Oncology
Association for Creatine Deficiencies
Association of Pediatric Hematology/Oncology Nurses
Asthma and Allergy Foundation of America
Avery's Hope
The Bardo Foundation
Barth Syndrome Foundation
Bear Necessities Pediatric Cancer Foundation
Bearing Hope
Beat Childhood Cancer Foundation
BJC Health System and Washington University School of Medicine
Bobby Jones Chiari & Syringomyelia Foundation
Boston Children's Hospital
Braden's Hope For Childhood Cancer Foundation
Cancer Support Community
Cancer*Care*
CancerFree KIDS
Carson Leslie Foundation
CDH International
Child Neurology Foundation
Childhood Cancer Awareness Group of Coffee County
Children's Brain Tumor Foundation
Children's Cancer Cause
Children's Hospital Association
Children's Hospital Colorado
Children's Hospital of Philadelphia
Children's Hospital of Wisconsin
Children's Mercy Kansas City
Children's of Alabama
Children's Oncology Group Foundation
Chondrosarcoma Foundation
Choroideremia Research Foundation
Christina Renna Foundation
Chronic Disease Coalition

Cincinnati Children's
Coalition Against Childhood Cancer (CAC2)
Congenital Hyperinsulinism International
Connect Melanoma
Crohn's & Colitis Foundation
Cure 4 The Kids Foundation
Cure CMD
CURE Epilepsy
Cystic Fibrosis Foundation
Cystic Fibrosis Research Institute
Dana-Farber Cancer Institute
Daniela Conte Foundation
Dragon Master Initiative
Dup15q Alliance
The E.WE Foundation
Elaine Roberts Foundation
Emory University Hospital
Epilepsy Alliance America
Epilepsy Foundation
The EVAN Foundation
EveryLife Foundation for Rare Diseases
FACES: The National Craniofacial Association
Family Voices
FOD (Fatty Oxidation Disorders) Family Support Group
For A Day Foundation
FOXG1 Research Foundation
The FPIES Foundation
Friends of Cathryn Foundation
Gaucher Community Alliance
Gillette Children's Specialty Healthcare
The Global Foundation for Peroxisomal Disorders
Glut1 Deficiency Foundation
Gold Rush Cure
Gorlin Syndrome Alliance
HCU Network America
Hemophilia Federation of America
Hemophilia Foundation of Southern California
Hepatitis B Foundation
Histiocytosis Association, Inc.
Hydrocephalus Association
Hypersomnia Foundation
Immune Deficiency Foundation
International Autoimmune Encephalitis Society
International Foundation for Gastrointestinal Disorders
International WAGR Syndrome Association
Jack's Angels
The Jansen's Foundation
JDRF
Joey’s Wings Foundation
Julia's Grace Foundation
JUST TRYAN IT
KidneyCAN
Kids v Cancer
Kier's Kidz
Ladybug House
Lennox-Gastaut Syndrome (LGS) Foundation
The Leukemia & Lymphoma Society
The Life Raft Group
The Lilabean Foundation
Livestrong
Living LFS
Lupus and Allied Diseases Association, Inc.
Lupus Foundation of America
Massachusetts General Hospital
Mattie Miracle Cancer Foundation
M-CM Network
The Mended Hearts, Inc.
Mesothelioma Applied Research Foundation
MIB Agents
Michigan Medicine
Mighty Millie Foundation
Mississippi Metabolics Foundation
Missouri Hospital Association
Mithil Prasad Foundation
Momcology®
A Moment of Magic
The Morgan Adams Foundation
MSUD-Family Support Group
Muscular Dystrophy Association
Mystic Force Foundation
National Ataxia Foundation
National Brain Tumor Society
National Cancer Registrars Association
National Eczema Association
National Eosinophilia Myalgia Syndrome Network
National Fragile X Foundation
National MALS Foundation
National Marrow Donor Program
National MPS Society
National MS Society
National Organization for Rare Disorders
National Pancreas Foundation
National Patient Advocate Foundation
National PKU Alliance
National Psoriasis Foundation
Nationwide Children's Hospital
Nemours Children's Health
Neuroblastoma Children's Cancer Society (NCCS)
Neurofibromatosis Midwest
NewYork-Presbyterian
Northwest Indiana Cancer Kids Foundation
Oncology Nursing Society
Organic Acidemia Association
Our Amazing Fighters

The Pablove Foundation
Parent Project Muscular Dystrophy
Partnership Health Center
The Pediatric Brain Tumor Foundation
People Against Childhood Cancer (PAC2)
Pheo Para Alliance
Pine Tree Apple Classic Fund
Pompe Warrior Foundation
PREP4Gold
Princess Nora's Warrior Foundation
Pull-thru Network, Inc
Pulmonary Hypertension Association
Rally Foundation for Childhood Cancer Research
Rare Epilepsy Network (REN) Coordinating Committee
RASopathies Network
Richi Childhood Cancer Foundation Inc.
Riley Children’s Health
The Ross K. MacNeill Foundation
Rutgers Cancer Institute of New Jersey
The RYR-1 Foundation
Sarcoma Foundation of America
SATB2 Gene Foundation
Saving Sophie
The Scott Carter Foundation
Seattle Children's
SebastianStrong Foundation
The Simon Foundation for Continence
SLC6A1 Connect
The Smasherson Foundation
Solving Kids' Cancer
Sophia's Fund
Spina Bifida Association
St. Baldrick's Foundation
St. Jude Children's Research Hospital
Stanford Children's Health
Steven G. Research Fund
Stop Children's Cancer, Inc.
STXBP1 Foundation
Swifty Foundation
Syngap1 Foundation
TargetCancer Foundation
Taylor Matthews Foundation
Team Telomere
Team Titin, Inc.
Texas Children’s Hospital
This Star Won't Go Out
Tough2gether Foundation
Triage Cancer
TSC Alliance
United MSD Foundation
United Porphyrias Association
Veterans for Common Sense
VOR - A Voice Of Reason
WITH Grace Initiative
Xia-Gibbs Society
Zoefia Alexandria Foundation Inc.

By Thomas J. Hwang, Florence T. Bourgeois, Jessica M. Franklin, and Aaron S. Kesselheim

Impact Of The Priority Review Voucher Program On Drug Development For Rare Pediatric Diseases

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HEALTH AFFAIRS 38,
NO. 2 (2019): 313 319

ABSTRACT Only an estimated 5 percent of rare pediatric diseases have a treatment, although collectively they affect more than ten million children in the US. To stimulate drug development for rare pediatric diseases, Congress expanded the priority review voucher (PRV) program in 2012. A pediatric PRV, which can be sold to another manufacturer, requires the FDA to provide priority six-month review rather than the standard ten-month review to another drug of the company's choosing. We compared rare pediatric disease drugs eligible for a PRV and rare adult disease drugs (which are not eligible for a PRV). We found that compared to drugs for rare adult diseases, drugs for rare pediatric diseases progressed more quickly through all phases of clinical testing and were more likely to be first-in-class. The voucher program was not associated with a change in the rate of new pediatric drugs starting or completing clinical testing, but there was a significant increase in the rate of progress from Phase I to Phase II clinical trials after the program was implemented. New policies may be needed to expand the pipeline of therapies for rare pediatric diseases.

Thomas J. Hwang (thwang1@partners.org) is a researcher in the Program on Regulation, Therapeutics, and Law in the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, both in Boston, Massachusetts.

Florence T. Bourgeois is an associate professor of pediatrics at Harvard Medical School and director of the Pediatric Therapeutics and Regulatory Science Initiative in the Computational Health Informatics Program at Boston Children's Hospital.

Jessica M. Franklin is an assistant professor of medicine in the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School.

Aaron S. Kesselheim is an associate professor of medicine at Harvard Medical School and director of the Program on Regulation, Therapeutics, and Law in the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

Rare diseases collectively affect more than ten million children in the US, but only an estimated 5 percent of rare diseases have a treatment.[1] In addition to economic obstacles, conducting clinical trials of new therapies for rare pediatric diseases can be complex, due in part to the relatively small number of patients available for enrollment in clinical trials and the limited number of specialists and expert centers.[2]

To stimulate drug development for rare pediatric diseases, in 2012 Congress established the rare pediatric disease priority review voucher (PRV) program as part of the Food and Drug Administration (FDA) Safety and Innovation Act of 2012. The PRV was originally established by Congress in 2007 for neglected tropical diseases. Voucher holders receive priority review for another product that otherwise would not have qualified for it. Priority review, which shortens the standard ten-month FDA review timeline to six months, is typically reserved for drugs that provide a significant improvement in safety or efficacy. The financial incentive from this voucher arises from the ability to market the other drug more quickly, as well as the potential to sell or transfer the voucher to another manufacturer seeking to expedite approval of one of its nonqualifying drugs.

From the program's creation in 2012 until April 2018, the FDA awarded thirteen rare pediatric disease PRVs, of which seven were sold for a total of $1.2 billion (the FDA also awarded five PRVs for neglected tropical disease drugs during that time).[3] In 2016, as part of the 21st Century Cures Act of 2016, Congress reauthorized the pediatric PRV program until 2020. However, the program has been controversial. Two expert working groups convened by the World Health

Organization noted "major flaws" in the use of PRVs as a policy tool for pharmaceutical development.[4,5] In a 2016 report by the US Government Accountability Office, FDA officials opposed the renewal of the pediatric PRV program, expressing concern about the interference with the FDA's prioritization of drugs with high clinical importance and the "significant adverse impact" of the workload from the voucher program on the FDA's public health mission.[6]

In this study we evaluated the association between the pediatric PRV program and the rate of new drugs for rare pediatric diseases starting clinical development. We compared trends in the development of drugs for rare pediatric diseases with those in the development of drugs intended to treat rare adult diseases, which are not eligible for the program and would not have been affected by its creation. Since the voucher could incentivize sponsors to continue developing products already in clinical trials, we also assessed the rates of successful progression of drugs to the next stage of development.

Study Data And Methods

STUDY COHORT Using two commercial databases of information on global pharmaceutical research and development (Adis Insight[7] and Citeline[8]), we identified all investigational drugs and therapeutic biologics that started Phase I clinical trials in the period January 1, 2008–December 31, 2015. We acquired follow-up information from Adis Insight, company filings, and ClinicalTrials.gov through April 1, 2018. These databases track the development of new drugs over their life cycles—from discovery through marketing—by mining public and proprietary sources such as company press releases, regulatory filings, investor presentations, scientific literature, conference abstracts, and direct communication with pharmaceutical companies.[9,10] These data were linked to the FDA's publicly available list of orphan drug designations and approvals, using a combination of the generic and brand names, sponsor, indication, and designation date.[11]

IDENTIFICATION OF ELIGIBLE DRUGS In section 908 the FDA Safety and Innovation Act defined a *rare pediatric disease* as one that primarily affects people ages from birth to age eighteen and that is a rare disease (defined, as in the Orphan Drug Act of 1983, as one that affects fewer than 200,000 people in the US). In a guidance document the FDA stated that it interpreted this statutory language to mean that more than 50 percent of the affected population in the US must be ages 0–18.[12] In addition to treating or preventing a rare pediatric disease, a drug is eligible for the pediatric PRV if it contains no previously approved active ingredient; relies on clinical data derived from studies that examined a pediatric population and dosages of the drug intended for that population; and does not seek approval for an adult indication in the original rare pediatric disease product application.

To identify drugs likely to be eligible for the voucher, we used a stepwise approach modeled on the statutory requirements, FDA guidance, and precedent cases of drugs that have received a pediatric PRV. First, a pediatrician (Florence Bourgeois) reviewed the primary indications and categorized them as eligible (for example, spinal muscular atrophy) or not eligible (for example, Huntington's disease) for a voucher based on clinical literature describing age-based prevalence and life-span estimates. A second clinician (Aaron Kesselheim) independently reviewed cases whose indications were not categorized in the first review. For classifications that remained undetermined after two reviews (roughly 5 percent of all cases), a third investigator (Thomas Hwang) communicated directly with the FDA to validate the viability of the indication as a rare pediatric disease. The final determination of potential eligibility for a pediatric PRV was resolved by consensus (see online appendix exhibits A1 and A2 for examples of eligible and ineligible indications).[13]

DATA EXTRACTION Information on drug characteristics (pharmacologic versus biologic), indication, orphan drug designation, and sponsor were extracted for all drugs in the study cohort. Status of regulatory approval was obtained through review of the approval lists for the FDA Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. For drugs that had not yet been approved, we obtained the current status of clinical development (in progress or discontinued), with follow-up information through April 1, 2018, from Adis Insight. We supplemented these data on drug discontinuations with a manual review of the ClinicalTrials.gov database; company press releases and annual reports; and transcripts of earnings and stock analyst reports. Finally, adapting methods developed by the FDA, one investigator (Bourgeois) assessed whether the drug would be the first FDA-approved therapy, defined as a drug intended to treat a disease for which the FDA had not yet approved any therapies as of the initiation of Phase I clinical trials.[14] To be conservative, we considered the first FDA-approved therapy to be the first treatment for any form of the condition.

STUDY OUTCOMES AND STATISTICAL ANALYSIS We used descriptive statistics to characterize the drugs in the study cohort and trends in the de-

velopment of rare pediatric drugs over time. Fisher's exact test was used to compare the proportions categorized as first FDA-approved therapy of drugs that were and were not eligible for a voucher.

We assessed the change in voucher-eligible pediatric drugs (as a proportion of all drugs) that started Phase I clinical trials before versus after the creation of the voucher program, compared to the change in the comparison group of drugs for rare adult diseases that were not eligible for a voucher. This group was chosen as the best available comparator since rare adult diseases and rare pediatric diseases have similar development challenges, but drug development for rare adult diseases should not have been affected by the creation of the pediatric PRV program.

We estimated the between-group difference after the voucher program's creation by fitting a flexible Poisson model with an indicator variable for voucher eligibility; a continuous time variable for trial year; pairwise interactions between time and voucher eligibility and between time and an indicator for the time after the creation of the voucher program; and a three-way interaction between time, voucher eligibility, and the indicator for the time after the program's creation. An offset term, defined as the natural logarithm of the number of drugs starting Phase I clinical trials each year, was included to allow interpretation of model coefficients as ratios of incidence rate ratios (IRRs). The coefficient of the three-way interaction can be interpreted as the differential change in the IRR of PRV-eligible drugs that started testing from before to after the creation of the voucher program, relative to the change in the comparison group of ineligible drugs.

We also evaluated progression to the next stage of development. The cumulative probability of eligible and ineligible drugs having progressed to the next stage of development after thirty-six months was estimated using the Kaplan-Meier method for each phase change (that is, from Phase I to Phase II, from Phase II to Phase III, and from Phase III to FDA approval), and discontinued products were censored at the time of announcement of development discontinuation. Hazard ratios (HRs) and associated 95% confidence intervals were calculated using Cox proportional hazards models. To evaluate the differential change between voucher-eligible and -ineligible drugs in ratios of HRs for phase progression before versus after creation of the voucher program, we fit a Cox proportional hazards model that included as covariates the same variables that we used in the multivariable Poisson analysis described above. As a sensitivity analysis, we excluded drugs that started trials in 2012 (as that was potentially a transition year).

LIMITATIONS Our study had several limitations. First, the median duration of follow-up from the start of Phase I trials until the end of data follow-up was roughly 5.6 years, and it is possible that in the future, more of the drugs in our cohort could progress to subsequent stages of development or that development could be restarted for drugs currently classified as discontinued. Future work would benefit from additional years of data on newer drug development as well as follow-up on the cohort of drugs in this study.

Second, unlike Orphan Drug Act designations, which are publicly reported, there is no list of drugs in development eligible for a pediatric PRV, nor is there a comprehensive list of rare pediatric diseases. Thus, we used clinical judgment and guidance from the FDA to classify investigational drugs as eligible or ineligible for a voucher.

Finally, other factors (such as research funding and prescription drug markets) might have also contributed to the observed differences between drugs for rare pediatric diseases and drugs for rare adult diseases after the creation of the pediatric PRV program in 2012.

Study Results

Thirteen rare pediatric disease priority review vouchers were awarded between the program's creation in 2012 and April 2018 (exhibit 1). Between January 2008 and December 2015, 386 new drugs intended to treat rare diseases started Phase I trials (exhibit 2). So did another 2,319 drugs for nonrare diseases (data not shown). Of the 386 rare disease drugs, 71 (18 percent) were determined to be in development for rare pediatric diseases and therefore eligible for the pediatric PRV program (exhibit 2 and appendix exhibit A3).[13] Most of the 71 eligible drugs were intended to treat neurological (31 percent), hematologic (13 percent), or other metabolic (20 percent) disorders (data not shown). Among the 315 drugs intended for rare adult diseases, 90 (29 percent) were intended to treat solid or blood cancers. The median duration of follow-up from the start of clinical development until April 1, 2018, was 5.6 years (interquartile range: 4.0–7.7 years).

INITIATION OF CLINICAL TRIALS FOR NEW THERAPIES Forty novel drugs eligible for a pediatric PRV started Phase I clinical testing in the period 2008–12, compared to thirty-one eligible products that started Phase I trials in the period 2013–15 (after the voucher program's creation). There was no significant change in the rate of drugs eligible for a pediatric PRV starting clinical

EXHIBIT 1

Drugs approved by the Food and Drug Administration (FDA) that were awarded a rare pediatric disease priority review voucher, July 9, 2012–April 1, 2018

Drug (trade name)	Year of award	Indication
Elosulfase alfa (Vimizim)	2014	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)
Dinutuximab (Unituxin)	2015	Pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy
Cholic acid (Cholbam)	2015	Bile acid synthesis disorders due to single enzyme defects
Uridine triacetate (Xuriden)	2015	Hereditary orotic aciduria
Asfotase alfa (Strensiq)	2015	Perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)
Sebelipase alfa (Kanuma)	2015	Lysosomal acid lipase (LAL) deficiency
Eteplirsen (Exondys 51)	2016	Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
Nusinersen (Spinraza)	2016	Spinal muscular atrophy (SMA)
Deflazacort (Emflaza)	2017	DMD in patients 5 years of age and older
Cerliponase alfa (Brineura)	2017	Pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) or tripeptidyl peptidase 1 (TPP1) deficiency
Tisagenlecleucel (Kymriah)	2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Vestronidase alfa-vjbk (Mepsevii)	2017	Pediatric and adult patients for the treatment of mucopolysaccharidosis type VII (MPS VII; Sly syndrome)
Voretigene neparvovec-rzyl (Luxturna)	2017	RPE65 mutation-associated retinal dystrophy

SOURCE Authors' analysis of information from the Food and Drug Administration.

EXHIBIT 2

Characteristics of drugs in clinical development for rare pediatric or adult diseases, 2008–15

Characteristic	Number	Percent
PHASE I TRIAL START YEAR		
2008	40	10.4
2009	37	9.6
2010	43	11.1
2011	41	10.6
2012	46	11.9
2013	59	15.3
2014	62	16.1
2015	58	15.0
ELIGIBLE FOR PEDIATRIC PRIORITY REVIEW VOUCHER PROGRAM		
Yes	71	18.4
No	315	81.6
THERAPEUTICALLY NOVEL		
Yes	157	40.7
No	229	59.3
DRUG TYPE		
Pharmacologic	204	52.8
Biologic	182	47.2

SOURCE Authors' analysis of information from commercial databases about the 386 drugs starting clinical development in 2008–15. **NOTES** Percentages might not sum to 100 because of rounding. Novelty is defined in the text.

testing, compared to the rate of ineligible drugs intended to treat rare diseases affecting adults (exhibit 3). As a proportion of all products in development during those time periods, the IRR ratios of starting clinical testing for eligible pediatric drugs versus ineligible adult drugs were 1.20 (95% CI: 0.94, 1.53) before versus 1.05 (95% CI: 0.93, 1.18) after implementation of the rare pediatric PRV program (ratio of after to before: 0.87; 95% CI: 0.73, 1.04; $p = 0.13$).

PROGRESS OF PRODUCTS THROUGH CLINICAL DEVELOPMENT Times to progression to the next stage of development were shorter among drugs eligible for a pediatric PRV, compared to ineligible drugs for rare adult diseases, across all three phases of clinical development. As of April 1, 2018, the estimated percentage of eligible versus ineligible drugs that had successfully progressed to the next stage of development at thirty-six months was 68 percent (95% CI: 57, 79) versus 51 percent (95% CI: 46, 56) in Phase I, 36 percent (95% CI: 23, 53) versus 27 percent (95% CI: 21, 34) in Phase II, and 41 percent (95% CI: 22, 68) versus 27 percent (95% CI: 18, 40) in Phase III.

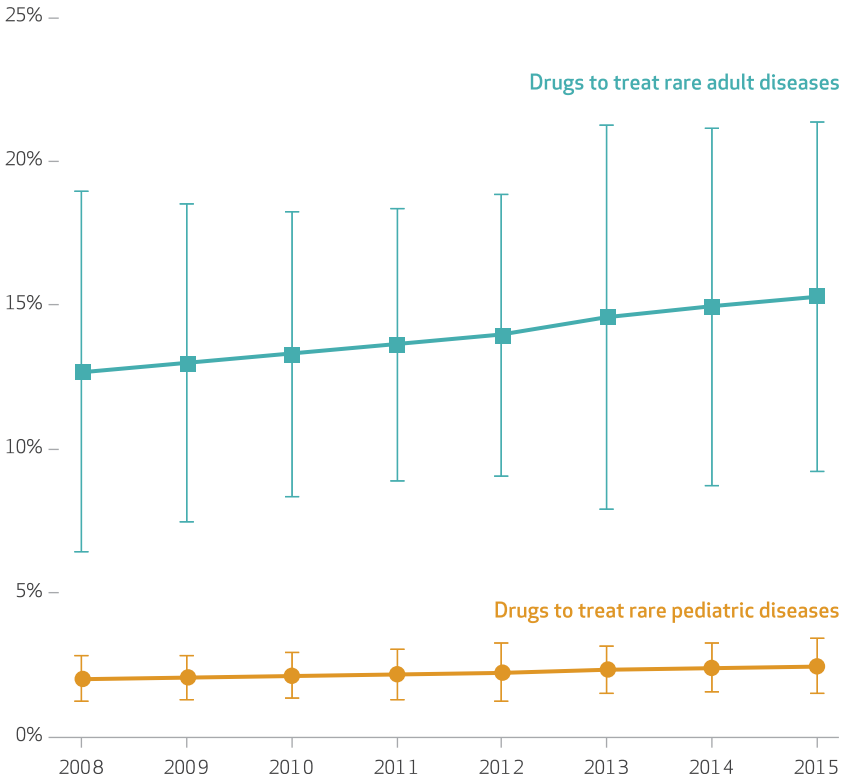
In multivariable Cox regression models, the creation of the rare pediatric disease PRV program in 2012 was associated with an increased

probability of progression to the next stage of development for eligible pediatric drugs, as compared to ineligible rare disease drugs, in Phase I. The ratios of HRs of progression to the next stage of development for eligible pediatric drugs versus ineligible adult drugs were 0.70 (95% CI: 0.52, 0.94) before versus 0.97 (95% CI: 0.84, 1.12) after implementation of the rare pediatric disease PRV program (ratio of after to before: 1.38; 95% CI: 1.11, 1.72; $p = 0.004$) (appendix exhibit A4).[13] There were no significant between-group differences associated with creation of the program in Phase II and Phase III (exhibit 4 and appendix exhibit A5).[13] Similar results were observed when we excluded trials that started in 2012 (the policy transition year).

FIRST THERAPIES FOR INTENDED INDICATION TO BE APPROVED Overall, a greater proportion of drugs eligible for a rare pediatric disease PRV, compared to ineligible drugs, were classified as targeting an indication for which they would be the first FDA-approved therapy (68 percent versus 35 percent; Fisher's exact $p < 0.001$). Similar between-group differences were observed before (65 percent versus 38 percent) and after (71 percent versus 32 percent) creation of the rare pediatric disease PRV program.

EXHIBIT 3

Trends in percent of new rare pediatric and adult disease drugs starting Phase I clinical trials, 2008–15



SOURCE Authors' analysis of information from commercial databases about drugs starting clinical development in 2008–15. **NOTES** Trend lines are from the multivariable Poisson analysis described in the text. The whiskers indicate 95% confidence intervals.

Discussion

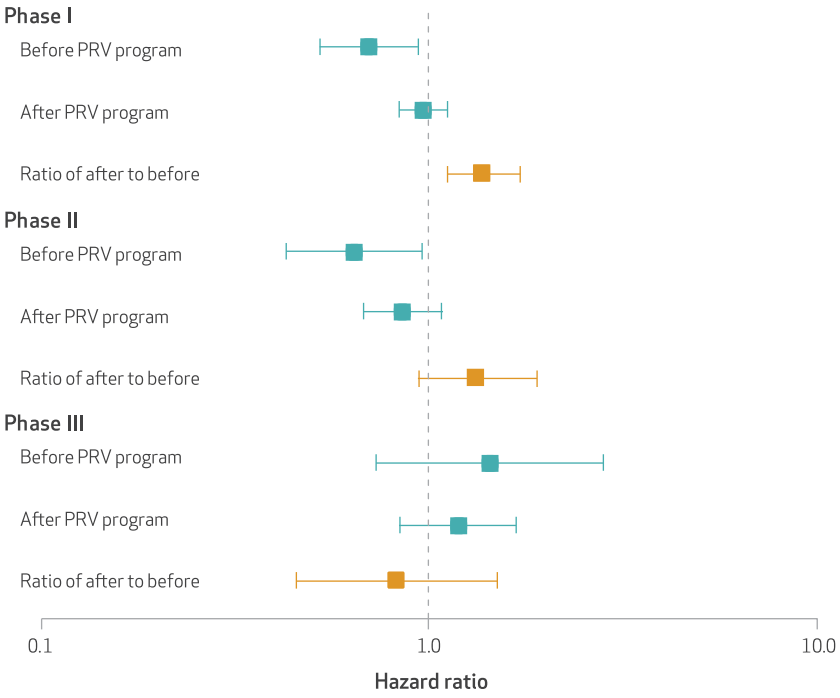
To our knowledge, this is the first study of the impact of the rare pediatric disease priority review voucher program on drug development. We found that the program was not associated with an increase in the number or rate of new rare pediatric disease drugs that started clinical trials since its inception in 2012. Recent studies of a parallel PRV program for neglected tropical diseases similarly found no or inconclusive effects of that voucher program's creation on the number of new drugs entering clinical development.[15,16]

Our data do provide some encouraging news on the development of drugs for rare pediatric diseases. Such drugs were more likely to advance from Phase I to Phase II trials, compared to drugs for rare adult diseases, after the PRV program's creation, although the same difference was not observed for progress in later stages of development. Further research that assesses the motivations of manufacturers affected by establishment of the rare pediatric PRV program could help shed light on the mechanism for this finding. We also observed certain advantages for rare pediatric disease drugs independent from the voucher program. For example, a greater proportion of these drugs progressed from Phase III to FDA approval, compared to drugs for rare adult diseases—though there was no association between these trends and the pediatric PRV program's creation. Moreover, a greater proportion of rare pediatric disease drugs than rare adult disease drugs were in development for diseases for which they would be the first FDA-approved therapies.

Understanding the impact of this new incentive on pediatric drug development is important as policy makers continue to expand the scope and number of PRVs. In 2016 Congress extended the voucher program to encompass new medical countermeasure products. Some legislators have proposed extending it to other drug classes, such as neonatal drugs, and commentators have suggested creating a similar voucher system for the drug approval process in the European Union.[17,18] However, the rapid proliferation of these programs must be considered carefully. It is possible that increasing the rate of noninnovative drugs advancing in development would divert resources from more promising drug candidates. The FDA has also warned that the voucher programs could impair its ability to meet public health priorities, by redirecting its limited

EXHIBIT 4

Trends over time and hazard ratios (HRs) for progression to the next stage of development for rare pediatric and adult disease drugs



SOURCE Authors' analysis of information from commercial databases about drugs starting clinical development in 2008–15 and of follow-up information through April 1, 2018. **NOTES** The whiskers indicate 95% confidence intervals. The ratio of after to before creation of the pediatric priority review voucher (PRV) program in 2012 refers to the ratio of HRs for rare pediatric disease drugs (eligible for a PRV) versus rare adult disease drugs (ineligible for a voucher) associated with the program's implementation. Ratios of HRs larger than 1 would suggest greater HRs for rare pediatric disease drugs versus rare adult disease drugs associated with the creation of the voucher program.

resources toward accelerating the review of drugs that would not otherwise merit priority review (for example, drugs treating highly prevalent conditions with existing therapies).[6] In addition, although voucher valuation could be influenced by multiple factors, an increase in the number of vouchers available for purchase, in particular, is expected to rapidly diminish the market value of any one voucher.[19]

Policy Implications

In the period 2017–27 the International Rare Diseases Research Consortium hopes to have a thousand new therapies approved for rare diseases, with most focusing on diseases lacking any approved therapeutic options.[20] Given the large number of rare pediatric diseases still without treatment options, our data suggest that the voucher program could be insufficient to meet this goal and that additional policies may be needed to bolster the development of new therapies. To date, policy making has largely focused on improving the pediatric study of drugs developed for adult conditions. Supplementary incentives could be fashioned to stimulate the entry into the pipeline of new therapies developed specifically for children. For example, new funding could be directed to the National Institutes of Health to expand a collaborative public-private development partnership for rare pediatric diseases. Economic modeling studies suggest that such public-sector investment could help mitigate the financial disincentives to pediatric research.[21] Such partnerships would also scale up funding for basic and translational research on rare disease and genetic mechanisms. In addition, the impact of concurrent policy changes on rare pediatric disease drug development should be carefully monitored. The Tax Cuts and Jobs Act of 2017 reduced the tax credit for orphan drug development from 50 percent to 25 percent—a change that may have implications for developers of drugs for rare pediatric diseases.

Conclusion

Roughly six years after the rare pediatric disease priority review voucher program was implemented, the program has not been associated with a change in the number or rate of new drugs starting clinical testing.

The voucher program was associated with a greater likelihood that drugs for rare pediatric diseases would advance from Phase I to Phase II clinical trials, compared to drugs for rare adult diseases, but a similar trend was not observed in later stages of development. Our analysis suggests that other policies are needed to expand the pipeline of drugs for rare pediatric diseases, particularly by stimulating the entry of new therapies developed specifically for children. ■

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13 To access the appendix, click on the Details tab of the article online.

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United States Government Accountability Office

Report to Congressional Committees

January 2020

DRUG DEVELOPMENT

FDA's Priority Review Voucher Programs

GAO-20-251

January 2020

DRUG DEVELOPMENT

FDA's Priority Review Voucher Programs

GAO Highlights

Highlights of GAO-20-251, a report to congressional committees

Why GAO Did This Study

Few drugs are currently available to treat certain tropical and rare pediatric diseases and to use as medical countermeasures, given their small market or potentially limited profitability. To help provide incentives for the development of such drugs, Congress created three PRV programs, which award PRVs to drug sponsors that develop drugs for tropical diseases, rare pediatric diseases, and medical countermeasures (e.g., drugs to mitigate harm from biological, chemical, radiological, or nuclear agents). FDA, an agency within the Department of Health and Human Services (HHS), administers these programs.

The 21st Century Cures Act included a provision for GAO to study the PRV programs. GAO examined the number of PRVs awarded and redeemed and the drugs for which they were awarded or redeemed, and what is known about the extent to which the PRVs provide incentives for developing drugs to meet unmet needs. GAO analyzed FDA data on awarded and redeemed PRVs for fiscal years 2009 through 2019 and other publicly available information on their transfers and sales. GAO conducted a literature review of peer-reviewed articles published from January 2009 through May 2019 that examined the PRV programs and interviewed FDA officials. GAO also interviewed seven stakeholder groups, seven academic researchers, and seven drug sponsors selected based on factors such as familiarity with PRV programs or drug development.

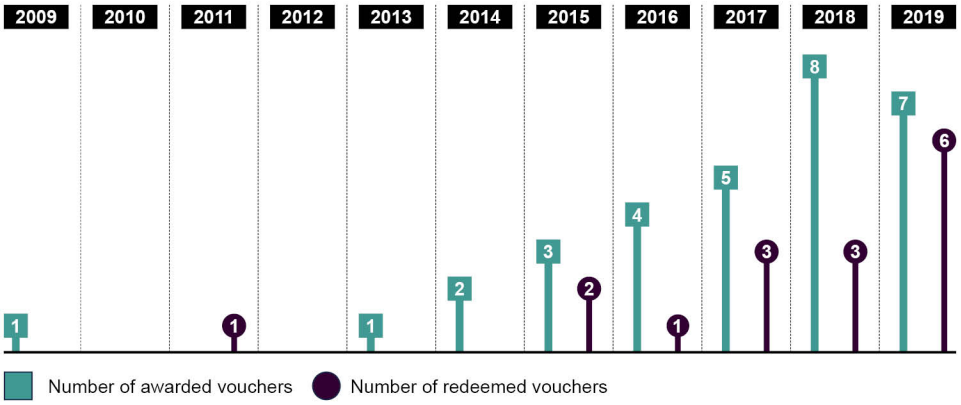
HHS provided technical comments on a draft of this report, which were incorporated as appropriate.

View GAO-20-251. For more information, contact John E. Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

The Food and Drug Administration (FDA) awards priority review vouchers (PRV) to drug sponsors that develop drugs for tropical diseases or rare pediatric diseases or to use as medical countermeasures. The PRV—which can be sold to another drug sponsor—may be redeemed later to receive priority review from FDA with a targeted review time of 6 months, rather than the 10-month standard review, for a drug application of the PRV holder's choice. The potential for additional revenue from either marketing a drug about 4 months sooner or from selling the PRV could provide an incentive for drug sponsors to develop drugs for these diseases or conditions. From fiscal year 2009, when the first PRV was awarded, through fiscal year 2019, FDA awarded 31 PRVs, mostly for drugs to treat rare pediatric diseases. Of the 31 PRVs awarded by FDA,17 were sold to another drug sponsor for prices ranging from about $67 million to $350 million, according to available data. As of September 30, 2019, available data show that drug sponsors had redeemed 16 of the 31 PRVs to obtain a shorter FDA review time for drugs to treat conditions and diseases such as human immunodeficiency virus (HIV), type 2 diabetes, and different forms of arthritis. These drug applications may not otherwise qualify for priority review.

Priority Review Vouchers Awarded and Redeemed, Fiscal Years 2009 through 2019



Source: GAO analysis of Food and Drug Administration (FDA) data and publicly available information. | GAO-20-251

GAO found few studies that examined the PRV programs, and those that did found the programs had little or no effect on drug development. However, all seven drug sponsors GAO spoke with stated that PRVs were a factor in drug development decisions—six sponsors said they were one of a number of factors, while one sponsor said they were pivotal in its development of a drug. Some academic researchers and stakeholders expressed concerns about the PRVs as incentives for drug development, including the potential for the expected revenue from the sale of a PRV to decline as more are awarded and available for sale.

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Abbreviations

FDA	Food and Drug Administration
PRV	priority review voucher
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
441 G St. N.W.
Washington, DC 20548

January 31, 2020

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Greg Walden
Republican Leader
Committee on Energy and Commerce
House of Representatives

Few drugs are available for certain tropical diseases, rare pediatric diseases, and material threat medical countermeasures (medical countermeasures), despite their potential to affect millions of people.[1] Drug sponsors—facing a lengthy and expensive drug development process—may be reluctant to develop treatments for these diseases or conditions given the small markets or potentially limited profitability for them.[2] Other challenges can make drug development for tropical diseases, rare pediatric diseases, and medical countermeasures more difficult than for other drugs. Specifically, tropical diseases often affect people living in low-income areas outside of the United States, making it difficult for drug sponsors to recover drug development costs; rare pediatric diseases affect a limited number of children, making it difficult to

[1]Tropical diseases, such as malaria and dengue fever, disproportionately affect poor and marginalized populations. Rare pediatric diseases, such as Duchenne muscular dystrophy and certain types of cystic fibrosis, are serious and life-threatening diseases where the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years. Medical countermeasures include drugs and vaccines that can diagnose, prevent, protect from, or treat the effects of exposure to emerging infectious diseases, such as pandemic influenza, and to chemical, biological, radiological, or nuclear agents.

[2]A drug sponsor is the person or entity that assumes responsibility for the development of a new drug, including responsibility for complying with applicable laws and regulations. While drug development time frames and costs can vary, the drug industry estimates that, on average, a sponsor spends over a decade developing a drug at an average cost of $2.6 billion. We use the term “drug” to refer to both chemically synthesized drugs and therapeutic biological products, such as vaccines.

identify and recruit sufficient numbers of patients to include in studies; and medical countermeasures treat high-priority threats that affect health security, making it difficult to test the drugs because exposing study volunteers to such threats would be an unethical and unacceptable risk.

To encourage the development of drugs to treat tropical diseases, treat rare pediatric diseases, and use as medical countermeasures, Congress established three priority review voucher (PRV) programs under which the Food and Drug Administration (FDA) awards a PRV to a drug sponsor upon approval of that sponsor's drug in one of these three areas.[3] A drug sponsor can later redeem the PRV when submitting a future drug application to treat any disease or condition, or sell or transfer it to another drug sponsor. When redeemed, a PRV entitles a drug sponsor to priority review by FDA—which has a goal of a 6-month review, rather than the 10-month goal for a standard review. The potential for additional revenue that comes from marketing a drug approximately 4 months sooner—or the proceeds that may come from selling the PRV to another drug sponsor—could provide an incentive for drug sponsors to develop drugs for tropical diseases, rare pediatric diseases, or medical countermeasures.

The 21st Century Cures Act included a provision for us to review and report on the PRV programs.[4] This report examines

1. the number of PRVs that have been awarded, and what is known about them and about the drugs for which they were awarded;
2. the number of PRVs that have been redeemed, and what is known about them and about the drugs for which they were redeemed; and
3. what is known about the extent to which PRV programs provide incentives for drug development to meet unmet needs.

To determine how many PRVs have been awarded and redeemed, as well as what is known about the drugs for which they were awarded or redeemed, we examined FDA information and publicly available information for all PRVs from the date of each program's inception

[3]To be awarded a PRV, the approved drug must meet applicable criteria for one of the three PRV programs.

[4]Pub. L. No. 114-255, § 3014, 130 Stat. 1033, 1093 (2016).

through fiscal year 2019.[5] Publicly available information included PRV sales (including sales prices), transfers, purchases, and redemptions reported by drug sponsors in documents such as press releases and Securities and Exchange Commission filings.[6] We compared the FDA data to FDA approval letters, press releases, and other publicly available sources and determined these data were sufficiently reliable for our purposes.

To examine what is known about the extent to which PRV programs provide incentives for drug development to meet unmet needs, we conducted a literature review of relevant articles published in peer-reviewed and other publications from January 2009 through May 2019. We reviewed these articles for information related to the PRV programs, including the extent to which PRVs are incentives for drug development and alternative incentives to the PRV programs for developing drugs for tropical diseases, rare pediatric diseases, and medical countermeasures.[7]

For all three objectives, we interviewed FDA officials; representatives from seven stakeholder groups, including trade associations, patient advocates, and organizations that partner with or provide funding to drug sponsors and are familiar with the PRV programs (hereafter, stakeholders); seven academic researchers with expertise in drug development, drug pricing, or the PRV programs (hereafter, researchers); and representatives from seven drug sponsors that have been awarded,

[5]Congress authorized the tropical disease PRV program in 2007, the rare pediatric disease PRV program in 2012, and the medical countermeasure PRV program in 2016. See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1102, 121 Stat. 823, 972 (2007); Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993, 1094 (2012); and 21st Century Cures Act, Pub. L. No. 114-255, § 3086, 130 Stat. 1033, 1145 (2016).

[6]According to FDA, drug sponsors are not required to provide sale prices of PRVs to FDA and may choose not to publicly disclose the sale prices.

[7]We identified articles through a search of bibliographic databases, including AgeLine, MEDLINE, and Scopus, using terms such as “priority review voucher,” “rare disease,” “tropical disease,” and “incentive.” Of the 155 citations we reviewed, we determined there were 77 relevant articles. We reviewed the 77 articles for background information on the PRV programs, information on the market for selling PRVs, alternatives to the PRV programs, and studies that analyzed data on the effects the PRV programs have had on drug development. Of the 77 articles we reviewed, we identified four that analyzed data on the effect the programs have had on drug development. We reviewed the methodology of these four articles and determined they were sufficiently reliable for our purposes. In addition, we reviewed other relevant publications, such as an evaluation prepared for the Department of Health and Human Services.

purchased, or redeemed a PRV.[8] We conducted these interviews to obtain information on (1) PRV awards and sales and insights into the characteristics of awarded PRVs and trends in PRV sales; (2) redemption data, reasons why a drug sponsor might redeem a PRV, and the effect the PRV redemptions have had on FDA resources; and (3) what is known about the extent to which PRV programs provide incentives for drug development to meet unmet needs. The perspectives of selected stakeholders, researchers, and drug sponsors are not generalizable.

We conducted this performance audit from February 2019 to January 2020 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Priority and Standard Review

For a priority review, the Food and Drug Administration (FDA) directs its resources to applications for new drugs that prevent, diagnose, or treat a serious condition and, if approved, would provide significant improvements in safety or effectiveness compared to available drugs. A drug may also receive priority review if the drug sponsor redeems a priority review voucher, among other things. FDA's goal is to complete the review of a priority application within 6 months.

Drugs that do not receive priority review receive standard review. FDA's goal is to complete the review of a standard application within 10 months.

Source: GAO review of FDA information. | GAO-20-251

FDA, an agency within the Department of Health and Human Services (HHS), is responsible for overseeing the safety and efficacy of drugs and biological products, such as vaccines, sold in the United States.[9] Before a drug sponsor can market a new drug, it generally must submit evidence of the drug's safety and effectiveness to FDA in a new drug application or biologics license application.[10] While FDA reviews most drug applications using its standard review process, FDA's priority review designation is intended to reduce the review time needed to bring a drug to market for

[8]The stakeholders we interviewed were the Bill and Melinda Gates Foundation, Biotechnology Innovation Organization, Drugs for Neglected Diseases Initiative, Médecins Sans Frontières, Medicines for Malaria Ventures, National Organization for Rare Disorders, and Pharmaceutical Research and Manufacturers of America. The drug sponsors we interviewed or obtained information from were BioMarin, Janssen Pharmaceuticals, Medicines Development for Global Health, Novartis, Sanofi, SIGA Technologies, and Ultragenyx. These sponsors were selected based on their different experiences with the three PRV programs and their interactions (e.g., selling and purchasing) with the PRV programs. In some cases, the drug sponsors elected to respond to our questions in writing; however, similar questions were provided to all drug sponsors.

[9]Unless otherwise indicated, we use the term "drug" in this report to refer to both chemically synthesized drugs and therapeutic biological products. Biological products—which include vaccines, blood products, and proteins, among other things—are derived from living sources such as humans, animals, and microorganisms.

[10]Hereafter, we use the term "drug application" to refer to both new drug applications and biologics license applications submitted to FDA for review.

certain drugs that treat serious conditions.[11] A drug application typically receives a priority review designation if the drug would provide a significant improvement in the safety or effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs, among other things (see sidebar).[12] FDA reviews all applications to determine if they qualify for priority review.[13]

FDA is also responsible for the implementation of the three PRV programs, which are intended to encourage development of drugs for tropical diseases, rare pediatric diseases, and medical countermeasures.[14] Qualifying diseases and conditions for the tropical disease PRV program and criteria for the rare pediatric disease PRV program are set forth in statute—though the list of eligible tropical diseases can be updated by order of the Secretary of HHS.[15] For the medical countermeasure PRV program, HHS publishes a list of high-priority threats that qualify for a PRV, including those that the Department of Homeland Security determines to pose a material threat sufficient to

[11]For more information on priority review and FDA's other programs intended to facilitate and expedite the development and review of new drugs that have the potential to address an unmet medical need for the treatment of serious conditions, see GAO, *Drug Safety: FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement*, GAO-16-192 (Washington, D.C.: Dec. 15, 2016).

[12]Drug applications may also be eligible for priority review if (1) the drug treats a disease designated as a qualified infectious disease, (2) it is a supplemental application for a drug that proposes a labeling change based on certain pediatric studies; or (3) it is submitted with a PRV.

[13]FDA assesses each drug application when it is submitted to determine if it qualifies for priority review; however, a drug sponsor may expressly request priority review. FDA informs the drug sponsor of a priority review designation within 60 days of the receipt of the drug application. Designation of a drug as "priority" does not alter the scientific or medical standard for approval or the quality of evidence necessary.

[14]We previously reported on the rare pediatric disease PRV program. See GAO, *Rare Diseases: Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program*, GAO-16-319 (Washington, D.C.: Mar. 2, 2016).

[15]The Secretary of HHS can add to the list of tropical diseases any infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.

affect national security.[16] (See table 1 for the types of drugs eligible for a PRV.)

[16]To be eligible for a medical countermeasure PRV, the drug must be intended for use either to (1) prevent or treat harm from a biological, chemical, radiological, or nuclear agent identified as a material threat under 42 U.S.C. § 247d-6b(c)(2)(A)(ii) or (2) mitigate, prevent, or treat harm from a condition that may be caused by administering a drug against a biological, chemical, radiological, or nuclear agent. The Secretary of Homeland Security is responsible for identifying such agents as a material threat, and new agents that present a material threat may be identified without public announcements. According to FDA, the publicly available list of agents that have been identified as material threats can be found in the Public Health Emergency Medical Countermeasure Enterprise Strategy and Implementation Plan; the threats identified in table 1 appear in the 2017-2018 plan.

Table 1: Types of Drugs Eligible for Priority Review Voucher (PRV) Awards, by Program, Publicly Available as of September 30, 2019

Tropical disease PRV program	Rare pediatric disease PRV program	Medical countermeasure PRV program
Application must be for a drug intended to prevent or treat a tropical disease. The diseases qualifying for a tropical disease PRV are the following: • tuberculosis • malaria • blinding trachoma • Buruli ulcer • cholera • dengue/dengue haemorrhagic fever • dracunculiasis (guinea-worm disease) • fascioliasis • human African trypanosomiasis • leishmaniasis • leprosy • lymphatic filariasis • onchocerciasis • schistosomiasis • soil transmitted helminthiasis • yaws • filovirus diseases • Zika virus disease • Chagas disease • neurocysticercosis • Chikungunya virus disease • Lassa fever • rabies • cryptococcal meningitis	Application must be for a drug intended to prevent or treat a rare disease or condition that is serious or life-threatening, and the serious or life-threatening manifestations must primarily affect individuals aged from birth to 18 years. A rare disease or condition is any disease or condition which affects less than 200,000 persons in the United States, or affects 200,000 or more people in the United States and there is no reasonable expectation of recovering the cost of drug development and marketing from U.S. sales.	Application must be for a drug intended to prevent or treat harm from a biological, chemical, radiological, or nuclear agent identified as a material threat, which include the following: • Bacillus anthracis (anthrax) • Multi-drug resistant B. anthracis (MDR anthrax) • Burkholderia mallei (glanders) • Burkholderia pseudomallei (melioidosis) • Clostridium botulinum toxin (botulism) • Ebola virus (Ebola hemorrhagic fever) • Francisella tularensis (tularemia) • Marburg virus (Marburg hemorrhagic fever) • Rickettsia prowazekii (typhus) • Variola virus (smallpox) • Yersinia pestis (plague) • acetylcholinesterase inhibitor nerve agents • cyanide salts (potassium and sodium cyanide) • hydrogen cyanide • Vesicants • radiological and nuclear threats[a]

Source: GAO summary of information from the Food and Drug Administration and the Department of Health and Human Services. | GAO-20-251.

Notes: In this table, the term “drug” refers to both chemically synthesized drugs and therapeutic biological products. The tropical disease PRV program was first authorized in 2007, the rare pediatric disease PRV program was first authorized in 2012, and the medical countermeasure PRV program was first authorized in 2016.

[a]A medical countermeasure application may also be for a drug intended to mitigate, prevent, or treat harm from a condition that may be caused by administering a drug against a biological, chemical, radiological, or nuclear agent. As of September 30, 2019, the list of agents included as material threats in this table are those that have been publicly identified in the 2017-2018 Public Health Emergency Medical Countermeasure Enterprise Strategy and Implementation Plan.

In order to be awarded a PRV, drug applications must meet additional criteria. For example, for all three PRV programs, the drug application must be eligible for priority review and a drug may be disqualified if its active ingredient has been previously approved by FDA in another drug application.[17] If a drug application meets the eligibility criteria for one of the PRV programs, the drug sponsor can include a request for a PRV in its application, including supporting documentation demonstrating how the application meets the PRV eligibility criteria. Once FDA receives a sponsor's drug application and PRV request, it reviews the information and considers whether the drug should be approved. If FDA approves the drug application, it includes its decision regarding whether to award a PRV in its approval letter.

Once FDA awards a PRV to a drug sponsor, the sponsor can redeem the PRV with the submission of a future drug application for a drug intended to treat any disease or condition, shortening FDA's targeted review time from the 10-month standard review to 6 months, even if the drug in that future application would not qualify for priority review on its own merits. The drug sponsor also has the option of selling or transferring the PRV to another drug sponsor, which may then choose to use it or similarly sell or transfer it.[18] PRVs may be transferred any number of times before they are used.[19] When the drug sponsor possessing the PRV ultimately decides to redeem it, the sponsor must notify FDA at least 90 days in

[17]For other, program-specific requirements, see 21 U.S.C. §§ 360n(a)(4) (tropical disease product application), 360ff(a)(4) (rare pediatric disease product application), and 360bbb-4a(a)(4) (medical countermeasure product application).

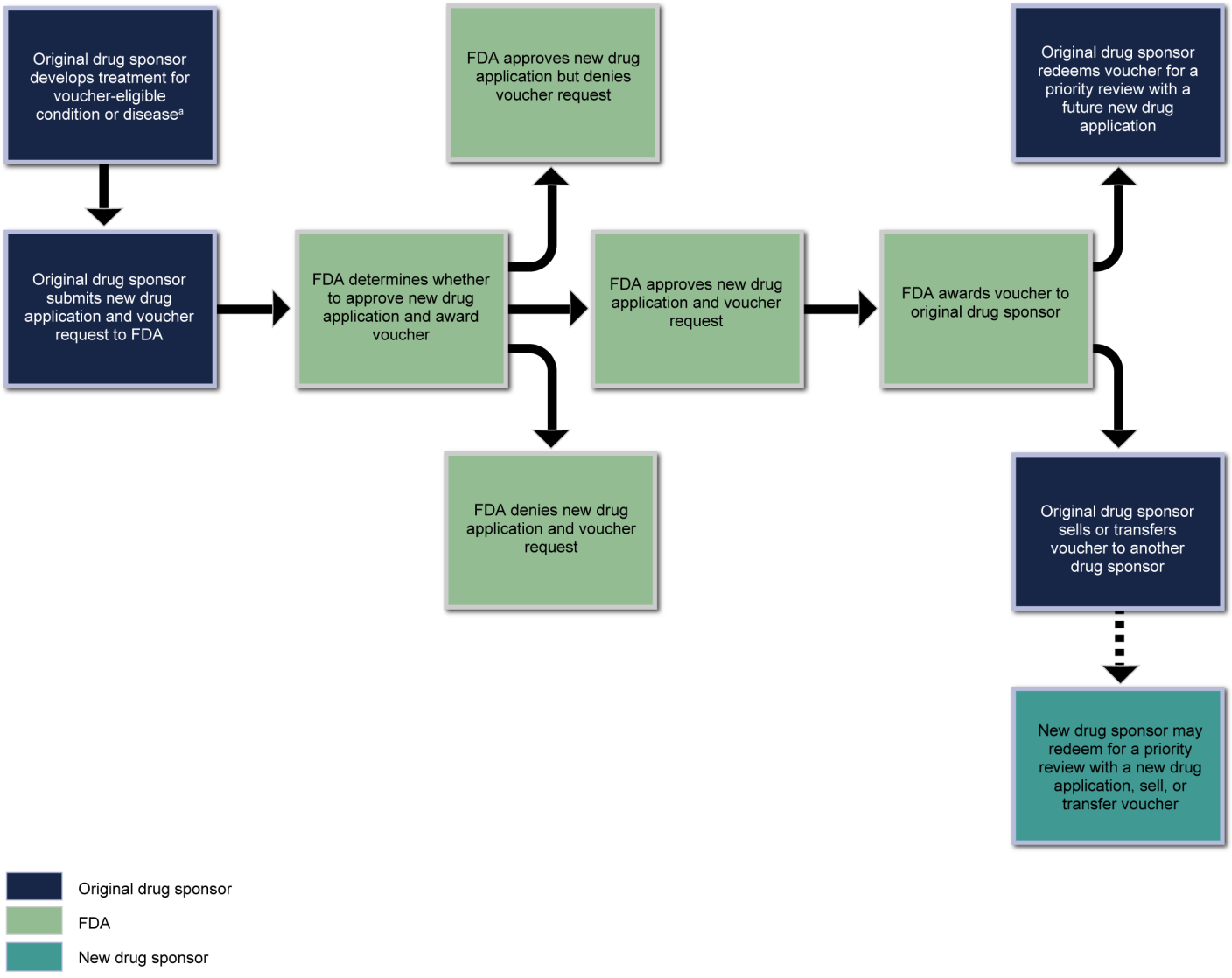
[18]FDA may revoke any rare pediatric disease PRV if the drug for which the PRV was awarded is not marketed in the United States within 1 year following the date of approval. 21 U.S.C. § 360ff(e)(1).

[19]Each person to whom a rare pediatric disease PRV is transferred must notify FDA of the change in PRV ownership within 30 days of the transfer. 21 U.S.C. § 360ff(b)(2)(B). For the tropical disease and medical countermeasure PRV programs, letters of transfer should be included when the PRV is redeemed, according to FDA guidance.

advance of submitting its drug application that is using the PRV. Figure 1 provides a general overview of the PRV programs.[20]

[20]For rare pediatric disease PRVs, a drug sponsor may request a rare pediatric disease designation for a drug that is still in development. In its designation request, a drug sponsor is to include information about, among other things, the drug and the rare pediatric disease for which the drug is being investigated, and the basis for concluding that the disease is rare and the serious or life-threatening manifestations primarily affect children. FDA reviews the provided information and generally informs a drug sponsor of its designation decision within 60 days of receiving the request. FDA encourages drug sponsors to request such a designation in order for the agency to have the necessary information to evaluate a drug's PRV eligibility and to ensure that drug sponsors have an adequate opportunity to provide this information before requesting a PRV. Although requesting such designation is not currently required in order to receive a rare pediatric disease PRV, after September 30, 2020, FDA may not award any rare pediatric disease PRV unless the drug is designated by September 30, 2020, and FDA has approved the drug application by September 30, 2022.

Figure 1: Overview of the FDA Priority Review Voucher (PRV) Programs



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-251

Notes: Among other things, a drug application submitted by a drug sponsor seeking a PRV must itself be deemed elig ble by FDA for a priority review.

[a]Each of the three PRV programs—for tropical diseases, rare pediatric diseases, and medical countermeasures—has its own criteria for the types of drugs that are eligible for a PRV.

The drug sponsor redeeming a PRV must also pay a PRV user fee (about $2.5 million in fiscal year 2019), in addition to other user fees required for all drug applications.[21] Because drug applications submitted to FDA with a PRV would not otherwise qualify for priority review, PRV user fees are intended to cover FDA's additional costs incurred when reviewing new drug applications with a PRV.[22] When a drug sponsor notifies FDA of its intent to redeem a PRV, its notification serves as a legally binding commitment to pay the PRV user fee.[23]

Of the three PRV programs, two—the rare pediatric disease and the medical countermeasure PRV programs—are set to expire in the coming years, unless they are reauthorized by Congress. The rare pediatric disease PRV program will begin to expire on September 30, 2020, and the program will end in September 2022.[24] The medical countermeasure PRV program will expire on October 1, 2023. After these end dates, FDA could no longer award a PRV for a rare pediatric disease or a medical countermeasure; however, the expiration dates do not affect PRV redemptions, as drug sponsors may redeem PRVs earned at any point in the future.

[21]In fiscal year 2019, the user fee for a drug application was about $2.6 million.

[22]For the tropical disease and medical countermeasure PRV programs, the PRV user fee is to be based on the average cost incurred by FDA in the review of drug applications subject to priority review in the previous fiscal year. For the rare pediatric disease PRV program, the PRV user fee is to be based on the difference between the average cost incurred by FDA in the review of drug applications subject to and not subject to priority in the previous fiscal year.

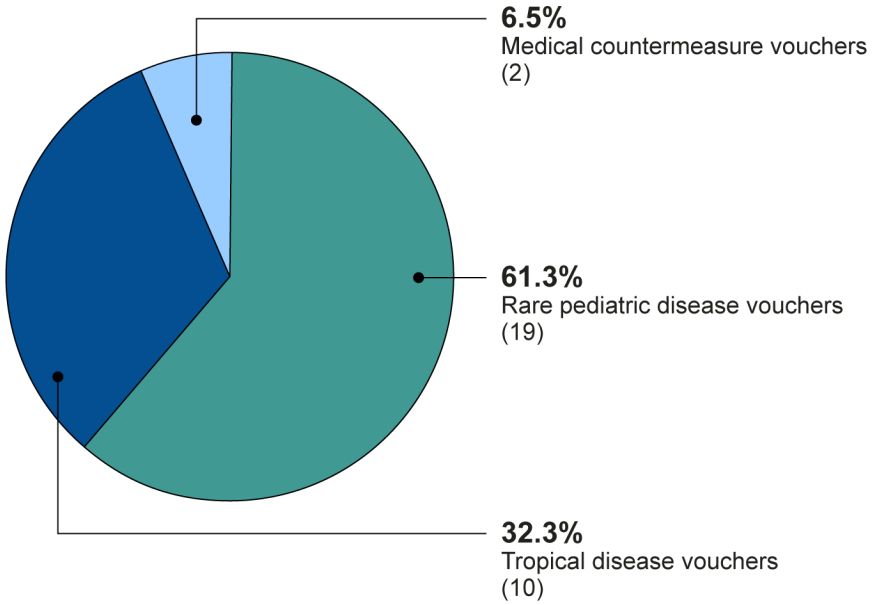
[23]According to FDA, for the rare pediatric disease, tropical disease, and medical countermeasure PRV programs, drugs sponsors may transfer their PRVs after notification is provided to FDA, if the sponsors have not yet submitted the drug application described in the notification letter. For the redemption of rare pediatric disease PRVs, user fees are paid by the drug sponsor when it notifies FDA that it intends to redeem a PRV. For the redemption of tropical disease and medical countermeasure PRVs, user fees are paid when the new drug application is submitted.

[24]FDA may not award any rare pediatric disease PRVs after September 30, 2020, unless the drug has received a rare pediatric disease designation by that date, and FDA has approved the drug application by September 30, 2022.

Most of the 31 PRVs Awarded by FDA Were for Drugs to Treat Rare Pediatric Diseases

As of September 30, 2019, FDA awarded 31 PRVs across the three PRV programs, with the majority being awarded through the rare pediatric disease PRV program (see fig. 2). According to FDA, all PRVs were awarded for drugs that met unmet medical needs. The 31 PRVs were awarded to 26 different drug sponsors; three sponsors were awarded two PRVs each and one sponsor was awarded three PRVs. FDA awarded the 31 PRVs for drugs that treat 27 different diseases. For five diseases—malaria, tuberculosis, smallpox, spinal muscular atrophy, and Duchenne muscular dystrophy—FDA awarded PRVs to two different drugs for their treatment, and FDA awarded one PRV for a drug that prevents two different diseases.[25] (See appendix I for more information about the drugs for which FDA awarded PRVs.)

Figure 2: Priority Review Vouchers (PRV) Awarded by FDA by Program Type, as of September 30, 2019



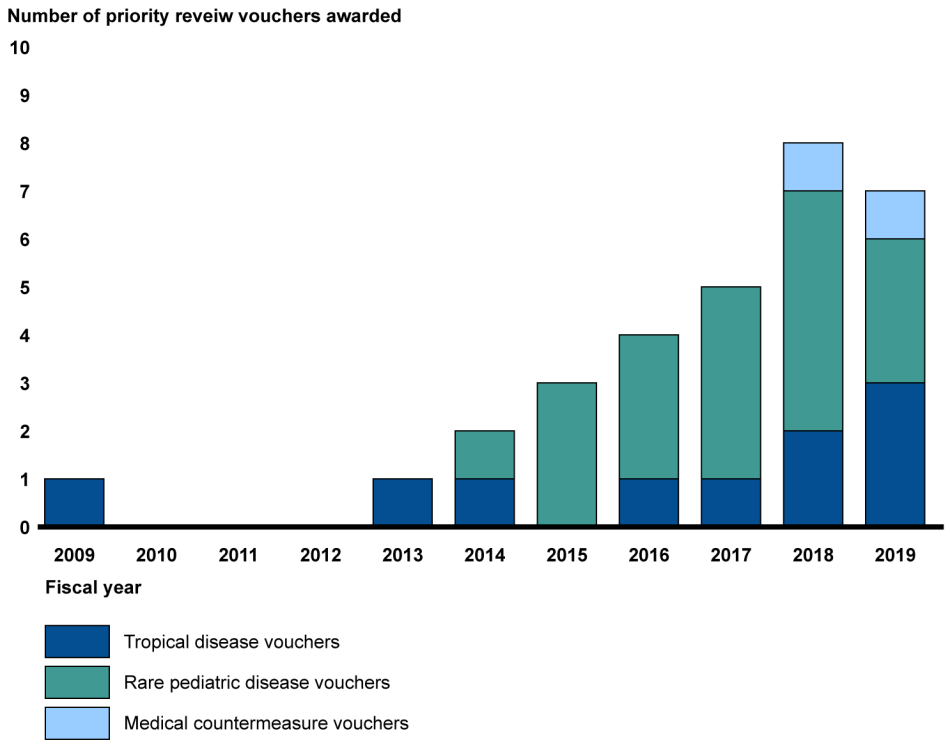
Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-251

Notes: Percentages do not add to 100 due to rounding. The tropical disease PRV program was first authorized in 2007, the rare pediatric disease PRV program was first authorized in 2012, and the medical countermeasure PRV program was first authorized in 2016.

[25]A medical countermeasure PRV was awarded for a drug that prevents both smallpox and monkeypox, a disease similar to smallpox.

The first PRV was awarded in fiscal year 2009, 2 years after the start of the tropical disease PRV program, and none were awarded in fiscal years 2010 through 2012. The first rare pediatric disease PRV was awarded in fiscal year 2014—about 2 years after that PRV program was authorized—and, beginning in fiscal year 2015, the majority of PRVs awarded were for rare pediatric diseases. In fiscal year 2018, FDA awarded eight PRVs, including the first medical countermeasure PRV, the most awarded in a single fiscal year (see fig. 3).

Figure 3: Number of Priority Review Vouchers (PRV) Awarded by FDA, by Program Type, Fiscal Years 2009-2019



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-251

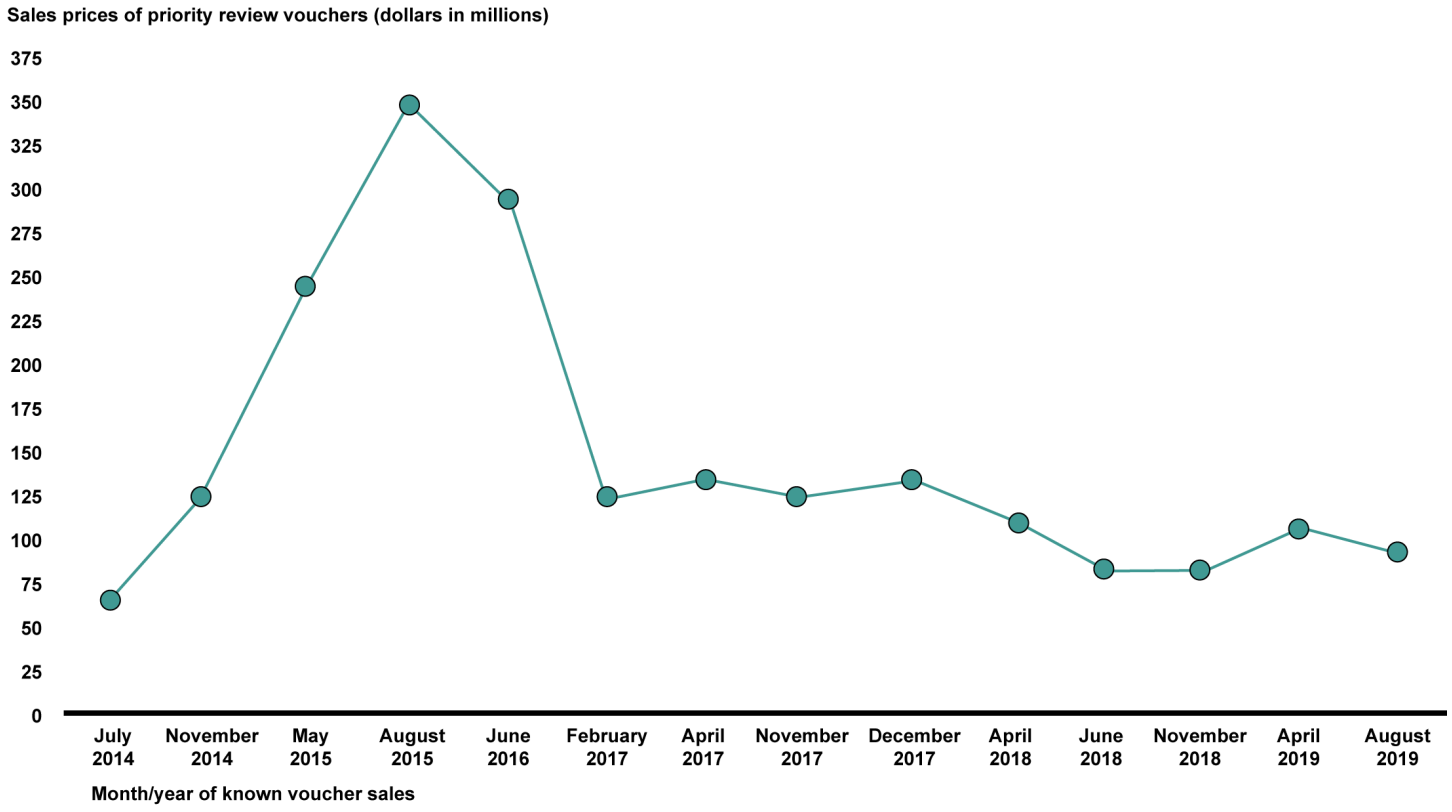
Note: The tropical disease PRV program was first authorized in 2007, the rare pediatric disease PRV program was first authorized in 2012, and the medical countermeasure PRV program was first authorized in 2016.

Of the 31 PRVs that FDA awarded to drug sponsors, available data indicate 17 PRVs were subsequently sold to another drug sponsor, providing revenue to the sponsor selling the PRV. For 14 of these 17 PRVs, we were able to determine a sales price, which ranged from $67.5 million for a PRV sold in fiscal year 2014 to $350 million for a PRV sold in

fiscal year 2015. However, the available sales prices of the PRVs sold since February 2017 have varied less than those sold previously, ranging from $80 to $130 million (see fig. 4). Because drug sponsors are only required to notify FDA of sales of rare pediatric disease PRVs at the time the sale occurs, additional transfers or sales of PRVs may have occurred.[26]

[26]FDA is notified of rare pediatric disease PRV sales or transfers when a PRV is transferred to another drug sponsor; however, the agency may only learn of tropical disease PRV and medical countermeasure PRV sales and transfers when a PRV is redeemed by another drug sponsor. As a result, FDA may not have information on PRV sales and transfers if PRVs have not yet been redeemed. Additionally, PRV sales prices are not reported to FDA. We obtained available PRV sales prices from company-issued press releases and other public statements and information filed with the Securities and Exchange Commission.

Figure 4: Available Sales Prices of Priority Review Vouchers (PRV), as of September 30, 2019



Source: GAO analysis of publicly available information on priority review voucher sales. | GAO-20-251

Note: This figure presents available sales price information for 14 PRVs. Two of these 14 PRVs were originally transferred to a different drug sponsor as part of the company's acquisition of drug-related assets and subsequently sold to another drug sponsor. The figure includes the reported sales price of the PRV when sold individually, not as part of the asset transfer. For three additional PRVs, the sales price or the seller was not publicly reported at the time of our analysis.

The drug sponsors, stakeholders, and researchers we interviewed noted that several factors could influence whether a drug sponsor keeps a PRV for future use, sells the PRV to another drug sponsor, or purchases a PRV to use on a drug that would not otherwise qualify for priority review. The PRV programs allow PRVs to be transferred multiple times, and according to stakeholders and drug sponsors we spoke with, the revenue gained from such sales may be a motivating factor for drug sponsors to sell them. For example, three stakeholders we interviewed said they believe drug sponsors consider the drugs in their development pipeline when deciding to keep, sell, or purchase a PRV, and one stated that drug sponsors need to determine if they would benefit more from using the PRV or the money they could make from selling it. One researcher

commented that price variation for PRVs can affect how a drug sponsor perceives the incentive and that low prices for PRVs may signify the need for additional incentives for drug development. However, two drug sponsors told us that they would continue to pursue PRVs as long as they were available and useful for a particular drug in their pipeline.

More than Half of the PRVs Awarded Have Been Redeemed for Drugs Treating a Variety of Conditions

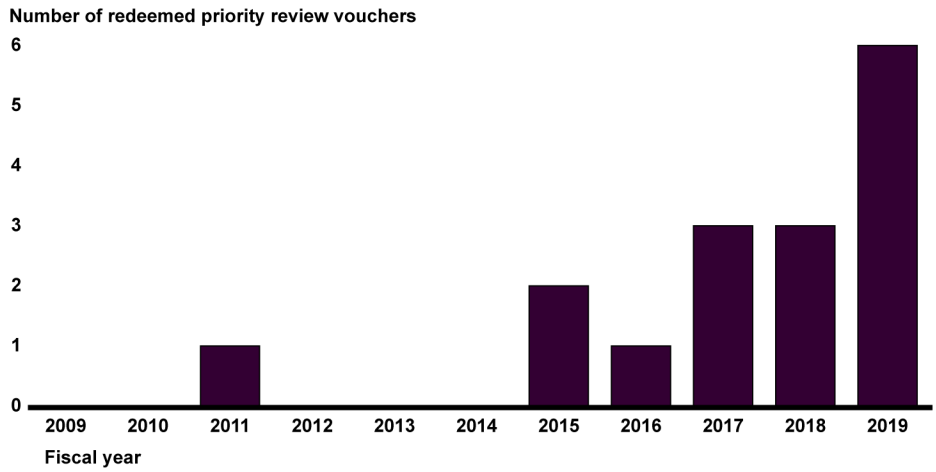
As of September 30, 2019, drug sponsors redeemed 16 of the 31 PRVs—that is, they submitted the PRV to obtain priority review for a drug application for a drug that would not otherwise qualify for a priority review.[27] The drugs for which the PRVs were redeemed treat or prevent a variety of conditions and diseases, including human immunodeficiency virus (HIV), type 2 diabetes, and different forms of arthritis. (See appendix II for a complete list of PRV redemptions.)

The first PRV was redeemed in fiscal year 2011, about 2 years after the first PRV was awarded, and the second PRV was redeemed in fiscal year 2015. Since 2017, drug sponsors have redeemed between three and six PRVs each year (see fig. 5).[28]

[27]For reporting purposes, PRVs are considered redeemed if FDA has completed review of the drug application for which they were redeemed or if the company has made public statements regarding its redemption. Additional PRV redemptions, if any, may not be reported in this report.

[28]For an overview of key milestone dates of the PRV programs, see app. III.

Figure 5: Redeemed Priority Review Vouchers (PRV) by Fiscal Year, Fiscal Years 2009 through 2019



Source: GAO analysis of Food and Drug Administration (FDA) data and publicly available information. | GAO-20-251

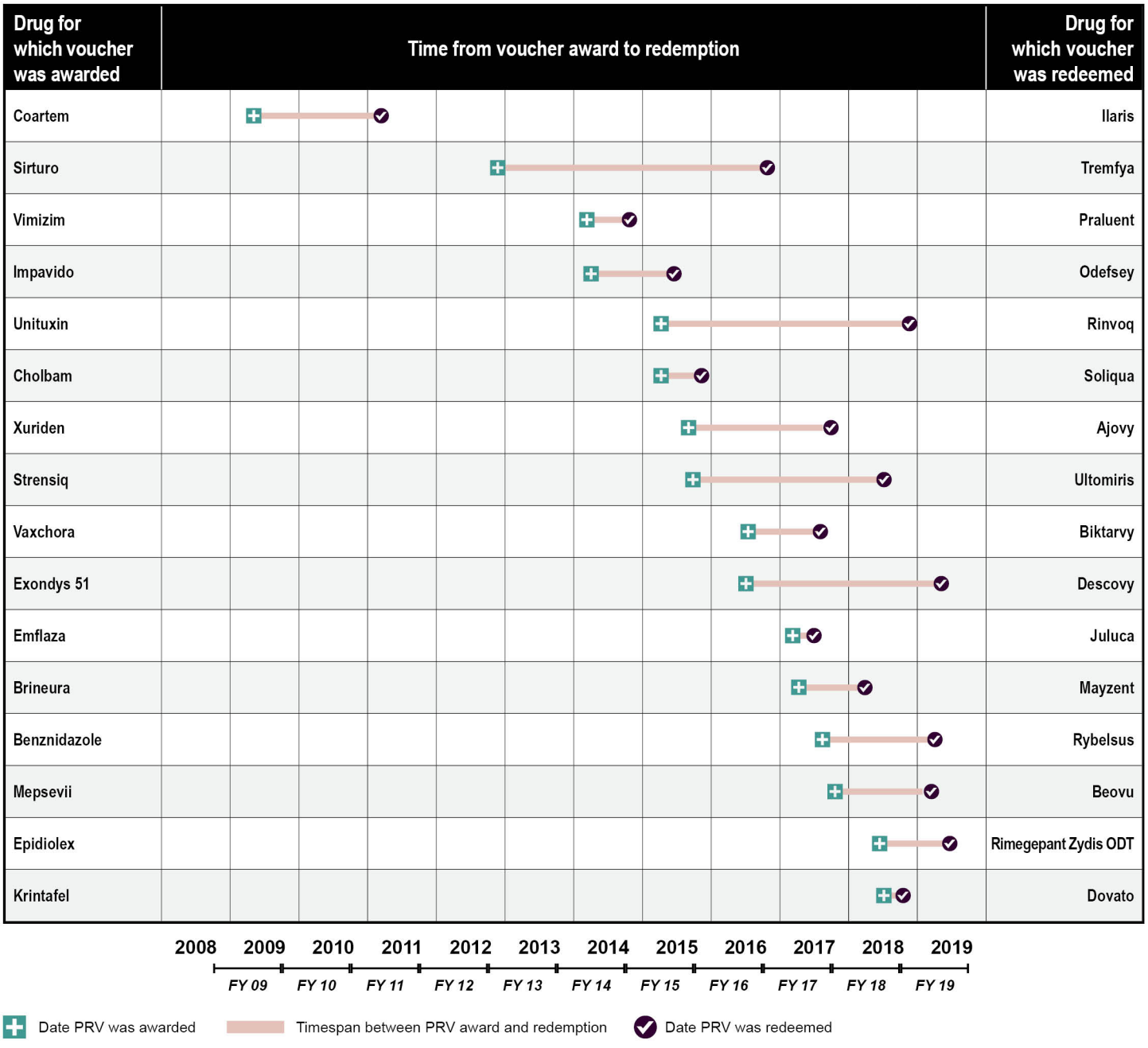
Notes: The first PRV was awarded in fiscal year 2009; no PRVs were redeemed in fiscal years 2009, 2010, 2012, 2013, or 2014. In this figure, PRVs are considered redeemed if FDA has completed review of the drug application for which they were redeemed or if the company has made public statements regarding its redemption. Additional PRV redemptions, if any, may not be reported in this figure.

The 16 PRVs were redeemed by 10 different drug sponsors.[29] Twelve of the 16 redeemed PRVs were purchased and redeemed by a drug sponsor different from the original PRV awardee.[30] All 16 redeemed PRVs were redeemed within 4 years of FDA awarding them (see fig. 6).

[29]Two drug sponsors redeemed two PRVs each, and two others redeemed three PRVs each; the remaining six drug sponsors each redeemed one PRV.

[30]These 12 PRVs have been redeemed by eight different drug sponsors.

Figure 6: Timespans of Redeemed Priority Review Vouchers (PRV), by Drug



Source: GAO analysis of Food and Drug Administration (FDA) data and publicly available information. | GAO-20-251

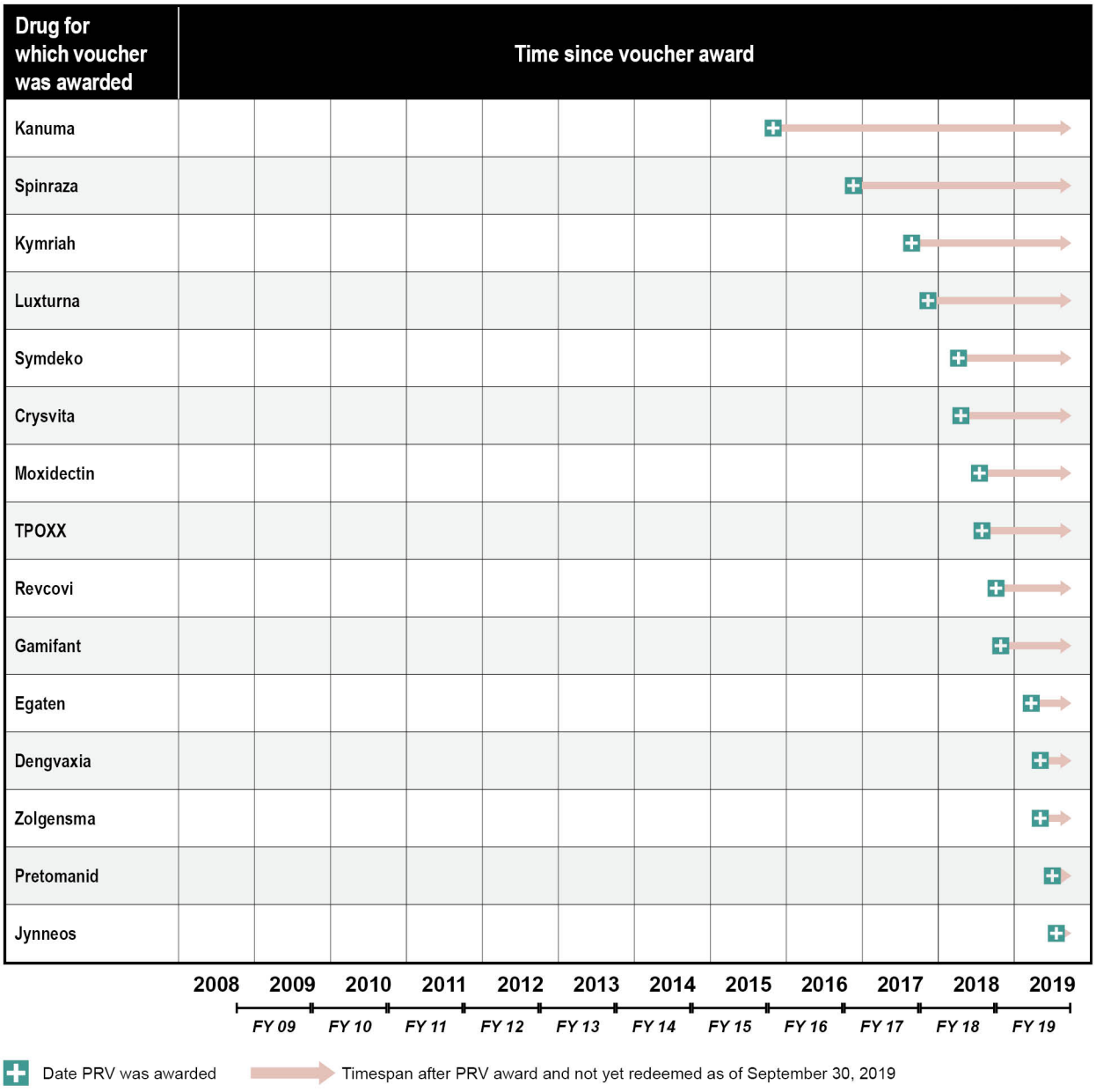
Notes: The drug sponsor awarded the PRV can use or sell the PRV to be redeemed by another drug sponsor. For this figure, PRVs are considered redeemed if FDA has completed review of the drug

application for which they were redeemed or if the company has made public statements regarding its redemption. Additional PRV redemptions, if any, may not be reported in this figure.

Of the 15 PRVs that were not redeemed as of September 30, 2019, 12 were awarded in fiscal years 2018 or 2019, and one was awarded in early fiscal year 2016.[31] (See fig. 7.)

[31]For reporting purposes, PRVs are considered redeemed if FDA has completed review of the drug application for which they were redeemed or if the company has made public statements regarding its redemption. As a result, some PRVs in this report may have been redeemed, but redemption information is not publicly available.

Figure 7: Timespans of Unredeemed Priority Review Vouchers (PRV), by Drug, as of September 30, 2019



Source: GAO analysis of Food and Drug Administration (FDA) data and publicly available information. | GAO-20-251

Notes: The drug sponsor awarded the PRV can use the PRV on a future drug or sell it to be redeemed by another drug sponsor. For this figure, PRVs are considered redeemed if FDA has completed review of the drug application for which they were redeemed or if the company has made public statements regarding its redemption. As a result, some PRVs in this figure may have been redeemed, but redemption information is not publicly available.

Drug sponsors we contacted told us that decisions on when to redeem PRVs are largely strategic and take into consideration their drug development pipeline and market competition. For example, three of the drug sponsors told us they might choose to redeem a PRV to help a drug reach the market faster than a competitor's drug, and two drug sponsors told us they may hold a PRV to use to obtain priority review for a particular drug that is in development. Another drug sponsor told us it considers the likelihood of a drug receiving approval from FDA when deciding when to use a PRV (since the PRV only affects the time frames for FDA's review and does not guarantee approval), and if a drug in its pipeline could receive priority review from FDA on its own merit.

Almost half of the awarded PRVs had not been redeemed as of the end of fiscal year 2019, which may affect FDA's ability to forecast resources needed in the future. In 2016, we reported that FDA told us that the rare pediatric disease PRV program placed a substantial strain on its workload, explaining that performing a priority review on a drug that would otherwise merit a standard review requires the agency to conduct significant work in a compressed time frame.[32] Between fiscal years 2011 and 2018, PRV redemptions have accounted for less than 1 percent of FDA's reviews in any given year, according to FDA.[33] While FDA receives 90 days' notice of a PRV redemption, the notice period may not be enough time to ensure the appropriate staff are available to review a drug application that the agency does not consider to be a public health priority, according to FDA. However, one researcher noted that this uncertainty exists for all drug applications, as FDA cannot know in a given year how many drug applications will be submitted in any particular therapeutic area or how many of these applications will qualify for priority review. Furthermore, two drug sponsors, one researcher, and one stakeholder we spoke with noted that FDA collects additional user fees for PRV redemptions specifically to support the priority review for a drug that would not normally qualify for one. Since fiscal year 2011, FDA has

[32]GAO-16-319, 14.

[33]These include reviews of all original new drug applications, biologics license applications, and efficacy supplements. PRV redemptions accounted for 1.4 percent of all priority reviews conducted in fiscal years 2011 through 2018, according to FDA. Data for fiscal year 2019 were not available at the time of our analysis.

collected almost $44 million in PRV user fees for the 16 redeemed PRVs.[34]

FDA does not track the resources it uses specifically for the PRV programs, so the agency cannot determine if the PRV user fees paid when PRVs are redeemed cover the associated costs. According to FDA, the agency cannot anticipate the therapeutic area for which a PRV will be redeemed, so PRV user fees may not ameliorate the effect of PRV redemptions on the review divisions or provide for rapid hiring of additional review staff with relevant experience and technical expertise. FDA officials told us that each new PRV program—and changes made to existing PRV programs—requires additional resources to implement. The agency reports that the services of over 11 offices within FDA are required to work on some aspect of the PRV programs, which may at times require FDA to shift resources from its public health priorities. According to FDA, the PRV programs also expend and divert agency resources to draft and revise PRV-related guidance; update webpages; research, draft, and publish notices and orders to add or decline to add diseases to the list of eligible tropical diseases; respond to inquiries from sponsors, potential sponsors, investors, attorneys, and other interested individuals; and respond to requests for a rare pediatric disease designation.

[34]Since fiscal year 2011, the user fees, set annually by FDA, have ranged from $2.33 million to $5.28 million. To redeem a PRV, a drug sponsor pays the PRV user fee in addition to other user fees required for all drug applications.

The Few Studies That Examined PRV Programs Found Little or No Effect on Drug Development; Improvements and Alternatives Were Suggested

The Few Studies Examining PRV Programs Found Little or No Effect on Drug Development and Views of the Programs Are Mixed

Our literature review found three studies—one for each of the PRV programs—that examined and drew conclusions about how PRV programs affect drug development; of these, one study found evidence of an effect of a PRV program on drug development.[35] Specifically, it found that drugs to treat rare pediatric diseases, which could be eligible for a rare pediatric disease PRV, were more likely to advance from phase I to phase II clinical trials when compared to rare adult disease drugs.[36] The studies examining the other two PRV programs did not find an effect on drug development.

- **Rare pediatric disease PRV program.** A 2019 study found that the rare pediatric disease PRV program was not associated with an increase in the number or rate of new pediatric disease drugs that started or completed clinical trials. However, the study found that, after the creation of the rare pediatric disease PRV program, drugs the study authors determined could be eligible for a rare pediatric

[35]One additional 2016 study we found concluded that the PRV programs appear to be on track to stimulate drug development, but more time was needed before a conclusion could be made on whether the programs have achieved their goals because of the long drug development cycle. See C. Bialas, E. Higbee-Dempsey, C. Y. Chen, C. Ward, O.A. Marcos-Contreras, D. Mulreany, A.B. Reitz, and D.M. Gross, "Analyzing the FDA Priority Review Voucher Program's Stimulation of Research and Public Health Impact," *Technology Transfer and Entrepreneurship*, vol. 3, no 2 (2016).

[36]Clinical trials are designed to evaluate and test new interventions, such as medications. Clinical trials are generally conducted in three phases, with a fourth phase for some drugs occurring after approval, and each phase has a different purpose. See 21 C.F.R. §§ 312.21 and 312.85 (2019).

disease PRV were more likely to advance from phase I to phase II clinical trials compared to rare adult disease drugs, which are not eligible for a PRV under this program. Additionally, the study found the time it took for drugs to progress to the next stage of development was shorter among drugs eligible for a rare pediatric disease PRV compared to drugs for rare adult diseases, across all three phases of clinical development.[37]

- **Tropical diseases PRV program.** A 2017 study found that this PRV program was not associated with an increase in tropical disease drugs starting clinical testing. The study found the proportion of tropical disease drugs among all drugs in development decreased slightly after the PRV program was created. Study authors suggested the relatively small number of approved tropical disease products in the last decade indicates the PRV program did not serve as a stimulus for completing late-stage drug development.[38]
- **Medical countermeasure PRV program.** A 2018 study reported that 25 of 26 medical countermeasures undergoing clinical trials received direct or indirect public support, such as funding from the Department of Defense. Authors stated that, given the extent to which development of medical countermeasures already occurs via direct or indirect federal funding, alternatives other than the PRV program could better stimulate development of medical countermeasures.[39]

While the few studies of the PRV program found little to no effect on drug development, the seven drug sponsors we contacted told us the PRV programs were an incentive—that is, a factor in their decisionmaking—for drug development. In contrast, the seven researchers and seven

[37]T. Hwang, F. Bourgeois, J.M. Franklin, and A.S. Kesselheim, "Impact Of The Priority Review Voucher Program On Drug Development For Rare Pediatric Diseases," *Health Affairs*, vol. 38, no 2 (2019).

[38]N. Jain, T. Hwang, J.M. Franklin, and A.S. Kesselheim, "Association of the Priority Review Voucher with Neglected Tropical Disease Drug and Vaccine Development," *JAMA,* vol. 318, no. 4 (2017). The study found that the tropical disease PRV program was not associated with an increase in innovative, early-stage development for neglected tropical disease drugs starting clinical testing. While this study examined new drugs for neglected tropical diseases entering phase I clinical trials before and after the creation of the tropical disease PRV program, it did not examine whether PRVs encouraged companies with drugs already in development into phase II and phase III clinical trials.

[39]M.S. Sinha, N. Jain, T. Hwang, and A.S. Kesselheim, "Expansion of the Priority Review Voucher Program under the 21st Century Cures Act: Implications for Innovation and Public Health," *American Journal of Law and Medicine*, vol. 44 (2018).

stakeholders we contacted reported mixed views of the PRV programs as an incentive for drug development.

- **Drug sponsors.** All seven drug sponsors told us the PRV programs were a factor in drug development decisions—six sponsors said it was one of a number of factors, and one sponsor said it was pivotal in its development of a drug. For example, three drug sponsors told us PRVs were important to help fund drug development and one of these drug sponsors told us the PRV program supported its decision to move a drug already under development to market. Four drug sponsors told us PRV programs may be a more significant incentive for small drug sponsors, with one small, nonprofit drug sponsor noting that it entirely relied on the profits from the sale of its PRV to ensure its drug would become available to those who need it. Additional factors drug sponsors reported considering included whether the sponsor has a drug in their development pipeline that could particularly benefit from a PRV, and whether its drug development program has public financial support, such as direct federal funding.
- **Researchers.** The seven researchers reported mixed views of the PRV programs as an incentive for drug development, and their perceptions of the three programs varied. For example, when asked to describe the incentive for drug development provided by the tropical disease PRV program, two researchers described it as “not significant,” and two researchers described it as “somewhat significant.” However, one of these researchers told us the tropical disease PRV program encouraged drug development, particularly for diseases such as tuberculosis and malaria for which a drug is potentially more commercially viable. Regarding the rare pediatric disease PRV program, three researchers told us they have heard anecdotally that the program is an incentive to develop or continue development of rare pediatric disease drugs. In contrast, one researcher told us many drug sponsors have received a rare pediatric disease PRV for drugs they would have produced anyway, and another told us he did not believe the rare pediatric disease PRV provided an adequate incentive for adding new drugs into a drug sponsor’s pipeline. Finally, four researchers told us it was too early to evaluate the medical countermeasure PRV program as an incentive.
- **Stakeholders.** The seven stakeholders also reported mixed views on the PRV programs as an incentive for drug development. For example, one stakeholder told us that drug sponsors have entered particular drug development areas because of the PRV programs, and the PRV program has been pivotal to the financial planning of small drug sponsors working in the medical countermeasures and rare

pediatric disease spaces. In contrast, two other stakeholders told us the PRV programs are an incentive to obtain FDA approval for a drug that has already been developed and marketed outside of the United States but are not an incentive for developing new drugs.[40] One of these stakeholders and an additional stakeholder also noted that PRVs are often a source of additional revenue to drug sponsors that would have developed their PRV drug anyway and did not need the PRV to finance drug development.

The number of PRVs awarded by FDA could influence the effectiveness of the PRV programs as incentives, according to several drug sponsors, researchers, and stakeholders we contacted. Specifically, some indicated that the potential revenue from the sale of a PRV could decline if more PRVs are awarded, and there is an increased supply of PRVs available for sale. Specific comments included the following:

- One drug sponsor told us that, while the number of PRVs on the market was a concern, they have remained valuable. Another drug sponsor told us it was not concerned with the relative value of PRVs, because it did not plan to sell its remaining PRVs and would purchase more in the future if PRVs would benefit drugs in its pipeline.
- One researcher told us lower prices for PRVs merited concern, because the PRV alone might not be sufficient to motivate drug development. The researcher indicated that a drug would also need either sufficient sales or additional government incentives.
- Two stakeholders told us the sales prices of PRVs (and potential revenue from selling them) might be more of a concern for small drug sponsors than large drug sponsors, as these stakeholders told us small drug sponsors are more likely to sell their PRV instead of using it for another drug in their portfolio.

Drug sponsors, researchers, and stakeholders we contacted also reported mixed views on whether the rare pediatric disease and medical countermeasure PRV programs—set to expire by 2022 and 2023,

[40]To qualify for the tropical disease PRV program, applications must contain reports of one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and conducted or sponsored by the sponsor, and an attestation from the sponsor that such reports were not submitted as part of an application for marketing approval or licensure by a regulatory authority in India, Brazil, Thailand, or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme prior to September 27, 2007. This may preclude certain drugs that were developed and marketed outside of the United States prior to 2007 from tropical disease PRV program eligibility.

respectively—should be reauthorized. While FDA officials reported that, as of April 2019, the agency does not have a position on the reauthorization of these two PRV programs, drug sponsors generally indicated support for their reauthorizations, with some noting that PRV program expirations may negatively affect overall drug development and the willingness of drug sponsors to work in these areas. The researchers we contacted offered mixed opinions on reauthorization. For example, one recommended reauthorizing both PRV programs, but indicated that his opinion could change if a better incentive was developed. In contrast, another researcher supported the expiration of these two programs, noting that their expiration could ultimately raise the potential revenue from the sale of an available PRV and could also make the tropical disease PRV program, which does not require reauthorization, more popular to encourage drug development. Most stakeholders we contacted did not offer a clear opinion on reauthorization; those that did generally supported reauthorization.

Drug Sponsors, Researchers, and Stakeholders Suggested Improvements and Alternatives to the PRV Programs

Drug sponsors, researchers, and stakeholders we contacted suggested several improvements to the PRV programs, including those described below.

- **Require innovation for PRV-eligible drugs.** Two researchers and two stakeholders noted that the PRV programs, particularly the tropical disease PRV program, have been criticized for not providing incentives for innovation and suggested PRV awards be limited to drugs new to the global market.[41] Currently, drug sponsors can receive a PRV for a drug that has already been developed and marketed outside of the United States, but which qualifies for a PRV because the drug has not been approved for marketing in the United States.[42] One researcher suggested the federal government should not provide an incentive, like a PRV, for drugs already in existence outside of the United States, for which most research and development was already completed. However, one drug sponsor told us that requiring a tropical disease drug to be approved first in the United States to qualify for a PRV would delay entry of the drug into

[41]We did not determine the extent to which awarded PRVs were for drugs that were not new to the global market.

[42]A drug may be disqualified if its active ingredient has been previously approved by FDA in another drug application. FDA does not evaluate whether the active ingredient is in use outside of the United States.

the international markets that need it the most. Additionally, two stakeholders told us that drugs that have already been developed may have significant benefits to patients when combined or used to treat other diseases.

- **Require drug sponsors to guarantee access to PRV-eligible drugs.** One researcher and two stakeholders suggested drug sponsors submit an access plan to help ensure the drug reaches the populations in need of the treatment, and one drug sponsor suggested they supply at cost the drugs for which the PRV was awarded. One of these stakeholders noted that a weakness of the PRV program is that drug sponsors awarded a PRV have no obligation to make the approved drug available at an affordable price. It suggested that requiring an access plan may result in drugs for which a PRV was awarded being more available and accessible to the populations that need them. However, three stakeholders noted that FDA may not have the resources or authority to enforce such access commitments.
- **Limit PRVs to drug sponsors with financial need.** One drug sponsor and one researcher suggested awarding a PRV only to drug sponsors that financially require it to develop their drug, such as a nonprofit organization that must leverage potential revenue from the PRV to help offset drug development costs.
- **Make administrative changes.** One drug sponsor told us FDA's process for determining the list of tropical diseases eligible for a PRV was not transparent and wanted clarification on FDA's timeline for editing this list.[43] Another drug sponsor told us it wanted clarification on whether a drug would merit priority review on its own, so the sponsor could determine whether to redeem a PRV for that drug.[44]

In addition to suggesting improvements to the PRV programs, drug sponsors, researchers, and stakeholders we contacted, as well as our

[43]FDA maintains a public docket in which interested parties can submit suggestions for the list of tropical diseases that qualify for a PRV. According to FDA's website, FDA reviews this public docket on an ongoing basis and intends to publish its decisions in the Federal Register four times per year.

[44]This drug sponsor also suggested allowing user fees for rare pediatric disease PRV redemptions to be paid upon the sponsor's submission of the PRV drug to FDA for review—as they are for the tropical disease and medical countermeasure programs—rather than when the drug sponsor notifies FDA of its intent to use the PRV. It suggested this change would prevent drug sponsors from losing their PRV user fees if they do not submit the drug application after notifying FDA it had intended to use the PRV. According to FDA, this change would require a statutory amendment.

literature review, identified potential alternatives to the PRV programs that provide incentives for drug development (see table 2).

Table 2: Potential Alternative Incentives for Drug Development According to Selected Drug Sponsors, Researchers, Stakeholders, and Literature

	Incentive	Description
Push incentives Incentives that reduce research and development costs to drug sponsors	Tax credits on research and development	Credits allowing pharmaceutical companies to deduct a percentage of qualifying research and development costs from the company's tax liability
	Direct federal funding or grant	Subsidies offered to organizations for the research and development of novel drugs
	Product development partnerships or public-private partnership	A collaborative agreement to share development risk and reward between a public or quasi-public organization and one or more private developers
Pull incentives Incentives that increase the market reward perceived by drug sponsors as they embark on a research and development program	Market exclusivity[a]	Certain delays and prohibitions on approval of competitor drugs available upon approval of a drug
	Advanced market commitment	An agreement to fully or partially finance the purchase of a specified amount of a medical product at a pre-arranged price, prior to its development
	Prize for successful research	A monetary reward that encourages the development of drugs in a particular area
	Patent extension	An extension of a property right granted by the United States Patent and Trademark Office anytime during the development of a drug

Source: GAO analysis of interviews conducted and literature reviewed. | GAO-20-251

Notes: This table presents information on potential alternative incentives to the priority review voucher programs to encourage development of drugs for tropical diseases, rare pediatric diseases, and medical countermeasures. These alternatives were identified by drug sponsors, researchers, and stakeholders we contacted, as well as in studies we reviewed.

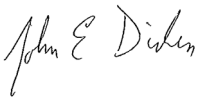
[a]Two drug sponsors, a researcher, and two stakeholders referred to transferrable exclusivity, in which market exclusivity rights can be transferred to another drug in the sponsor's portfolio.

Agency Comments

We provided a draft of this report to HHS for review and comment. HHS provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the appropriate congressional committees, the Secretary of Health and Human Services, and other interested parties. In addition, the report is available at no charge on GAO's website at http://www.gao.gov/.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or dickenj@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix IV.



John E. Dicken
Director, Health Care

Appendix I: Priority Review Vouchers (PRV) Awarded by the Food and Drug Administration

Table 3: Characteristics and Transfer Status of Awarded Priority Review Vouchers (PRV) as of September 30, 2019

Date PRV was awarded	Drug name Drug sponsor	Indication	Transfer status	Sale date	PRV purchaser[a]	Sales price (dollars in millions)
Tropical disease PRVs						
April 2009	Coartem Novartis Pharmaceuticals Corporation	Treatment of acute, uncomplicated malaria infections	✗	—	—	—
December 2012	Sirturo Janssen Pharmaceutical Companies	Treatment of pulmonary multi-drug resistant tuberculosis	✗	—	—	—
March 2014	Impavido Paladin Therapeutics, Inc.[b]	Treatment of various leishmaniasis strains	✓	November 2014	Gilead Sciences, Inc.	125
June 2016	Vaxchora Pax Vax Bermuda Ltd.	Indicated for use as a cholera vaccine for travelers	✓	June 2016	Gilead Sciences, Inc.[c]	290
August 2017	Benznidazole Chemo Research S.L.	Treatment of Chagas disease	✓	Unknown	Novo Nordisk Inc.	Unknown
June 2018	Moxidectin Medicines Development for Global Health	Treatment of onchocerciasis, also known as river blindness	✓	May 2019	Novo Nordisk Inc.	Unknown
July 2018	Krintafel GlaxoSmithKline	To prevent relapse of Plasmodium vivax malaria	✗	—	—	—
February 2019	Egaten Novartis Pharmaceuticals Corporation	Treatment of fascioliasis	✗	—	—	—
May 2019	Dengvaxia Sanofi	Prevention of dengue disease	✗	—	—	—
August 2019	Pretomanid The Global Alliance for TB Drug Development (TB Alliance)	Treatment of multidrug resistant pulmonary tuberculosis	✗	—	—	—
Rare pediatric disease PRVs						
February 2014	Vimizim BioMarin Pharmaceutical Inc.	Treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)	✓	July 2014[d]	Sanofi	67.5

Date PRV was awarded	Drug name Drug sponsor	Indication	Transfer status	Sale date	PRV purchaser[a]	Sales price (dollars in millions)
March 2015	Unituxin United Therapeutics Corporation	Treatment of children with high risk neuroblastoma	✓	August 2015	AbbVie Inc.	350
March 2015	Cholbam Asklepion Pharmaceuticals, LLC	Treatment of (1) bile acid synthesis disorders due to single enzyme defects, and (2) peroxisomal disorders	✓	May 2015	Sanofi[e]	245
September 2015	Xuriden Wellstat Therapeutics Corporation	Treatment of hereditary orotic aciduria	✓	September 2015	Teva Pharmaceutical USA, Inc.[f]	Unknown
October 2015	Strensiq Alexion Pharmaceuticals Inc.	Treatment of hypophosphatasia (HPP)	✗	—	—	—
December 2015	Kanuma Alexion Pharmaceuticals Inc.	Treatment of Lysosomal Acid Lipase (LAL) deficiency	✗	—	—	—
September 2016	Exondys 51 Sarepta Therapeutics, Inc.	Treatment of Duchenne muscular dystrophy (DMD) in patients with a DMD gene mutation	✓	February 2017[g]	Gilead Sciences, Inc.	125
December 2016	Spinraza Biogen, Inc.	Treatment of spinal muscular atrophy	✗	—	—	—
February 2017	Emflaza Marathon Pharmaceuticals, LLC	Treatment of Duchenne muscular dystrophy (DMD)	✓	Between February and June 2017	ViiV Healthcare Company[h]	130
April 2017	Brineura BioMarin Pharmaceutical Inc.	Treatment of tripeptidyl peptidase 1 (TPP1) deficiency (Batten disease)	✓	November 2017	Novartis Pharmaceuticals Corporation[i]	125
August 2017	Kymriah Novartis Pharmaceuticals Corporation	Treatment of B-cell precursor acute lymphoblasticleukemia (ALL) that is refractory or in second or later relapse	✗	—	—	—
November 2017	Mepsevii Ultragenyx Pharmaceutical Inc.	Treatment of mucopolysaccharidosis type VII (MPS VII, Sly syndrome)	✓	December 2017	Novartis Pharmaceuticals Corporation	130
December 2017	Luxturna Spark Therapeutics, Inc.	Treatment of biallelic RPE65 mutation-associated retinal dystrophy	✓	April 2018	Jazz Pharmaceuticals plc	110

Date PRV was awarded	Drug name Drug sponsor	Indication	Transfer status	Sale date	PRV purchaser[a]	Sales price (dollars in millions)
February 2018[j]	Symdeko Vertex Pharmaceuticals Inc.	Treatment of cystic fibrosis with certain mutations	✗	—	—	—
April 2018	Crysvita Ultragenyx Pharmaceutical Inc.	Treatment of X-linked hypophosphatemia (XLH)	✓	June 2018[k]	Gilead Sciences, Inc.	80.6
June 2018	Epidiolex GW Research, Ltd.	Treatment of seizures associated with Lennox Gastaut-Syndrome and Dravet syndrome	✓	April 2019	Biohaven Pharmaceuticals, Inc.[l]	105
October 2018	Revcovi Leadiant Biosciences, Inc.	Treatment of adenosine deaminase-severe combined immunodeficiency (ADA-SCID)	✗	—	—	—
November 2018	Gamifant Novimmune S.A.	Treatment of primary hemophagocytic lymphohistiocytosis (HLH)	✓	July 2019	AstraZeneca[m]	95
May 2019	Zolgensma Avexis, Inc.	Treatment of pediatric patients with spinal muscular atrophy (SMA)	✗	—	—	—
Medical countermeasure PRV						
July 2018	TPOXX SIGA Technologies, Inc.	Treatment of smallpox disease	✓	November 2018	Eli Lilly and Company	80
September 2019	Jynneos Bavarian Nordic A/S	Prevention of smallpox and monkeypox	✗	—	—	—

Legend: ✓ = transferred from original drug sponsor; ✗ = no public announcement of transfer; — = not applicable.

Source: GAO analysis of Food and Drug Administration (FDA) information and publicly available accounts of PRV sales information. | GAO-20-251

Notes: This table presents known award and transfer information for PRVs as of Sept. 30, 2019. FDA is notified of rare pediatric disease PRV sales when a PRV is transferred to another drug sponsor; however, the agency may only learn of tropical disease PRV and medical countermeasure PRV sales or transfers when a PRV is redeemed by another drug sponsor. As a result, FDA may not have information on these PRV sales or transfers if the PRVs have not yet been redeemed. Additionally, PRV sales prices are not reported to FDA. A complete list of indications is not included for the drugs in the table; please refer to drug labeling for complete information.

[a]PRV purchaser indicates the PRV owner as of Sept. 30, 2019.

[b]Paladin Therapeutics, Inc. submitted a new drug application for Impavido in April 2013. In February 2014, Endo Health Solutions, Inc. acquired Paladin Therapeutics, Inc. From this transaction, Knight Therapeutics, Inc., a subsidiary of Paladin Therapeutics, formed as a new independent company. Knight Therapeutics, Inc. subsequently received rights to Impavido and the awarded PRV.

[c]PaxVax Bermuda Ltd. announced that it sold its PRV in 2016 to an undisclosed purchaser. In a Securities and Exchange Commission filing, the company disclosed that it sold its PRV for $290 million in 2016. Gilead Sciences, Inc. indicates in Securities and Exchange Commission filings that it purchased a PRV in the second quarter of 2016, meaning sometime between April 1 and June 30, 2016.

[d]In a press release, BioMarin Pharmaceutical Inc. announced that it had sold a PRV for $67.5 million.

[e]In January 2015, Retrophin, Inc. entered into an agreement with Asklepion Pharmaceuticals, LLC to acquire the rights and ownership of assets related to cholic acid, the active ingredient in Cholbam, upon FDA approval. The drug was approved as Cholbam in March 2015. In May 2015, Retrophin, Inc. announced that it had sold the PRV to Sanofi for $245 million.

[f]Wellstat Therapeutics Corporation announced that it had sold the PRV to AstraZeneca, but it did not disclose the sales price. In a Securities and Exchange Commission filing, Teva announced that it had redeemed a PRV for fremanezumab, approved as Ajovy. Teva reported purchasing the PRV for $150 million but did not identify the seller. It is unknown if the PRV was transferred additional times before it was redeemed by Teva.

[g]Sarepta Therapeutics, Inc. disclosed in a press release that it sold a PRV for $125 million.

[h]ViiV Healthcare Company announced in a press release that it used a PRV it purchased for $130 million when it redeemed a PRV for the drug Juluca.

[i]BioMarin Pharmaceutical Inc. announced in a press release that it sold the PRV for $125 million.

[j]FDA initially declined to award a rare pediatric disease PRV when Symdeko was approved but later determined that the PRV should have been granted. FDA considers February 2018 the date the PRV was awarded, as it was the date the PRV was earned by the sponsor.

[k]Ultragenyx sold the PRV awarded for Crystiva for $80.6 million in June 2018, according to a Securities and Exchange Commission filing.

[l]GW Research, Ltd. announced in a March 2019 press release that it sold its PRV for $105 million. On the same day, Biohaven Pharmaceuticals, Inc. announced it purchased a PRV for $105 million.

[m]In July 2019, Sobi announced that it gained access to the PRV from Novimmune SA as part of an acquisition of Gamifant-related assets. In August 2019, Sobi announced that it had sold the PRV to AstraZenca for $95 million.

Appendix II: Redeemed Priority Review Vouchers (PRV)

Table 4: Characteristics of Redeemed Priority Review Vouchers (PRV) as of September 30, 2019

Redemption date	Redeeming drug sponsor	Drug and indication	Date original PRV was awarded	Drug sponsor originally awarded PRV
Tropical diseases PRVs				
February 2011	Novartis Pharmaceuticals Corporation	Ilaris Treatment of gouty arthritis	April 2009	Novartis Pharmaceuticals Corporation
July 2015	Gilead Sciences, Inc.	Odefsey Treatment of HIV-1 infection	March 2014	Paladin Therapeutics, Inc.
November 2016	Janssen Pharmaceutical Companies	Tremfya Treatment of adult patients with moderate-to-severe plaque psoriasis	December 2012	Janssen Pharmaceutical Companies
June 2017	Gilead Sciences, Inc.	Biktarvy Treatment of HIV-1 infection	June 2016	Pax Vax Bermuda Ltd.
October 2018	ViiV Healthcare Company[a]	Dovato Treatment of HIV-1 infection	July 2018	GlaxoSmithKline
March 2019	Novo Nordisk Inc.	Rybelsus An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	August 2017	Chemo Research, S.L.
Rare pediatric disease PRVs				
November 2014	Sanofi	Praluent A lipid altering agent	February 2014	BioMarin Pharmaceutical Inc.
December 2015	Sanofi	Soliqua Long-acting human insulin analog	March 2015	Asklepion Pharmaceuticals, LLC
June 2017	ViiV Healthcare Company	Juluca Treatment of HIV-1 infection	February 2017	Marathon Pharmaceuticals, LLC
October 2017	Teva Pharmaceuticals USA, Inc.	Ajovy Preventive treatment of migraine in adults	September 2015	Wellstat Therapeutics Corporation
March 2018	Novartis Pharmaceuticals Corporation	Mayzent Treatment of relapsing forms of multiple sclerosis (MS)	April 2017	BioMarin Pharmaceutical Inc.
June 2018	Alexion Pharmaceuticals Inc.	Ultomiris Treatment for adults with paroxysmal noctural hemoglobinuria	October 2015	Alexion Pharmaceuticals Inc.
December 2018	AbbVie Inc.	Rinvoq Treatment of adults with moderately to severely active rheumatoid arthritis	March 2015	United Therapeutics Corporation

Redemption date	Redeeming drug sponsor	Drug and indication	Date original PRV was awarded	Drug sponsor originally awarded PRV
April 2019	Gilead Sciences, Inc.	Descovy To reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV	September 2016	Sarepta Therapeutics, Inc.
February 2019	Novartis Pharmaceuticals Corporation	Beovu For the treatment of wet age-related macular degeneration (AMD)	November 2017	Ultragenyx Pharmaceutical Inc.
April to June 2019	Biohaven Pharmaceuticals, Inc.	rimegepant Zydis orally dissolving tablets (ODT) For acute and preventive treatment of migraine	June 2018	GW Research, Ltd.

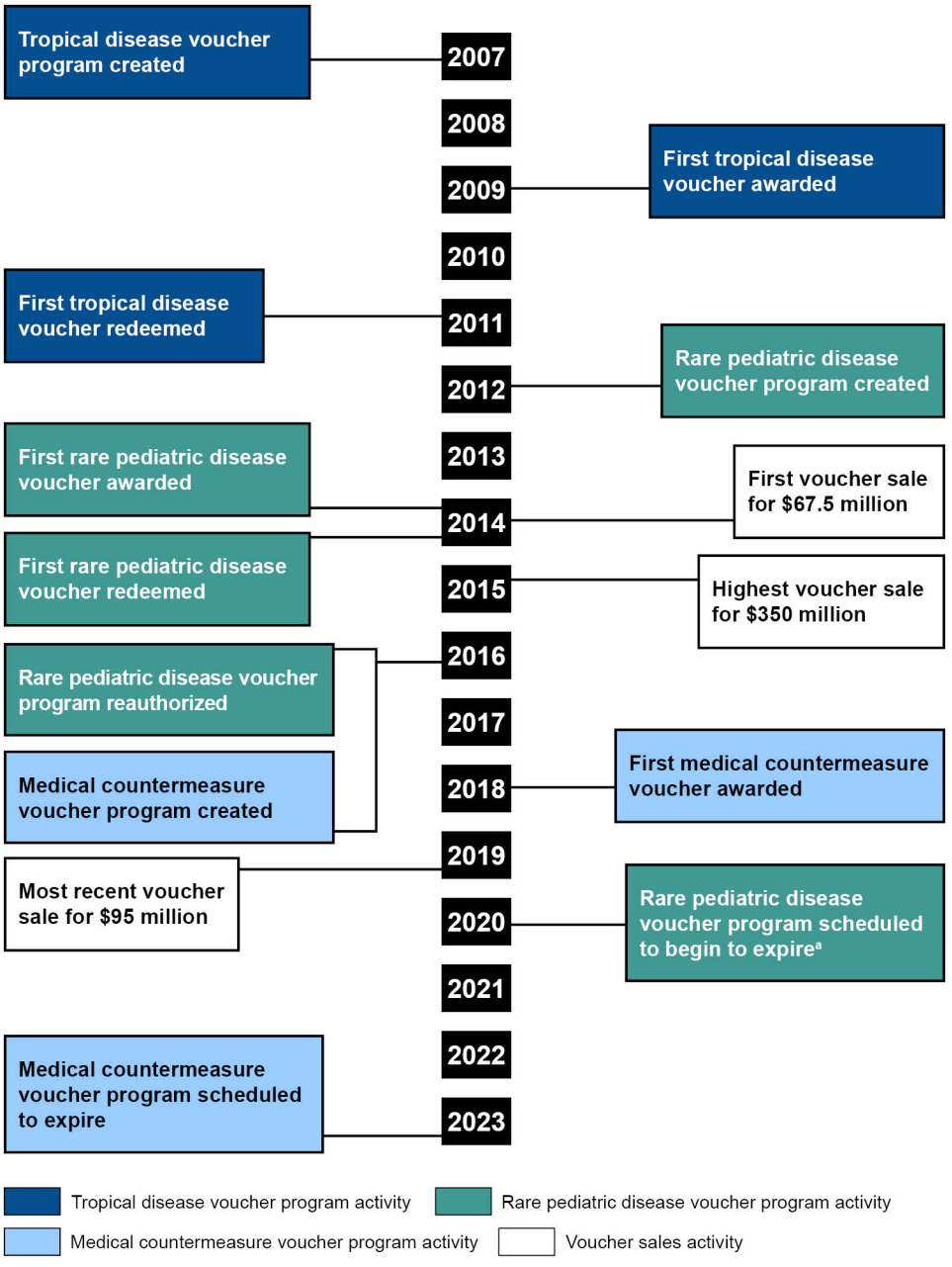
Source: GAO analysis of Food and Drug Administration (FDA) data and publicly available information. | GAO-20-251

Note: For this table, PRVs are considered redeemed if FDA has completed review of the drug application for which they were redeemed or if the company has made public statements regarding its redemption. Additional PRV redemptions, if any, may not be reported in this table. A complete list of indications is not included for the drugs in the table; please refer to drug labeling for complete information.

[a]ViiV Healthcare is majority owned by GlaxoSmithKline.

Appendix III: Key Milestones of the Priority Review Voucher Programs

Figure 8: Key Milestones of the Priority Review Voucher Programs



Source: GAO analysis of priority review voucher related legislation, Food and Drug Administration (FDA) data on awarded and redeemed priority review vouchers, and publicly available information on priority review voucher sales. | GAO-20-251

[a]FDA may not award any rare pediatric disease priority review vouchers after September 30, 2020, unless the drug has received a rare pediatric disease designation by that date, and FDA has approved the drug application by September 30, 2022.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

John E. Dicken at (202) 512-7114 or dickenj@gao.gov

Staff Acknowledgments

In addition to the contact named above, Kim Yamane (Assistant Director), Erin C. Henderson (Analyst-in-Charge), Kaitlin Farquharson, Laurie Pachter, Vikki Porter, Helen Sauer, Meghan Shrewsbury, and Merrile Sing made key contributions to this report. Also contributing were Leia Dickerson, Hayden Huang, and Yesook Merrill.

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Strategic Planning and External Liaison

James-Christian Blockwood, Managing Director, spel@gao.gov, (202) 512-4707
U.S. Government Accountability Office, 441 G Street NW, Room 7814,
Washington, DC 20548

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COMMENTARY

Priority Review Vouchers: GAO Report Provides Scant Evidence of Success

Robert J. Meyer[1,2,*]

Priority Review Voucher (PRV) programs are in place to provide incentives for drug development in areas of unmet need where traditional incentives are felt to be insufficient. PRV incentives were first passed into law in 2007 for neglected tropical diseases and subsequently expanded to rare pediatric diseases and medical countermeasures. In 2016, Congress tasked the Government Accounting Office (GAO) to conduct a "study addressing the effectiveness and overall impact of the…priority review voucher programs." That report was published recently and as it provides weak evidence of "overall impact," it deserves scrutiny by policy makers and legislators as they consider the value of PRV incentives in driving targeted therapeutic innovation.[1]

COMMENTARY

In 2006, faculty from Duke University published an article proposing that the US government adopt a novel program to incentivize therapeutic development in neglected tropical infectious diseases. The article posited that existing incentives were insufficient to attract drug development in these disease due to inadequate US market size resulting in insufficient projected revenues to offset the substantial costs of clinical development.[2] Existing incentives at that time included government cost-sharing in development ("push" incentives; e.g., orphan drug grants) and extending periods of data exclusivity ("pull" incentives; e.g., orphan drug exclusivity). Importantly, these incentives impart economic cost to the government and taxpayers, either directly, such as with grants, or indirectly by delaying generic competition given longer market exclusivity.

The 2006 paper proposed a new incentive where drugs that treated certain designated tropical diseases, upon US Food and Drug Administration (FDA) approval, would be granted a transferable voucher for a "Priority Review." These vouchers would allow the holder to submit a subsequent application to the FDA for a non-priority drug (i.e., either not treating a serious condition and/or not an important therapeutic advance) and yet receive a 6-month "priority" review period rather than the standard 10-month review. The authors posited that getting to market 4 months earlier could be worth US $300 million or more, providing a large potential economic value to the grantee that could be realized by exercising it for another of their own drug programs or through sale of the voucher. The paper also stated that unlike traditional push and pull incentives, PRVs would provide a public good without costs to the government, beyond those needed for the FDA to do an expedient review. Following this publication, Congress passed a PRV program for neglected tropical diseases in 2007. Congress later expanded PRVs to rare pediatric diseases and to medical countermeasures. The first PRV was granted by the FDA in 2009; 31 total PRVs were awarded through 2019, yet only 16 have been redeemed (**Figure 1**). Of note, the majority of these PRV grants and redemptions have been in the last 5 years.

As a part of the 2016 law called the 21st Century Cures Act, Congress required the GAO to evaluate the PRV programs; the GAO published its report in January 2020. The report is intended to inform future congressional actions regarding any renewal of existing PRV programs (the pediatric PRV program begins sunsetting at the end of fiscal year (FY)2020, medical countermeasures PRVs in 2023) or expanding PRVs to other areas. The report provides a mixed picture of the value of these incentive programs, with little evidence PRVs truly drive new drug development. Further, the report offers no clear conclusions on the actual "costs" to the FDA and its overall mission. As Congress considers future legislation on PRVs, there are several points related to the assumptions of the 2006 paper, the subsequent changes in the drug development and the regulatory environment, and the findings by the GAO that are important to consider. Some of these are discussed below.

The 2006 paper proposed that the value of obtaining market approval 4 months early upon redeeming a voucher could be worth US $322 million, importantly offsetting the costs of clinical development for a designated product. Although the paper expressed uncertainties on what that actual value might prove to be, it stated the figure could be considerably higher. The GAO report found that whereas one early PRV sold for US $350 million, the publicly available data on the 9 PRVs sold since 2017 showed prices paid between $80 and $130 million, a far lower number. Although the prices paid may not be a perfect measure of overall value, particularly as many PRVs have not been sold or redeemed, the prices support that the original paper's assumptions were significant overestimates and therefore the financial incentives are not as robust as assumed when the PRVs were first legislated.

[1]Public Health Sciences, University of Virginia School of Medicine, Charlottesville, Virginia, USA; [2]Drug and Biologics Consulting, Greenleaf Health, Charlottesville, Virginia, USA. *Correspondence: Robert J. Meyer (rjm7cd@virginia.edu)
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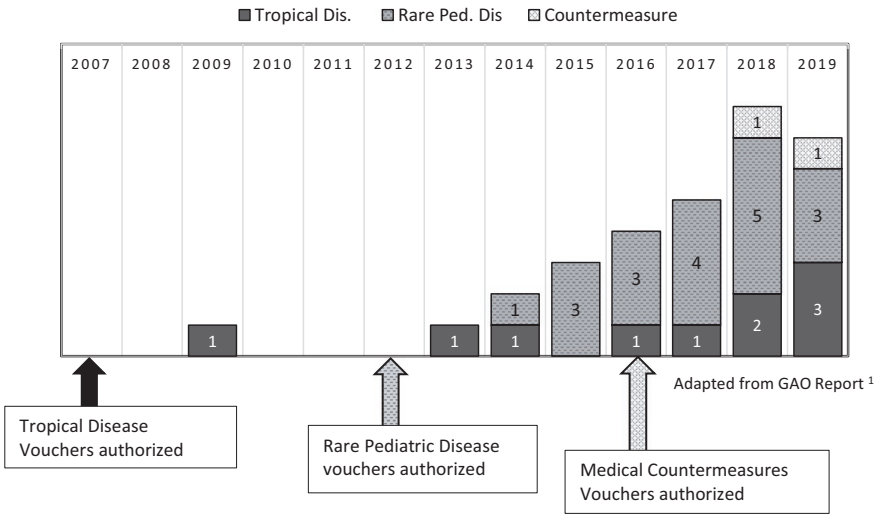

Figure 1 Number and types of priority review vouchers granted fiscal year (FY)2009–2019. GAO, Government Accounting Office.

A measure of success of these incentives is the robustness of PRVs granted and clinical development in the relevant disease areas (see **Figure 1**). In the 13 years PRVs have been in place for neglected tropical diseases, the report states that only 10 vouchers have been awarded. One analysis cited in the report states that in years since the first PRV legislation, the proportion of drugs in development for the designated tropical diseases has marginally decreased relative to the general development pipeline.[3] The lack of a proportional increase in development and the paucity of vouchers granted for tropical diseases suggest the PRVs have not had a significant impact. For medical countermeasures against biological threats, only two PRVs have been granted to date. On the other hand, the recent efforts by Biomedical Advanced Research and Development Authority (BARDA) and the administration on "Project Warp Speed" to rapidly develop coronavirus disease 2019 (COVID-19) vaccines provides a striking example of how aggressive and directed application of more traditional push incentives may produce timely and robust results.[4]

The most successful PRV program in terms of PRVs awarded has been in rare pediatric diseases, with 19 PRVs awarded since that program was instituted in 2012. One important point is that 7 of these 19 were granted by 2016. With fewer than 4 years from legislation to the FDA approvals for which these 7 vouchers were granted, the relevant drugs were likely well into development when the program started, as clinical development commonly lasts 6–7 years.[5] For at least these seven drugs, the incentives were likely not a factor in initiating development. Indeed, another study cited by the report found no effect of the rare pediatric disease program on drugs entering or successfully completing development for relevant diseases.[6]

It is important to understand that rare diseases already had existing incentives, notably orphan drug incentives, which include both broader and longer exclusivity periods than standard drugs (pull incentives), as well as tax breaks and clinical development grants (push incentives). Given the GAO's findings, it seems likely that providing stronger traditional incentives for pediatric drug development could be more successful than PRVs. Further, unlike assumed in the 2006 paper, recent market trends show that products approved for rare pediatric diseases may be able to garner significant United States revenue For instance, the average annual pricing of drugs approved under the Orphan Drug programs was reported to be over US $180,000 in 2018.[7] Many of the drugs granted rare pediatric disease PRVs are reportedly priced considerably higher than that, with the highest price reported for a drug granted a PRV of ~ $2.1 million (a gene therapy for spinal muscular atrophy, albeit this is a one-time administration).[8] Although the GAO report does not delve into ultimate pricing of products granted PRVs, it is important to consider if PRVs are still needed in driving development, particularly in rare pediatric diseases. Notably, the report cites discussions with seven sponsors granted PRVs. These sponsors reported that whereas PRVs were a factor in development decisions, only one sponsor reported that the prospect of a PRV was a primary factor in moving a drug into pediatric development.

Besides assumptions on value and effectiveness, another important consideration are the costs of the programs to the FDA. The GAO report considers the US $44 million of additional User Fees collected for the 16 redeemed PRVs as a potential balance to any associated resources needed to conduct these expedient reviews. However, the report further notes that the FDA does not track resources in a way that allowed for an analysis of the sufficiency of this offset. Regardless, one must understand that the FDA is not rife with spare capacity. First, the FDA is chronically under-resourced in its professional staff, due to issues with both hiring and retention.[9] Further, the agency cannot hire flexibly to meet surges in workload. This reality is further compounded by the FDA not being able to predict when or in what therapeutic area a PRV may be redeemed. To meet the demands when a voucher is redeemed, the FDA has to shift resources away from other important activities, such as authoring new product guidances or providing additional interaction sponsors. Although not having data on

the "costs" of a redeemed voucher to the drug review program, the report states that the administration of the PRV programs imposes its own demands on the FDA, including drafting PRV-related guidance, writing regulations to modify the eligible diseases, and responding to requests for rare pediatric disease designations. Whereas not explicitly considered in the report, the fundamental basis of the program is tantamount to putting the FDA service up for sale to the highest bidder. Any perception of such is particularly problematic, as critics have implied that user fees themselves have made the FDA more beholden to sponsors, leading to an increase in drug safety issues.[10] Although this author disagrees with this implication, trust in the FDA's independence is critical to the public trust in the safety and efficacy of US therapeutics.

In summary, the GAO report provides little evidence that the PRV programs have significantly incentivized development in the three areas where PRVs are currently in place. In considering renewal of the Rare Pediatric and/or the Medical Countermeasure PRV programs and/or any potential expansion of the PRV programs to other disease areas, it is critical for Congress to assess the true burden and costs of the program for the FDA in a way the GAO could not and the impact of PRVs on the FDA's mission, particularly since the GAO report shows weak evidence of PRVs truly incentivizing development. Further, critical appraisals of PRV incentives must include assumptions that reflect contemporary evidence development drivers, how drug development and regulatory review have changed since 2007, as well as experience with drug pricing of products granted PRVs, rather than continuing to rely on assumptions from an analysis authored in 2006 that appear to no longer fully hold.

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PATIENTS FOR AFFORDABLE DRUGS NOW™

Statement of David E. Mitchell
Founder, Patients For Affordable Drugs Now

to the

Subcommittee on Health

of the

United States House Of Representatives Energy and Commerce Committee

for a hearing on

"Legislative Proposals to Support Patients with Rare Diseases"

February 29, 2024

Section I. Background and Introduction

I want to thank you for holding this hearing "to discuss solutions to support patients living with rare diseases." I am one of those patients. My name is David Mitchell. I am the founder of Patients For Affordable Drugs Now. We are the only national patient advocacy organization focused exclusively on policies to lower prescription drug prices. We are independent, bipartisan and we don't accept funding from any organizations that profit from the development or distribution of prescription drugs.

Since we launched seven years ago, we have collected over 34,000 stories[1] from patients across all 50 states struggling to pay high drug prices. And we have built a community of over three-quarters of a million patients and allies supporting policies to lower drug prices.

More importantly for today, I am a rare disease patient. I have a rare, incurable blood cancer, and prescription drugs are keeping me alive — literally.

My oncologists currently have me on a four-drug combination of infused and oral cancer drugs. These four drugs carry a combined list price of more than $1 million per year. Just one of my

[1] (2024, February 26). *Patients For Affordable Drugs Map*. Patients For Affordable Drugs. https://map.patientsforaffordabledrugs.org/

oral drugs, called Pomalyst, is priced at more than $22,400 for 21 capsules, which I must buy every 28 days. And because Medicare beneficiaries like me pay our out-of-pocket costs based on list price, I spent more than $16,500 out-of-pocket last year — just for Pomalyst. To help manage the cost of my infused drugs, I spend another $3,731 per year to purchase a Part B supplement. And of course, I have the base costs of Medicare to pay as well.

For people with my cancer — multiple myeloma — drugs account for 60 percent of the cost of treatment.[2] Sixty percent.

I am a very lucky man — these drugs are currently keeping my cancer at bay, and I tolerate them pretty well. But the reason I am on four drugs is because each began to stop working, so the doctors first increased the dose, then increased the frequency, and then added another drug. Eventually, I will fail on this combination, too. When that happens, I will be what is called "triple refractory" to all of the three major classes of drugs used to treat my disease. The cancer will begin to increase in my blood and I will need a new treatment. Fortunately, there are options out there.

But one of the new drugs approved recently that I might be a candidate for carries a list price of $465,000.[3] That's just for the drug — it doesn't cover the hundreds of thousands of dollars required to administer the drug and manage my health in the wake of the treatment.[4] And each of the new drugs comes with its own risks: The treatment I am referring to is called Chimeric Antigen Receptor T-Cell therapy (CAR-T) and it carries a black box warning that it may actually cause secondary cancers.[5] I don't know what's ahead in my journey as a cancer patient.

But the point is: I need these innovative new drugs. I care deeply about innovation and new drug development. My life depends on it. Without innovation, I will die sooner than I hope to. That is just an unfortunate fact.

But my more than 13-year journey as a cancer patient has taught me one irrefutable fact: Drugs don't work if people can't afford them.

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[2]Tran, D., Kamalakar, R., Manthena, S., & Karve, S. (2019, November 13). *Economic Burden of Multiple Myeloma: Results from a Large Employer-Sponsored Real-World Administrative Claims Database, 2012 to 2018*. Blood, 134, 3414. https://doi.org/10.1182/blood-2019-131264

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[4]K.Hansen, D., Xiaioxiaio, L. et al. (2023, November 2). *Cost per Responder Analysis of Patients with Lenalidomide-Refractory Multiple Myeloma Who Received Cilta-Cel from the Cartitude-4 Trial.* The American Society of Hematology. https://ashpublications.org/blood/article/142/Supplement%201/5083/504878/Cost-per-Responder-Analysis-of-Patients-with

[5]Jewett, C. (2024, January 23). *F.D.A. Issues Warning of Cancer Risk Linked to CAR-T Therapies.*The New York Times. https://www.nytimes.com/2024/01/23/health/fda-cancer-car-t-warning.html

Section II. The Price of Drugs and Need for Further Reforms

Drugs are too expensive in the United States, and there is no justification for the high prices. When drug makers hike prices each year, they don't do so because the drug becomes more valuable. Drug companies raise prices because they can. We let them.

The result is that Americans pay more than four times what people in other wealthy nations pay for the exact same brand-name drugs. Even after applying an estimate of rebates to arrive at net prices, Americans are paying more than three times what people in other wealthy nations pay for the same brand name drugs.[6]

Consequently, about three in ten Americans report having difficulty affording their medications.[7] When their prescription drug prices are too high, Americans face challenges affording other expenses, such as food and housing. One survey found that over 20 percent of people took on debt or declared bankruptcy because of their medications.[8]

High drug prices disproportionately harm communities of color. One in two Latinos in the United States takes a prescription medication, and more than 20 percent are uninsured.[9] Black and Latino adults aged 65 and older were more likely to report difficulty affording prescription medications than White adults. Further, Black Americans are more likely to live with chronic pain, diabetes, and high blood pressure than white Americans and are nearly two times more likely to be uninsured.[10]

As expensive as my drugs are, even with Medicare, I never lose sight of the fact that roughly 26 million Americans don't have any health insurance at all and are exposed to the full list price.[11]

People struggle to pay the prices with and without insurance.

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[6]Mulcahy, A., Schwam, D., and Lovejoy, S. *International Prescription Drug Price Comparisons: Estimates Using 2022 Data.* (2024, February 1). RAND Corporation. https://www rand.org/pubs/research_reports/RRA788-3 html

[7]Kirzinger, A., Montero, A., Sparks, G., Valdes, I., Hamel, L. (2023, August 21). *Public Opinion on Prescription Drugs and Their Prices.* KFF. https://www kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/

[8] Nguyen, A. (2021, March 22). Survey: Americans Struggle to Afford Medications as COVID-19 Hits Savings and Insurance Coverage. *GoodRx*. https://www.goodrx.com/blog/survey-covid-19-effects-on-medication-affordability/

[9](2021, January). *A Vicious Cycle of Health Inequity: How High Prescription Prices Hurt Latino Health and Prosperity*. UnidosUS Action Fund. https://www.lowerdrugpricesnow.org/wp-content/uploads/UNIDOS-RX-REPORT-Vicious-Cycle.pdf

[10] (2020, December 14). *High Prescription Drug Prices Perpetuate Systemic Racism. We Can Change It*. Patients For Affordable Drugs Now. https://patientsforaffordabledrugsnow.org/2020/12/14/drug-pricing-systemic-racism/

[11](2023, November 9). *The Share of Americans Without Health Insurance in 2022 Matched A Record Low.* Peter G. Peterson Foundation. https://www.pgpf.org/blog/2023/11/the-share-of-americans-without-health-insurance-in-2022-matched-a-record-low

Americans have been demanding relief for years. A KFF poll in July of 2023 found three out of four Americans said there is not enough government regulation when it comes to limiting the price of prescription drugs. That includes 82 percent of Democrats, 67 percent of Independents, and 68 percent of Republicans.[12] In the wake of the enactment of the Inflation Reduction Act which is helping millions of people–Americans want more done.

Section III. The Inflation Reduction Act Is A Huge Step Forward Helping Millions Of People

The historic Inflation Reduction Act (IRA) is lowering prescription drug prices and reducing out-of-pocket costs for millions of people in this country. The benefits include:

- Insulin costs in Medicare are capped at $35 monthly. "About 1.5 million Medicare beneficiaries who use insulin would have saved $734 million in Part D and $27 million in Part B out-of-pocket costs in 2020 if these caps had been in effect in 2020."[13]
- Recommended vaccines that would have cost $100-200 per vaccination are now free under Medicare Part D. "In 2021, 3.4 million people received vaccines under Part D, and annual out-of-pocket costs were $234 million."[14]
- Due to the inflation rebates under the IRA, "Medicare Part B beneficiaries have already enjoyed lower coinsurance for 20 drugs from April 1 to June 30 and for 43 drugs from July 1 to September 30 2023"[15]
- Low-income subsidies were expanded starting January of this year. The "expanded financial assistance in Medicare's Low-Income Subsidy (LIS) Program would have benefited nearly 461,000 Partial LIS enrollees had the provision been in effect in 2020. An additional 2.9 million Part D enrollees who were eligible but not enrolled in LIS would also have benefited from the program."[16]
- Starting in 2026, negotiated prices will take effect on 10 of the highest-cost drugs for Medicare, lowering prices and out-of-pocket costs for millions of beneficiaries. That number will rise to 60 drugs in the coming years, extending the benefits of negotiation to many more millions of people.

"The Inflation Reduction Act's redesign of Medicare Part D, including a $2,000 out-of-pocket cap is estimated to reduce enrollee out-of-pocket spending by about $7.4 billion annually among

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[12]Kirzinger, A., Montero, A., Sparks, G., Valdes, I., Hamel, L. (2023, August 21). *Public Opinion on Prescription Drugs and Their Prices.* KFF. https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices//

[13] (2023, August 16). *The Inflation Reduction Act of 2022: One Year Anniversary Highlights from ASPE Drug Pricing Report.* ASPE. https://aspe.hhs.gov/reports/inflation-reduction-act-2022-one-year-anniversary-highlights-aspe-drug-pricing-reports

[14] IBID

[15] IBID

[16] Feyman, Y., Ruhter, J.,Finegold, K., Buchnueller, T., De Lew, N., Zuckerman, R., Sheingold, S. (2024, January 31). *Medicare Enrollees and the Part D Drug Benefit: Improving Financial Protection through the Low-Income Subsidy.* ASPE. https://aspe.hhs.gov/reports/expanded-financial-protections-under-low-income-subsidy-program

more than 18.7 million enrollees (36 percent of Part D enrollees) in 2025 – nearly $400 per person among enrollees who have savings in out-of-pocket costs under the IRA."[17] The IRA annual Medicare out-of-pocket spending limits began to phase in this year, and people taking expensive brand-name drugs will see their spending capped at the catastrophic level at about $3,300-3,500.

Let me tell you about my personal experience with the phasing in of the out-of-pocket cap this year. My total out-of-pocket expense for all my Medicare Part D drugs last year was $16,916 because there was no out-of-pocket cap in place. This year, thanks to the IRA's phasing in of an out-of-pocket cap for beneficiaries who reach the catastrophic phase of the benefit this year, I paid $3,308 for my first fill of Pomalyst and will be paying no more out-of-pocket for Pomalyst or any of my Part D drugs for the rest of the year. That's a savings of more than $13,600. For so many patients who are stuck with diseases or chronic conditions that require high-priced brand drugs, it is life-changing.

Take Sue from Wilmington, Delaware. She writes: "I have Waldenstroms Macrobulemia, a form of blood cancer. I take Imbruvica which is $18,000 a month. After insurance, I pay the first $8,000 in 2-months copay and then $1,000 a month thereafter. I am 76 years old and working full time to afford this medication." Sue will save between $12,000-14,000 this year with the out-of-pocket cap phasing in.

It's critical to remember that the way out-of-pocket costs are being reduced without unacceptable premiums or tax increases is by lowering the underlying prices of drugs in Medicare. If Congress weakens the IRA allowing higher prices than the law as written will deliver, we will see higher costs to both beneficiaries like Sue and myself, the government, and taxpayers.

Section IV. The Inflation Reduction Act Achieves Balance To Ensure Innovation We Need At Prices We Can Better Afford

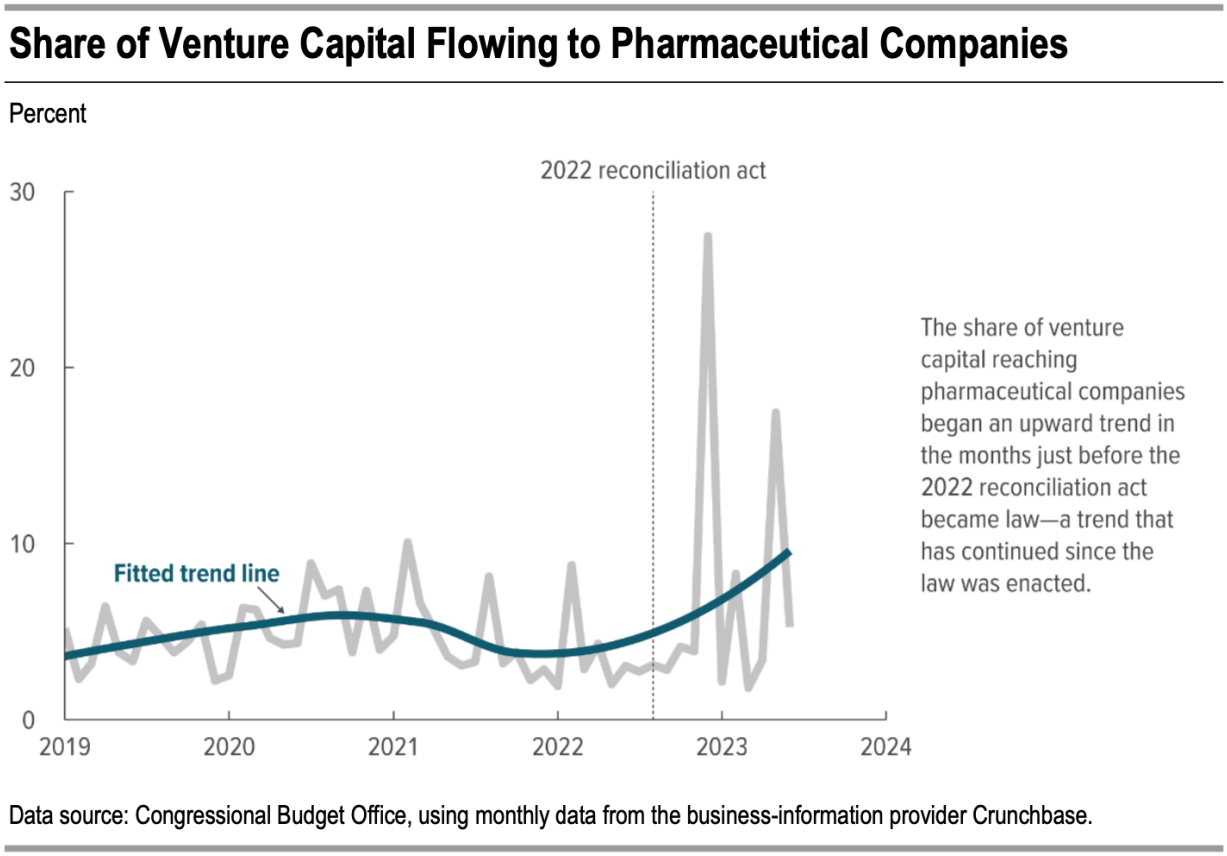
In the run-up to the enactment of the IRA, the drug industry kept telling us that the legislation would stifle investment and kill innovation and access to new drugs. No one cares more about innovation than patients. But if you pull back the curtain on this pharma fear-mongering and look at what has actually happened since the IRA enactment, the argument doesn't hold up. Here are nine reasons why.

[17]IBID

The industry has plenty of money for innovation. In the wake of the Inflation Reduction Act passage, investors are upbeat. Drug company stocks are doing fine.[18] The industry is flush with cash and has great access to capital.[19]

According to the Congressional Budget Office (CBO), despite Big Pharma's claims that the implementation of the Inflation Reduction Act would stifle innovation and significantly impact profit margins, there has been a consistent and continuous increase in venture capital investment in pharmaceutical companies, demonstrating stability and resilience within this sector as shown in Figure 1.[20]

Figure 1.



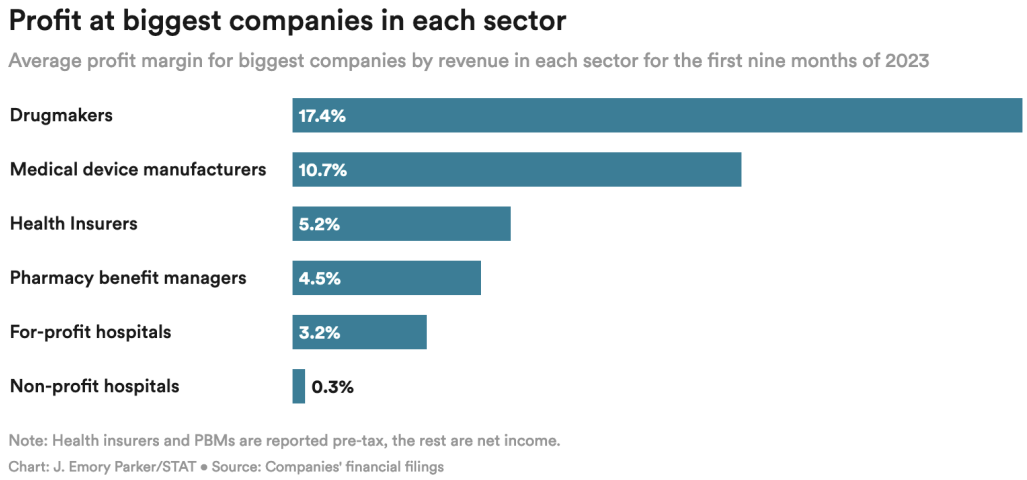
[18]Cheddar Berk, C., (2022, December). *Health-care stocks are looking good for 2023 and not just because the sector is a 'safe haven'* CNBC. https://www.cnbc.com/2022/12/21/health-care-stocks-2023-big-pharma-still-favored-but-good-bets-in-biotech-are-out-there.html

[19]Cranmer, J. (2023, March 21). *Market rebound on hold, but pharmas open for business, says J.P. Morgan's Gaito*. BioCentury. https://www.biocentury.com/article/647325

[20](2023, December 21). *Re: Additional Information About Drug Price Negotiation and CBO's Simulation Model of Drug Development.* Congressional Budget Office. https://www.cbo.gov/system/files/2023-12/59792-Letter.pdf

Drug companies are flush with cash and remain by far and away the most profitable sector of the healthcare industry–more than tripling the profit of Pharmacy Benefit Managers (PBMs) and insurers.[21]

Figure 2.



Since the passage of the Inflation Reduction Act:

- Pfizer acquired biotech company Seagen for $43 billion.[22]
- Sanofi bought a diabetes product company for $2.9 billion.[23]
- Novartis spent $15 billion in a stock buyback.[24]
- Even in the face of the Inflation Reduction Act, drug companies reported *increased* investment in research and development (R&D). For example, in 2022 10-K filings, Johnson & Johnson reported an 11.8 percent increase in R&D spending in 2022, Merck reported an 11 percent increase in R&D spending, and Moderna reported a 65 percent increase in R&D spending and projected further increases in 2023.[25]

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[21] Bannow, T., Trang, B. (2024, January 2). *Here's who's profiting the most in health care.* STAT News. https://www.statnews.com/2024/01/02/heres-whos-profiting-the-most-in-health-care/

[22] Dunleavy, K. (December 14, 2023). *Done deal: Pfizer completes $43B acquisition of Seagen, doubling its oncology pipeline.* Fierce Pharma. https://www fiercepharma.com/pharma/done-deal-pfizer-completes-43b-acquisition-seagen-doubling-its-oncology-pipeline

[23] Feuerstein, A., (2023, March 13). *French pharma Sanofi buys maker of diabetes treatment for $2.9 billion.* STAT News. https://www.statnews.com/2023/03/13/french-pharma-sanofi-buys-maker-of-diabetes-treatment-for-2-9-billion/

[24] Burger, L. (2023, March 13). *Novartis initiates new trading line for share buybacks.* Reuters. https://www reuters.com/business/healthcare-pharmaceuticals/novartis-launches-new-share-buyback-up-10-its-stock-2023-03-13/

[25] Patients For Affordable Drugs Now. (2022, April). *Talking Points Based on Review of 2022 SEC 10K filings.* https://patientsforaffordabledrugsnow.org/wp-content/uploads/2023/04/TPs-10-K-0315202380.pdf

- "Bayer plans to invest $1 billion on research and development this year in an effort to double its sales in the United States within a decade."[26]
- Sanofi said that it would increase the number of Phase 3 studies it is conducting by 50 percent between 2023 and 2025 at a financial cost of about $700 million a year.[27]

The Inflation Reduction Act *incentivizes* innovation by curbing drug companies' ability to drive profits by raising prices on old drugs at will.

- To make more money, drug companies will have to develop high-value new drugs that can command high prices, instead of repurposing old products.
- The negotiation process includes the consideration of therapeutic advances and meeting unmet needs, which will reward more innovative drugs.
- The law maintains the key incentive for innovation that currently exists in the U.S. by allowing drugmakers to be compensated handsomely for investment and risk by setting their launch prices, maintaining the Food and Drug Administration (FDA)-awarded period of exclusivity, and exempting all medications from negotiated prices for a 9 to 13 year period.
- The U.S. will continue to pay the highest drug prices and offer the largest pharmaceutical market in the world. Drug companies will continue to innovate in order to have access to such a lucrative market.

The Congressional Budget Office (CBO) says the Inflation Reduction Act will have a minimal to non-existent impact on new drug development.

- According to the CBO, the Inflation Reduction Act will decrease the number of new drugs over the next 30 years by only about 15 out of 1,300 expected – that's only a little over one percent.[28]
- Since only 10 to 15 percent of "new" drugs represent true therapeutic advancements, of the 15 new drugs foregone, only one or two might actually be true innovations.[29]
- Pharma cries poor every time policy reforms take even a small piece of change out of its pocket. But the reduction in drug industry revenue from the Inflation Reduction Act will be very small overall — estimated at less than one percent through 2032.[30] Figure 3

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[26]Cohrs, R. (2023, June). *How drug pricing reforms are affecting Bayer's investments.* STAT News. https://www.statnews.com/2023/06/20/drug-pricing-bayer/

[27] Herper, M. (2023, December 6). *Sanofi says it has 12 blockbusters in its back pocket. Will investors believe it?*. STAT News. https://www.statnews.com/2023/12/06/sanofi-says-it-has-12-blockbusters-in-its-back-pocket/

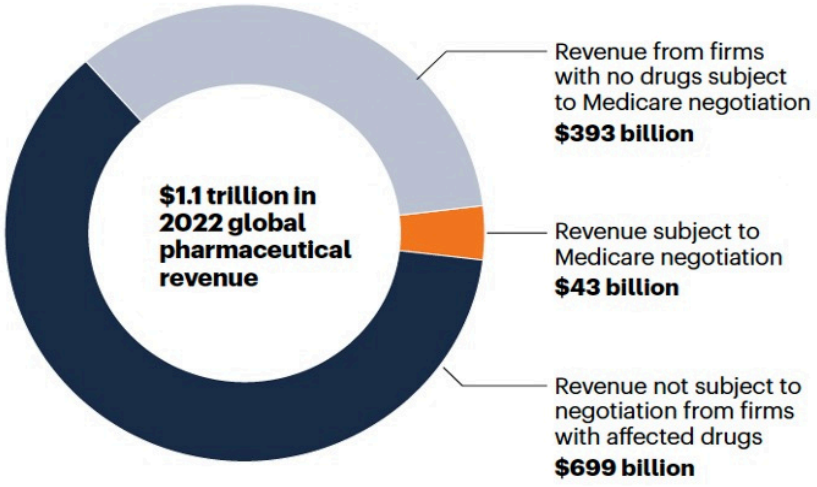
[28](2022, July 8). *Estimated Budgetary Effects of Subtitle I of Reconciliation Recommendations for Prescription Drug Legislation.* Congressional Budget Office. https://www.cbo.gov/publication/58290

[29] Light, D., Lexchin, R. *Pharmaceutical research and development: what do we get for all that money?* BMJ. https://www.bmj.com/content/345/bmj.e4348

[30] Hopkins, J. (2023, January 14). *A New U.S. Law Aims to Reduce Drug Prices. But First, It Might Raise Them*. The Wall Street Journal. https://www.wsj.com/articles/inflation-reduction-drug-prices-11673628922

shows we are barely making a dent in the drug industry's global revenues with Medicare negotiation, which the industry is spending an enormous sum of money to prevent in the courts.[31]

Figure 3.



Share of 2022 global pharmaceutical revenue subject to Medicare drug price negotiation. Forty-three billion dollars of the global pharmaceutical industry's $1,135 billion in revenues would have been subject to a negotiated price in 2022. The 31 companies that would have had a drug with a Medicare negotiated price in effect in 2022 had an additional $699 billion in global revenue not subject to negotiation. Another $393 billion in revenue was generated by companies with no drugs subject to negotiation.

- Far from the draconian price setting Big Pharma has complained about, AstraZeneca CEO Pascal Soriot told a Senate committee a few weeks ago that initial steps in Medicare negotiation are positive: "So far, what we've seen is relatively encouraging."[32]
- Raymond James analyst Chris Meekins wrote: "As we have been saying since the Inflation Reduction Act first passed, we believe the sector-wide impact of the Inflation Reduction Act, including negotiation, on the pharmaceutical industry to be minimal."[33]

[31]Vogel, M., Kakani, P., Chandra, A., Conti, R., *Medicare price negotiation and pharmaceutical innovation following the Inflation Reduction Act.* (2024, January 31) Nature. https://www.nature.com/articles/s41587-023-02096-w
[32]Joseph, A. (2024, February 8). *As Medicare drug pricing negotiations begin, AstraZeneca stays mum on government's offer.* STAT News. *https://www.statnews.com/2024/02/08/astrazeneca-medicare-drug-pricing/*
[33]Owens, C. (2023, August 23). *Medicare drug price negotiations could have limited impact at first.* Axios https://www.axios.com/2023/08/30/biden-medicare-drug-pricing-negotiations-impact

Taxpayers are the source of early high-risk, basic science that drives innovation — not industry.

- The National Institutes of Health (NIH) is the single largest source of biomedical research in the world. Its budget in 2023 was almost $48 billion.[34] The NIH contributed to research associated with *all 356 new drugs approved by the FDA from 2010-2019*, totaling more than $230 billion.[35]
- The reason President Biden has established the Cancer Moonshot and the Advanced Research Projects Agency for Health (ARPA-H) with billions in funding to accelerate early, high-risk research is because Big Pharma won't take the risks on its own. Taxpayers must underwrite this early work to find bold new treatments and perhaps cures.

Lower drug prices help people access existing, innovative drugs they need right now, but can't afford.

- Innovation is worthless if people can't get access to it.
- CBO reports one of the ways the IRA saves money is by improving adherence to drug therapies which lead to better health through lower prices.[36]

The American public no longer buys Big Pharma's threats to innovation. Policymakers shouldn't fall for them either.

- Bipartisan polling shows that American voters do not buy drug industry arguments against drug price reform, as nearly 80 percent of respondents say the pharmaceutical industry can live with slightly lower profits and still provide the innovation patients need.[37]

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[34](2023, March 8). *National Institutes of Health (NIH) Funding: FY1996-FY2023*. Congressional Research Service. https://crsreports.congress.gov/product/pdf/R/R43341/45#:~:text=In%20total%2C%20the%20NIH%20FY2023,until%20the%20end%20of%20FY2025.

[35] Ledley, F., Clearly, E., Jackson, M. (2020, September 2). *US Tax Dollars Funded Every New Pharmaceutical in the Last Decade.* Institute for New Economic Thinking. https://www.ineteconomics.org/perspectives/blog/us-tax-dollars-funded-every-new-pharmaceutical-in-the-last-decade

[36](2023, February). *How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act.* Congressional Budget Office. *Page 31* https://www.cbo.gov/system/files/2023-02/58850-IRA-Drug-Provs.pdf

[37](2023, September 18). *Americans Overwhelmingly Oppose Big Pharma's Assault On Medicare Negotiation.* Patients For Affordable Drugs Now. https://patientsforaffordabledrugsnow.org/2023/09/18/new-poll-americans-overwhelmingly-oppose-big-pharmas-assault-on-medicare-negotiation/

Finally, Big Pharma consistently threatens that patients will lose access to newly developed drugs. It notes that more drugs are available — and are available faster — in the United States than in other wealthy countries. Pharma frequently cites a white paper from the White House Council of Economic Advisers (CEA) to explain why: "Drug manufacturers usually pursue market access in the United States before other markets due to the higher prices in the United States."[38] The CEA could also have mentioned the other big reason drug companies file for approval first in the United States: It is the largest market in the world.[39, 40] *After the IRA is fully implemented our country will still offer the highest prices by far in the largest market in the world, preserving the incentive to file first for approval in the United States.*[41]

There are other important policies in the U.S. drug pricing system that lead to more drugs being available here compared to other countries, none of which are altered by lowering prices under the IRA:

- Medicare must cover all drugs in six protected classes, which even the Pharmaceutical Research and Manufacturers of America (PhRMA) acknowledges ensures access to these drugs.[42, 43]
- Medicare must cover at least two drugs in each class of drugs.[44]

Medicaid must cover *every drug* offered by a manufacturer in the United States if the manufacturer agrees to give Medicaid a best-price guarantee.[45]

The pharmaceutical industry's threats to innovation and access don't hold up. The IRA restores balance to move us in the direction of fair prices and profits while still getting the innovation we need.

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[38](February, 2018). *Reforming Biopharmaceutical Pricing at Home and Abroad*. The Council of Economic Advisers. https://trumpwhitehouse.archives.gov/wp-content/uploads/2017/11/CEA-Rx-White-Paper-Final2.pdf
[39](2020, March 5). *Global Medicine Spending and Usage Trends*. IQVIA. https://www.iqvia.com/en/insights/the-iqvia-institute/reports/global-medicine-spending-and-usage-trends
[40] (2020). *Association of Community Cancer Centers v. Alex M. Azar II. Civil Action No. CCB-20-3531.* PhRMA https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMA-Complaint-on-MFN-Rule-Filed-2020-12-04.pdf
[41] Mulcahy, A. W., Whaley, C., Tebeka, M. G., Schwam, D., Edenfield, N., & Becerra-Ornelas, A. U. (2021). *International Prescription Drug Price Comparisons*. RAND Corporation. https://www.rand.org/pubs/research_reports/RR2956.html
[42](2019, May 16). *Medicare Advantage and Part D Drug Pricing Final Rule (CMS-4180-F)*. Centers for Medicare & Medicaid Services. https://www.cms.gov/newsroom/fact-sheets/medicare-advantage-and-part-d-drug-pricing-final-rule-cms-4180-f
[43] Powaleny, A. (2015, December 10). *Medicare Part D's six protected classes*. PhRMA. https://catalyst.phrma.org/medicare-part-d-six-protected-classes
[44] (2021, May 3). *What Medicare Part D drug plans cover*. CMS.gov. https://www.medicare.gov/drug-coverage-part-d/what-medicare-part-d-drug-plans-cover
[45] (2019, May 1). *Medicaid's Prescription Drug Benefit: Key Facts*. Kaiser Family Foundation. https://www.kff.org/medicaid/fact-sheet/medicaids-prescription-drug-benefit-key-facts/

Section V. H.R. 5547 and H.R. 5539 Are Misguided Because They Are Based On False Premises

H.R. 5547 is a solution in search of a problem that doesn't exist in actuality and is only being raised by the industry to reduce the impact of Medicare negotiation and keep prices on more drugs higher for longer. The supposed problem posited by industry is that relative to the previous law, the reforms in the Inflation Reduction Act economically disadvantage small-molecule drugs compared to biologics, which will hurt innovation, increase prices, and harm the people who need these medicines.

This claim is completely misleading, and unsupported by the facts. The Inflation Reduction Act actually *narrows the advantage* for biologics over small molecules.

The pharma industry's complaint is specious, which can be seen clearly in that, over time, its stances have been completely inconsistent. Biologics were given a huge advantage over small-molecule medicines because the pharmaceutical industry insisted on receiving seven years more market exclusivity for biologics than for small-molecule drugs when the Biologics Price Competition and Innovation Act (which was included in the Affordable Care Act) was being structured.[46, 47, 48, 49]

Here's what the trade association BIO said to justify a longer period of exclusivity for biologic drugs:

> *"Biologics research and development is a high-risk endeavor, with higher capital costs, higher material costs, greater manufacturing costs and uncertainties, longer development times, and lower late-stage success rates than compared to small molecule drugs."*[50]

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[46] Osborne, R. (2009, August). *Brand biologics grab 12 years' exclusivity, for now*. Nature. link.gale.com/apps/doc/A206534644/AONE?u=anon~94b8b41f&sid=googleScholar&xid=fbd50971

[47](2015, October). *Reducing Data Protection For Biologics Would Slow Medical Progress And Chill R&D Investments In The U.S.* PhRMA. https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/D---F/Data-Exclusivity-for-Biologics-Fact-Sheet.pdf

[48] Kilic, B., Pine, C. (2015, July 27). *Decision Time On Biologics Exclusivity: Eight Years Is No Compromise*. Intellectual Property Watch. https://www.ip-watch.org/2015/07/27/decision-time-on-biologics-exclusivity-eight-years-is-no-compromise/

[49] (2016, February 12). *Implementation of the Biologics Price Competition and Innovation Act of 2009.* US FDA. https://www fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009

[50] *Data Exclusivity Protects Innovators and Assures Investors.* Biotechnology Innovation Organization (BIO). https://archive.bio.org/articles/data-exclusivity-protects-innovators-and-assures-investors

At the time, the pharmaceutical industry did not suggest that this enormous advantage for biologics would lead to the development of fewer small-molecule drugs, which it didn't. Since 2010, more than 75 percent of new drugs approved by the FDA have been small molecules.[51]

The Inflation Reduction Act actually contains more generous incentives for small-molecule medicines because it narrows the difference in years of exclusion from Medicare negotiation between biologics and small molecules to four years. And the negotiation exemption periods for small molecules (nine years) and biologics (13 years) are longer than the existing market exclusivity periods granted by the Food and Drug Administration (FDA), which are five years and 12 years, respectively.

Drug companies now assert that both types of drugs should be treated equally for purposes of negotiation — pharma's chosen solution is, naturally, to increase the exemption period for small molecules to 13 years to match that of biologics.[52] To put this into perspective, other high-income countries provide small-molecule and biologic drugs with identical periods of market exclusivity.[53] The only reason the U.S. is not on that list is because the pharma industry lobbied the United States Congress aggressively for a longer monopoly period for biologics.[54]

This misleading complaint — that the Inflation Reduction Act will stifle the development of small molecule drugs — is not supported by facts and is inconsistent relative to the pharmaceutical industry's long-held positions on the need for advantageous treatment for biologic drugs.

In fact, since the enactment of the IRA, investment in small molecules *has not* declined–it has increased and investors are bullish:

- In the 9 months following the passage of the IRA, big drug companies acquired more small-molecule drugs than in the 9 months preceding the law, indicating drug companies still find small molecules an attractive investment.[55]

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[51] G. De la tore., B., Albericio, B., (2022, February 27). *The Pharmaceutical Industry in 2021. An Analysis of FDA Drug Approvals from the Perspective of Molecules.* National Library of Medicine. https://www ncbi.nlm nih.gov/pmc/articles/PMC8839730/

[52] Armstrong, A., (2022, July 15). *VC firms, biotechs push back on drug pricing bill that would render small molecule drugs 'uninvestable'.* Fierce Biotech https://www fiercebiotech.com/biotech/vc-firms-biotechs-push-back-drug-pricing-reforms-would-render-small-molecule-drugs

[53](2017, September 8). *Policy Proposal: Reducing the Exclusivity Period for Biological Products.* Pew Charitable Trust. https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2017/09/policy-proposal-reducing-the-exclusivity-period-for-biological-products

[54]Pollack, A. (2009, July 22). *Costly Drugs Known as Biologics Prompt Exclusivity Debate*. The New York Times. https://www.cnbc.com/2009/07/22/costly-drugs-known-as-biologics-prompt-exclusivity-debate.html

[55] Frank, R., W. Huang, R., (2023, August 23) *Early claims and M&A behavior following enactment of the drug provision.* Brookings Institute.

- Industry sources are projecting nearly 8 percent annual growth in small molecule sales for the years 2022 to 2032 which amounts to a doubling of sales over the period.[56]
- Bristol Myers Squibb has signed a $4.8 billion deal to buy Mirati Therapeutics and its small molecule cancer drug Krazati.[57]
- Lilly spent $2.4 billion to acquire a small molecule drug for development in July 2023.[58]
- Forward Therapeutics secured $50 million in Series A financing, signaling robust investor confidence in advancing next-generation small molecule therapies for chronic immunological and inflammatory disorders.[59]
- Respected venture capitalist, Vineeta Agarwala of Andreessen Horowitz, said recently: "Every Pharma company, despite the IRA, is talking about small molecules."[60]
- Another of biotech's biggest financiers, venture capital company Flagship Pioneering, says: "Flagship continues to see great value in developing small molecule drugs. The IRA hasn't changed that.[61]

The so-called "pill penalty" seems simple on its face, which no doubt is part of the reason pharma picked it as a rallying cry. But, if you do the math, it's easy to see just how ridiculous the industry argument is. Drug companies will still continue to make massive profits on small molecules. To qualify for negotiation, a drug must, among other things, have annual Medicare sales of at least $200 million. Given that Medicare accounts for roughly 30 percent of total U.S. sales, an eligible drug would have more than $600 million in annual U.S. sales. Nine years of sales at $600 million annually produces revenue of more than $5.4 billion. Based on independent research, it costs an average of less than a billion dollars to bring a new drug to market–including covering costs of failures. That means a company with a drug qualifying for negotiation can easily make more than a 500 percent return on a small molecule before facing negotiated prices

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https://www.brookings.edu/articles/early-claims-and-ma-behavior-following-enactment-of-the-drug-provisions-in-the-ira/

[56] (2022, December). *Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2023-2032.* Precedence Research.
https://www.precedenceresearch.com/small-molecule-drug-discovery-market

[57]Liu, A., (2023, October 9).*Bristol Myers Squibb buys Mirati for up to $5.8B as I-O giant branches out into targeted therapy for cancer.* Fierce Pharma.
https://www fiercepharma.com/pharma/bristol-myers-buys-mirati-58b-i-o-giant-branches-out-targeted-therapy-cancer

[58]LaHucik, K. (2023, June 20). *Lilly inks $2.4B cash deal to buy DICE and its immunology pipeline.* Endpoints.
https://endpts.com/lilly-inks-2-4b-cash-deal-to-buy-dice-and-its-immunology-pipeline/

[59] (2023, November 8). *Forward Therapeutics Announces $50 Million Series A Financing*. Forward Therapeutics.
https://forward-tx.com/forward-therapeutics-announces-series-a-financing/

[60]Brennan, Z. (2024, February 2). *Corrected: Bipartisan IRA fix seeks to align small molecule and biologic negotiation period.* Endpoints.
https://endpts.com/44-house-republicans-co-sponsor-ira-fix-to-align-small-molecule-and-biologic-negotiation-periods/

[61]DeAngelis, A. (2023, June 21). *One of biotech's biggest financiers launches small-molecule startup, in spite of IRA's looming shadow.* STAT News.
https://www.statnews.com/2023/06/21/flagship-empress-therapeutics-small-molecule-drugs/

in Medicare.[62] In fact, this simple math exercise greatly underestimates how much revenue these small molecule drugs can command when you consider that in 2023 average sales of small molecule drugs protected by exclusivity with over $200 million in annual revenue and nine or more years on the market is actually $2.86 billion.

The simple fact is that healthy profit is guaranteed on safe and effective small-molecule drugs because the IRA allows drug companies to set initial launch prices. That is the principal way we reward risk and investment to bring an innovative drug to market, and nothing in the IRA changed that core element of our system. Companies can set prices to ensure a healthy return before possibly being selected for negotiation. *It is a no-lose proposition.*

All of these points apply to the gene technologies that are the focus of H.R. 5547. With 5,000 gene therapy trials listed at the NIH–if only 10 percent come to market, mandating 13 years of exclusivity instead of nine years before negotiated prices take effect would raise Medicare spending dramatically.[63]

The whole argument about 9 vs 13 years is not really about the interests of the millions of Americans who rely on medicines to get healthy — or stay alive. The drug industry simply wants 13 years of exemption from negotiated prices for *all* drugs to make as much profit as possible. Period. *If drug companies now want equal timing for the negotiation of all drugs, we should equalize them all at nine years.*

H. R. 5539 proposes to undo a critical reform in the IRA to ensure drug companies can't abuse orphan drug status.

This issue deeply affects patients including myself. I have an orphan disease and three of the four cancer drugs I am currently taking were initially approved as orphan drugs–Velcade, Darzalex, and Pomalyst.[64, 65, 66] We need to protect incentives for orphan drug development, but we must stop the abuse of the orphan drug designation which extends monopolies indefinitely and hurts patients through the imposition of unjustified high prices.

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[62]J Wouters, O., McKee, M., Luyten, J., (2020, March 3). *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018*. JAMA. https://pubmed ncbi.nlm.nih.gov/32125404/

[63]Marks, P., Philippidis, A., Grinstien, D. (2024, February 14) *On Your Marks: An Interview with Peter Marks*. Liebertpub. https://www.liebertpub.com/doi/full/10.1089/genbio.2024.29128.pma

[64](2003, September). *Velcade®, New Science and New Hope: A Case Study.* NIH. https://www.techtransfer nih.gov/sites/default/files/documents/pdfs/VelcadeCS.pdf

[65](2015, December 25). *FDA Approves Darzalex for Previously Treated Multiple Myeloma.* Oncology Times. https://journals.lww.com/oncology-times/Fulltext/2015/12250/FDA_Approves_Darzalex_for_Previously_Treated.15.aspx

[66](2020, May 15) *U.S. Food and Drug Administration Approves Bristol Myers Squibb's Pomalyst® (pomalidomide) for AIDS-Related and HIV-Negative Kaposi Sarcoma.* Bristol Myers Squibb. https://news.bms.com/news/corporate-financial/2020/US-Food-and-Drug-Administration-Approves-Bristol-Myers-Squibbs-Pomalyst-pomalidomide-for-AIDS-Related-and-HIV-Negative-Kaposi-Sarcoma/default.aspx

The abuse of orphan status by drug companies was documented in detail by Kaiser Health News (KHN now KFF News) more than seven years ago.[67] Here is a key conclusion from that investigation:

> "'What we are seeing is a system that was created with good intent being hijacked,' said Bernard Munos, a former corporate strategy advisor at drug giant Eli Lilly and Co. who reviewed the KHN analysis of several FDA drug databases. It's 'quite remarkable that it has gone on for so long.'"

It's time for the abuse to stop while protecting key incentives for orphan drug development, and that is exactly what the Inflation Reduction Act does.

- Orphan drugs that treat a rare disease with a patient population of less than 200,000 are excluded from negotiation completely.
- Small biotech firms – many of which make orphan drugs – are excluded from negotiation until 2028.
- All existing incentives for orphan drug development are maintained, including tax credits for clinical trials and granting of priority review vouchers, worth more than $100 million.[68]
- Orphan drugs with more than one indication for small patient populations – or even multiple indications – are *highly unlikely* to ever be included in negotiation because they won't ever meet the spending threshold.
- It will be almost impossible for drugs with multiple ultra-rare designations to ever reach spending levels to qualify for negotiation.
- About 50 percent of rare diseases are pediatric, and children, with very few exceptions, do not qualify for Medicare. Their treatment is paid for by other payers, such as Medicaid and commercial health plans, which don't have access to the payment rates that Medicare ends up negotiating. So negotiation will have little to no impact on pediatric drug development.[69]
- Drug companies can still make increased revenue by expanding the populations they treat with additional orphan designations before negotiation should they qualify for

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[67]Tribble, S.J., Lupkin, S. (2017, January 17). *Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies.* KFF Health News. https://kffhealthnews.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/

[68] (2022, February 9). *BioMarin Sells Priority Review Voucher for $110 Million.* BioMarin. https://www.prnewswire.com/news-releases/biomarin-sells-priority-review-voucher-for-110-million-301478459.html

[69] (2016, February 1). *Researchers seek to expand our understanding and develop new treatments.* National Institute of Health. https://www.nichd nih.gov/newsroom/resources/spotlight/020116-rare-disease-day#:~:text=Researchers seek to expand our understanding and develop new treatments & text=A disease is considered rare,all rare diseases affect children

negotiation, and turn a pretty profit in Medicare even after negotiation. It may just not be as big a profit as they would like.

Consistent with the overall approach of the IRA, the orphan drug provisions strike a balance that will stop abuse of patients by drug companies while still maintaining strong incentives for continued orphan drug development.

Section VI. What Else Should We Do? Curb Patent Abuse and Reform Pharmacy Benefit Managers (PBMs)

Patents For Innovation–Not To Block Competition and Lower Prices

When a drug company makes a truly innovative discovery, it should be rewarded with a patent and receive a fair return for risk and investment. Our patent system is designed to facilitate these rewards for innovation so that drug companies are incentivized to pursue true clinical breakthroughs and inventions that bring meaningful benefits to patients.

But the drug industry would have you believe that every patent is deserved and that the sheer volume of patents granted is an appropriate indicator of innovative achievements. That couldn't be further from the truth.

Neither new patents nor new drugs equal new innovation. Worse, manufacturers are abusing America's patent and exclusivity system in too many cases to prevent free-market competition and block affordable generic and biosimilar drugs from coming to market.

Between 2005 and 2015, at least 78 percent of the new drug patents issued were for drugs already on the market.[70]

Of the roughly 100 best-selling drugs, nearly 80 percent obtained additional patents to extend their monopoly period.[71]

In fact, gaming of the patent system to extend monopolies beyond the time intended under law inhibits true innovation that patients like me and millions of others need. If drug companies can block competition and raise prices at will on old drugs to drive profits and executive bonuses, they have far less incentive to take risks and invest in Research and Development (R&D) to find innovative new drugs that could command high prices and save lives.

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[70]Koons, C. (2017, November). *Most New Drug Patents Are for Old Remedies, Research Shows.* Bloomberg News. https://www.bloomberg.com/news/articles/2017-11-01/most-new-drug-patents-are-for-old-remedies-research-shows

[71]Feldman, R. (2018). *May your drug price be evergreen.* Journal of Law and the Biosciences. https://academic.oup.com/jlb/article/5/3/590/5232981?login=true

There are a variety of strategies used by drug corporations to extend monopolies, including product hopping, patent thicketing, pay-for-delay deals, and abuse of the Food and Drug Administration's (FDA) citizen petition process. All of these practices thwart competition and allow drug corporations to keep drug prices high. There have been several bipartisan pieces of legislation advanced in this Congress to address these issues and allow for more generic drugs and biosimilars to enter the market, which is critical to making drugs more affordable for patients.

P4ADNow strongly supports H.R. 3839, which was included in the Lower Costs, More Transparency Act, and passed the House on a strong bipartisan vote. In addition, P4ADNow supports bipartisan legislation that would reduce patent thicketing, curb product hopping, ban pay-for-delay agreements, reduce abuse of citizen petitions at the FDA, and improve coordination between FDA and the US Patent Trademark and Office (USPTO). Importantly, all of these measures would produce billions of dollars in savings that could be used to offset other health care priorities.

We must ensure patents are used as intended to reward *true* invention and innovation–not to extend monopolies and block lower prices through competition. To achieve true innovation at prices we can afford over the long haul, we must reform our patent and exclusivity system.

<u>Increase Transparency and Stop Anticompetitive Practices By Pharmacy Benefit Managers (PBMs)</u>

While the headwaters of our drug pricing problems are the list prices set by drug corporations, there are other reforms needed downstream in the supply chain. Pharmacy benefit managers (PBMs) are black boxes that cut secret, mutually beneficial rebate deals with manufacturers, and none of it is transparent.

It is simply wrong that patients like me don't know if the preferred drug on a PBM formulary is there because it is the best drug, because it is the least expensive drug among equally effective options, or because the PBM got a big, legal kickback from the manufacturer. Without transparency, it is impossible to know how much of a rebate is going to the PBM, to the insurer, to lower my premiums, or to reduce my out-of-pocket costs at the pharmacy counter. With the Big Three PBMs–Cigna, Optum Rx, and CVS Health–in control of 80 percent of the $633 billion in U.S. spending on drugs, that is more than half a trillion dollars flowing through just those

three entities annually.[72, 73] And vertical integration uniting all three major PBMs with insurers only increases their market power. Opaque practices with that kind of money involved are a bad way to run a railroad.[74] It's time for transparency to ensure PBMs are operating in the best interests of those they are supposed to serve — patients and consumers.

Drug companies and PBMs also enter into rebate arrangements that are designed to thwart lower-cost competition. These are commonly called "rebate walls," defined as:

> "Exclusionary contracting practices that a drug manufacturer deploys to limit the ability of rivals from gaining preferred access to the formulary, or any access at all. Branded manufacturers leverage their position as market leaders by offering financial incentives to pharmacy benefit managers and health insurers in the form of 'all or nothing' conditional volume-based rebates, in exchange for virtually exclusive positioning on the formulary. ...If the payer does not accept the rebate agreement for a particular indication, it may lose all rebates for its product on all covered indications."[75]

Let's be clear: These deals are designed to benefit both the manufacturer seeking to block competition and the PBM that gets a bigger rebate. These deals are not designed to help patients like me by lowering prices or increasing patient choice. They are emblematic of our drug pricing system which has been built to benefit those who profit from it at the expense of those it is supposed to serve.

P4ADNow supports reforming the practices of PBMs, including transparency requirements in order to determine how rebates are actually working — how much is going to reduce premiums and out-of-pocket for patients and consumers and how much is going to increase profits for the PBMs or insurer plan manager.

We're pleased that the Lower Costs, More Transparency Act included several provisions to improve PBM transparency and eliminate spread pricing, among other elements. We also support reforms to "de-link" administrative fees from drug prices and to pass more of the savings collected through negotiated discounts along to patients and consumers whether through lower prices, lower out-of-pocket, or lower premiums. We hope that Congress will consider many of these measures for inclusion in upcoming health care legislation.

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[72]Mikulic, M. (2023, May 23). *Market share of the top pharmacy benefit managers in the U.S. prescription market in 2022*. Statista.
https://www.statista.com/statistics/239976/us-prescription-market-share-of-top-pharmacy-benefit-managers/
[73]Tichy M. E., Hoffman, J., Tadrous, M. et al. (2023, July 7). *National trends in prescription drug expenditures and projections for 2023.* https://pubmed.ncbi nlm nih.gov/37094296/
[74](2019, March 8). *The Prescription Drug Landscape, Explored*. Pew Charitable Trusts.
https://www.pewtrusts.org/en/research-and-analysis/reports/2019/03/08/the-prescription-drug-landscape-explored
[75]Cohen, J. (2021, March 1). *Rebate Walls Stifle Prescription Drug Competition.* Forbes.
https://www forbes.com/sites/joshuacohen/2021/03/01/rebate-walls-stifle-prescription-drug-competition/?sh=1ccc940366ae

We are also following closely and supporting the Federal Trade Commission (FTC) investigation of these issues as well. We hope Congress will ensure the ability of the FTC to seek damages and monetary penalties for consumer protection and competition cases.

Section VII: Conclusion

Let's be clear: Big Pharma is not fighting for the interest of patients or because lowering its prices a bit will cripple innovation. It's fighting to maintain its economic power over the American people to dictate prices of brand-name drugs–a power it has in no other nation on the planet. The head of the powerful trade association, PhRMA, affirmed that fact in a moment of candor when he said in an interview not long ago that his industry is "particularly adept at … rolling the tanks, if you will, to push back against policy proposals *adverse to the industry's interests*."[76] The industry's multiple lawsuits to block Medicare negotiation that will touch only about four percent of its global revenue is further evidence this struggle is about keeping the U.S. market as the one place in the world where it can dictate prices at the expense of people's lives and livelihoods.

Of course, Big Pharma wants to disguise that truth. Instead, it blames others and distracts attention from its central role in making drugs unaffordable.

And it tries to scare us by saying that if we don't bend to its will, we won't get the drugs we need for the future. It poses questions like: How much would you pay to save a life?

And that's easy. When it's you or someone you love, the answer is anything. You'll empty your bank account, mortgage your home, cash out your 401k. You'll do whatever you have to do.

But that's the wrong question. We should be asking: *How do we strike and maintain a balance to ensure we get the innovation we need at prices we can afford?*

While Patients For Affordable Drugs Now would have gone further in the Inflation Reduction Act, it clearly was built with striking that balance as a foundational principle. That point is driven home by a fact that is worthy of repeating: **The IRA does not change the key way our nation rewards investment and risk-taking for innovation–we continue to allow drug companies to set launch prices and maintain those prices for a minimum of 9 to 13 years before potentially facing negotiated prices.**

This story from Cheryl in Louisville captures so well the challenges patients face and the need to lower drug prices. Cheryl writes: "All my inhalers, like Trelegy, are such a high cost, I do

[76] Florko, N. (2021, April 13). *PhRMA chief talks strategy — and he's surprisingly optimistic about drug pricing reform.* STAT News. https://www.statnews.com/2021/04/13/phrma-chief-talks-strategy/

without until I have a bad episode. These inhalers cost from $350 to $800 a month. This is crazy just to be able to breathe every day. Something is wrong here."

Cheryl is right. I feel incredibly grateful to spend *my* retirement fighting to fix what's wrong so that people like Cheryl can one day enjoy theirs. We must protect the Inflation Reduction Act from being weakened. And we must move ahead with patent and PBM reforms to make our system work better for the people it is supposed to serve with lower prescription drug prices for all.

Thank you.

FAMILIESUSA
THE VOICE FOR HEALTH CARE CONSUMERS

Statement for the Record

House Energy and Commerce Subcommittee on Health

Hearing on "Legislative Proposals to Support Patients with Rare Diseases."

February 29, 2024

Prepared by *Families USA*

1225 New York Avenue, NW
Suite 800
Washington, DC 20005
(202) 628-3030

Chair McMorris Rodgers, Health Subcommittee Chair Guthrie, Ranking Member Pallone, and Health Subcommittee Ranking Member Eshoo, thank you for holding this hearing and the important discussion around opportunities to improve research, treatment options, and access to care for people dealing with rare diseases. More than 30 million people in the United States live with a rare disease, many of whom experience life-threatening conditions with limited options for effective treatment.[i] The breadth of bipartisan bills considered in today's hearing is a testament to the work of this committee in prioritizing the unique health needs of people living with rare diseases who desperately need new and innovative treatments and medications to maintain and improve their health.

Specifically, we appreciate the opportunity to discuss the importance of access to prescription drugs and the ongoing affordability crisis that many families face when trying to obtain lifesaving and sustaining medications. Currently, 60% of U.S. adults take at least one prescription medication and 25% take four or more.[ii] Over the past 15 years, launch prices – the initial prices of drugs set by manufacturers – grew more than 20% each year.[iii] And even after launching, prices continue to increase at staggering rates leaving families and individuals paying more and more, year after year for their needed medications. For example, the price of Victoza (a popular diabetes and weight loss medication launched in 2010) increased a staggering 42% in just five years, rising from $7,936 per year in 2015 to $11,300 per year in 2020.[iv] This is a crisis that demands comprehensive solutions.

One of the most important steps towards addressing the high cost of drugs was passage of the *Inflation Reduction Act of 2022* (IRA), which included critical reforms such as giving Medicare the authority to negotiate for fair drug prices. The administration is currently working to implement those reforms faithfully, the full impact of which will be felt by patients and their families when negotiated prices go into effect for the first ten drugs in 2026. **Families USA has concerns that some of the legislation discussed in today's hearing would create unnecessary delays or carve-outs from IRA Medicare negotiation, in turn allowing big drug companies to continue price gouging families at the expense of their access to lifesaving and sustaining medication.**

<u>Legislation to lengthen exclusivity period before negotiation</u>

Currently, the IRA allows for drugs to become eligible for Medicare negotiation after a set length of time on the market: Small molecule drugs are eligible after being on the market for 7 years whereas biologics can only be eligible after they have been on the market for 11 years.[v] These time periods are longer for some types of drugs than the periods of exclusivity granted by federal bodies like the Food and Drug Administration, which grants exclusivity periods of 5 and 12 years (for small molecules and biologics respectively).[vi] The IRA ensures that drug companies are given an ample window of time to cover the costs of research and development (R&D) before their drugs are eligible for negotiation.

Yet, some of the proposed legislation, including H.R. 5539 *Optimizing Research Progress Hope and New (ORPHAN) Cures Act* and H.R. 5547 *Maintaining Investments in New Innovation (MINI) Act,* would lengthen the time a drug must be on the market prior to being eligible for Medicare price negotiation. Families USA has concerns that this kind of change would further limit the number of drugs eligible for negotiation to an even more narrow list, while allowing drug companies to continue abusing market exclusivity to drive up costs and unreasonably high profit margins.

Time and again, drug companies have shown that it is easier and more profitable for them to abuse their market and patent exclusivity privileges through tactics like pay-for-delay schemes and patent thickets

as a way to limit competition and raise prices rather than investing in new and innovative treatments that help people live longer, healthier lives.[vii] Congress should not allow the IRA, a law that will bring relief to millions of Americans who need affordable, accessible medication, to become another pawn in drug companies' gaming of the prescription drug market.

Legislation to exclude orphan drugs from Medicare drug negotiation

In order to ensure drug companies are incentivized to invest in R&D on innovative drugs for rare diseases, the IRA excludes rare drugs with a single designation for a rare disease or condition from being included in the Medicare drug negotiation program.[viii] These "orphan drugs," which are drugs that treat small populations of people with rare diseases or conditions, can provide lifelines for people with very limited treatment options.[ix] Drug companies also receive significant additional supports for investment in orphan drug development, including market and patent exclusivity, expedited access to markets, as well as 25% tax credits on qualified clinical trials.[x]

Families USA has concerns that attempts to further exempt orphan drugs from Medicare price negotiation under the IRA will allow drug companies to continue to move the goal posts for some of the drugs where price negotiation is most needed to ensure patient affordability. **H.R. 5539, *Optimizing Research Progress Hope and New (ORPHAN) Cures Act*, which would provide further orphan drug exemption from Medicare drug negotiation, unnecessarily creates further exemptions in the law for big drug companies.**

We need companies to invest in the development of new therapies that give new hope to people with limited or no treatment options, but those people also need to be able to afford the resulting medication in order to benefit from it. It is critical to strike a fair balance between drug innovation and affordability – orphan drugs are often some of the more expensive drugs on the market and their prices are rapidly growing. Drugs that treat rare diseases are *25 times more expensive* than non-orphan drugs and in 2017 the average annual cost for an orphan drug was $186,758.[xi]

Orphan drugs are quickly becoming a larger share of the drug market. In 2023, 43% of new drugs received orphan drug indications.[xii] From 1990 to 2022, 491 novel orphan drugs received approval, 15% of which have been approved for multiple conditions.[xiii] Adding additional types of orphan drugs to the list of exempt drugs under the proposed legislation would further chip away at the list of potential drugs eligible for negotiation. If Congress continues to add additional exclusions, particularly for growing portions of the drug market, the ability of the program to actually provide savings for millions of people who rely on Medicare winnows.

Orphan drugs are the prime example of why Medicare negotiation is so needed. Companies are charging exorbitantly high prices, even though they have benefited from significant financial incentives to research and create the drug – and the people who rely on them for chronic health conditions and all taxpayers that who contribute to the Medicare program are paying the price. The financial relief provided by Medicare negotiation would be most keenly felt by those with rare diseases. Conversely, exempting additional medications would be rewarding the predatory, profiteering behavior that necessitated creation of the Medicare negotiation program in the first place.

Conclusion

Affordability of a medication is at the heart of accessibility. If a person is forced to choose between filling their prescription and filling their fridge, or is skipping, taking over-the-counter medications instead of their prescription, or not filling their prescriptions at all because of cost – as almost 30% of adults in the U.S. taking medications do every year – then that treatment is not accessible to them.[xiv]

At a time when millions of families need relief from high costs, specifically in health care, Congress should focus on legislation that would bring costs down. Unfortunately, many of the proposed bills discussed in today's hearing not only fail to bring down costs, but further allow big drug companies to abuse their market exclusivity and perpetuate false arguments around research and development costs, all of which contributed to creating such high drug prices in the first place.

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[iii] Benjamin N. Rome, Alexander C. Egilman, and Aaron S. Kesselheim, "Trends in Prescription Drug Launch Prices, 2008- 2021," JAMA 327, no. 21 (2022): 2145–2147, https://jamanetwork.com/journals/jama/article-abstract/2792986.

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[x] Alexis-Danielle Roberts, and Roopma Wadhwa, "Orphan Drug Approval Laws," StatPearls [Internet], June 5, 2023, https://www.ncbi.nlm.nih.gov/books/NBK572052/#:~:text=The%20Orphan%20Drug%20Approval%20Law,ethical%20concerns%20and%20clinical%20significance.; Julie Kagan, Margaret James, and Michael Logan, "Orphan Drug Credit: What It Is, How It Works," Investopedia, July 31, 2021 https://www.investopedia.com/terms/o/orphan-drug-credit.asp#citation-1; 26 U.S. Code § 45C, https://www.law.cornell.edu/uscode/text/26/45C

[xi] "Drug Prices for Rare Diseases Skyrocket While Big Pharma Makes Record Profits," AHIP, September 10, 2019, https://www.ahip.org/news/press-releases/drug-prices-for-rare-diseases-skyrocket-while-big-pharma-makes-record-profits

[xii] Sean Tu, "WVU research shows how much pharmaceutical companies are capitalizing on rare drug incentives," WVU Today, June 12, 2023, https://wvutoday.wvu.edu/stories/2023/06/12/wvu-research-shows-how-much-pharmaceutical-companies-are-capitalizing-on-rare-drug-incentives

[xiii] Kathleen L. Miller, and Michael Lanthier, "Orphan Drug Label Expansions: Analysis of Subsequent Rare and Common Indication Approvals," Health Affairs, January 2024, https://www.healthaffairs.org/doi/10.1377/hlthaff.2023.00219

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National
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February 29, 2024

The Honorable Cathy McMorris Rodgers
Chair
House Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Frank Pallone, Jr.
Ranking Member
House Committee on Energy and Commerce
U.S. House of Representatives
2322A Rayburn House Office Building
Washington, D.C. 20515

RE: National Multiple Sclerosis Society Comment on E&C Subcommittee on Health Hearing, "Legislative Proposals to Support Patients with Rare Diseases"

The National Multiple Sclerosis Society (Society) thanks the Committee for holding a hearing focused on solutions to support patients living with rare diseases. While MS is not a rare condition, like many rare conditions, there is not yet a cure for MS. As the Committee undertakes its important work, we urge you to consider how to support research and foster innovation while ensuring such solutions are affordable and accessible to all. The Society has been strongly supportive of the Inflation Reduction Act (IRA), and we remain encouraged by its potential to bring down costs across the healthcare system for the 1 million people living with MS in the United States and the many more patients who rely on expensive life-changing medications.

Multiple sclerosis (MS) is an unpredictable disease of the central nervous system. Symptoms vary from person to person and may include disabling fatigue, mobility challenges, cognitive changes, and vision issues. The progress, severity, and specific symptoms of MS in any one person cannot yet be predicted but advances in research and treatment are leading to better understanding and moving us closer to a world free of MS. While there is not yet a cure, we do know that early diagnosis and treatment are critical to minimize disability and maximize health outcomes. For people with relapsing forms of MS, more than 20 disease modifying therapies

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(DMT) are available to reduce the number of relapses, slow disease progression, and protect the brain from damage due to the disease. Too often, however, these life-changing medications are financially out of reach for people with MS. The experiences of people with MS show us that conversations about innovation and solutions must go hand in hand with access and affordability.

MS is an expensive chronic disease, with the average total cost of living with MS at $88,487 per year.[1] MS may impact one's ability to work and can generate steep out-of-pocket costs related to medical care, rehabilitation, home/auto modifications, and more. For individuals living with MS, medical costs are an average of $65,612 more than for individuals who do not live with this disease. DMTs are the single most significant component of medical costs. As of February 2024, the median annual brand price of MS DMTs is more than $107,000. Five out of seven of the DMTs that have been on the market for at least 13 years are priced over $100,000 annually and continue to see regular price increases. List prices for the MS disease modifying treatments as of February 2024 are included along with this letter, first for all MS DMTs and then for brand only DMTs.

A 2019 survey conducted by the Society found that 40% of people living with MS alter or stop taking their medications due to high cost. These interruptions in DMT usage have adverse outcomes, including disease progression and increased risk of disease relapse. To live their best lives, individuals living with a chronic illness, like MS, need to know that they will be able to access life-changing medication. To ensure access to these essential therapies, all stakeholders in the healthcare industry (e.g., pharmaceutical manufacturers, payors, pharmacy benefit managers, etc.) must act transparently. Novel treatments are only helpful if people have access to them at an affordable price.

For the above-stated reasons, the Society supported the IRA to lower drug prices and increase affordable access to life-changing medications. We believe the IRA should be given the opportunity to work before bills like H.R. 5547 change provisions that will result in potentially higher costs for patients over a longer period of time.

[1] "B. Bebo et al. A Comprehensive Assessment of the total economic burden of multiple sclerosis in the United States. ECTRIMS 2021. 15, October, 2021.

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If you have any questions, please direct your staff to contact Natasha Silva, Senior Director of Federal Government Relations at natasha.silva@nmss.org.

Respectfully,

Bari Talente

Bari Talente
EVP, Advocacy and Healthcare Access
National MS Society

CC:
Chair Brett Gutherie (R-KY)
Ranking Member Anna Eshoo (D-16)

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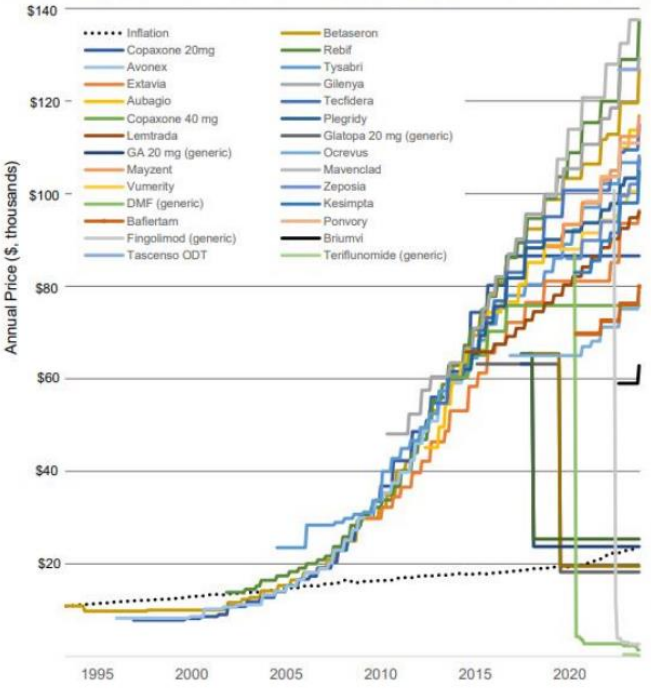
Trends in annual price for disease-modifying therapies for multiple sclerosis; 1993 to 2024



Notes: Annual price estimated from wholesale acquisition costs (First Databank)
Dashed line is projected annual price of Betaseron assuming only inflationary increases in price (CPI)
Lemtrada is based on four 12 mg vials (Package insert dosing: 12 mg/day (5 vials) for five consecutive days in first year; 12 mg/day (3 vials) for three days in year 2); DMF=dimethyl fumarate; GA=glatiramer acetate
Briumvi is based on maintenance dose of 450 mg (3 vials) twice a year;
*2023 to 2024 (January); **Generic, lowest WAC reported
Updated 2.19.2024 (Data through January 2024)

Drug (manufacturer; market entry)	1 Year Change*	Annual Price 2024
Interferons		
Betaseron (Bayer, July 1993)	6.0%	$126,787
Avonex (Biogen, May 1996)	5.6%	$107,456
Rebif (EMD Serono, Mar 2002)	6.5%	$137,354
Extavia (Novartis, Aug 2009)	3.0%	$96,373
Plegridy (Biogen, Aug 2014)	5.6%	$107,456
Glatiramer Acetate		
Copaxone 20mg (Teva, Dec 1996)	0.0%	$86,554
Copaxone 40 mg (Teva, Jan 2014)	0.0%	$75,816
Glatopa 20 mg (generic, Apr 2015)	0.0%	$18,250
Glatopa 40 mg (generic, Feb 2018)	0.0%	$19,500
GA 20 mg (generic, Oct 2017)	0.0%	$23,725
GA 40 mg (generic, Oct 2017)	0.0%	$25,350
S1P Receptor Modulators		
Gilenya (Novartis, Sept 2010)	2.0%	$129,349
Mayzent (Novartis, Mar 2019)	4.0%	$116,840
Zeposia (BMS, March 2020)	8.6%	$108,160
Ponvory (Janssen, March 2021)	0.0%	$110,916
Tascenso ODT (Cycle, Jan 2023)	0.0%	$126,813
*Fingolimod (generic, Aug 2022)***	-31.2%	$2,679
Fumarates		
Tecfidera (Biogen, Mar 2013)	5.5%	$114,916
Vumerity (Biogen, Nov 2019)	7.1%	$105,039
Bafiertam (Banner, Sept 2020)	5.0%	$80,000
*DMF (generic, Aug 2020)***	-50.0%	$1,369
Other Oral DMTs		
Aubagio (Sanofi, Sept 2012)	3.5%	$113,707
Mavenclad (EMD Serono, Mar 2019)	3.8%	$137,566
*Teriflunomide (generic, Mar 2023)***	-	$214
Monoclonal Antibodies		
Tysabri (Biogen, Nov 2004)	0.0%	$106,722
Lemtrada (Sanofi, Nov 2014)	3.8%	$95,994
Ocrevus (Genentech, Mar 2017)	5.0%	$78,858
Kesimpta (Novartis, Aug 2020)	7.0%	$104,827
Briumvi (TG Therapeutics, Jan 2023)	6.5%	$62,835

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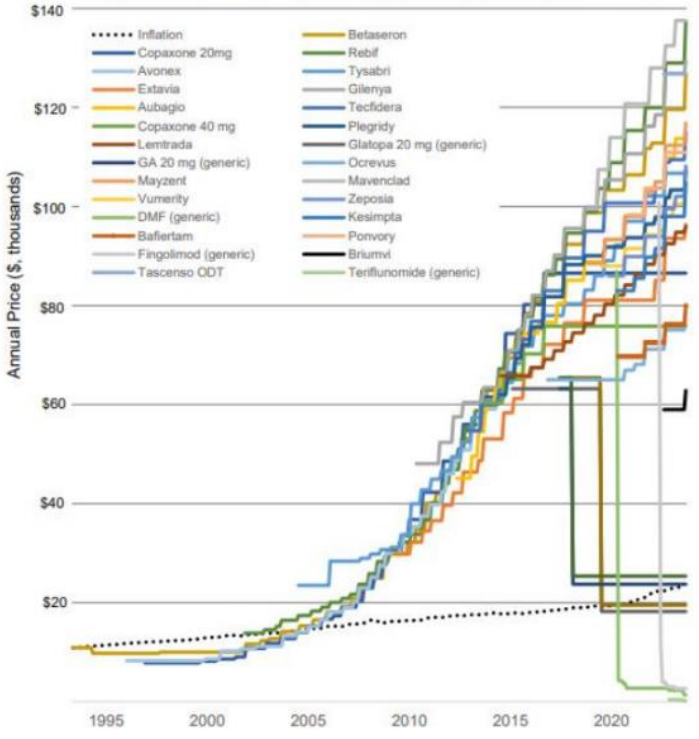
Trends in annual price for disease-modifying therapies for multiple sclerosis; 1993 to 2024



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Submitted Public Comment of Steve Wosahla, Chief Executive Officer,
Children's Cancer Cause

House Energy and Commerce, Health Subcommittee
Hearing on "Legislative Proposals To Support Patients With Rare Diseases"
February 29, 2024

Chair, Ranking Member, and other Members of the Committee,

Thank you for holding this important hearing about supporting patients with rare diseases.

Children's Cancer Cause is a leading national childhood cancer advocacy organization, dedicated to creating a brighter future for children, survivors, and their families. Founded in 1999, we promote policies and programs to accelerate the development of safer, more effective cancer therapies for children and improve care for the lifelong health challenges experienced by childhood cancer survivors. Childhood cancers are rare diseases, with about 15,000 cases diagnosed annually in the United States in individuals younger than 20 years according to the National Cancer Institute (NCI). We are pleased to support several of the bills included in the House Energy and Commerce Committee hearing of February 29, 2024.

We support H.R. 6664, introduced by Representatives Eshoo and McCaul, the Innovation in Pediatric Drugs Act of 2023, and appreciate the Committee's work on the bill. H.R. 6664 will speed access to therapies to children who need them—including children with cancer and other rare diseases—by allowing the Food and Drug Administration (FDA) to ensure that required pediatric drug studies are completed on time.

The biology of childhood cancers are different from cancers in adults. Drugs to treat children must be developed and tailored for children. The Innovation in Pediatric Drugs Act of 2023 builds upon the Research to Accelerate Cures and Equity (RACE) For Children Act to increase pediatric studies of novel drugs to treat childhood cancers. H.R. 6664 is an important step to ensure that the FDA can require completion of RACE Act studies in children as it does for studies in adults.

H.R. 6664 enhances the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), laws that incentivize and require the study of drugs in children. Data from BPCA and PREA studies are added to drug labels to give providers and families essential information on the safety and efficacy of drugs used in children.

- The Innovation in Pediatric Drugs Act amends PREA to lift its orphan exemption, ensuring that children with rare diseases can benefit fully from its pediatric research requirements as follows:
- FDA can require postmarketing studies in adults but cannot require these studies for children. FDA is prohibited from penalizing companies for failure to conduct postmarking studies in children, under PREA, but is allowed to penalize companies for failure to conduct these studies in adults. The Innovation in Pediatric Drugs Act will amend PREA to give FDA the authority to ensure that legally required pediatric studies are completed in a timely way, parallel to its authority for adult studies.
- The Innovation in Pediatric Drugs Act would also increase the authorization of a BPCA program at the National Institutes of Health from $25 million to $50 million. The BPCA NIH program has been flat-funded at $25 million since its original authorization in 2002. This program is key to prioritizing research on off patent drugs, vital to childhood cancer treatment.

Second, we support H.R. 3089, the Accelerating Kids' Access to Care Act, introduced by Representatives Trahan and Miller-Meeks. The Accelerating Kids' Access to Care Act simplifies the Medicaid out-of-state provider enrollment process by allowing children access to care from a provider out of their home state. Early treatment of childhood cancer is critical to treatment outcomes, and delays in early access to therapy can prove dire. Currently, an out-of-state provider must first be screened and enrolled in a child's home state Medicaid program despite being enrolled in the out of state Medicaid program. The Accelerating Kids' Access to Care Act will create a national enrollment pathway to alleviate the administrative burden on providers and ensure that children are able to receive the timely out-of-state cancer care that they need.

Finally, we support H.R. 7384, the Creating Hope Reauthorization Act of 2024, introduced by Representatives McCaul and Eshoo. The Creating Hope Reauthorizing Act of 2024 will extend reauthorization until September 30, 2028, an FDA program that awards Pediatric

Rare Disease Vouchers to companies obtaining approval for drugs and biologics that target rare pediatric diseases.

In closing, I want to emphasize the need to work together to ensure access to lifesaving therapies for children with cancer. We look forward to the opportunity to work with the Subcommittee on this critical issue.

February 26, 2024

The Honorable Brett Guthrie
Chair, Energy & Commerce Committee's
Subcommittee on Health
U.S. House of Representatives
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Energy & Commerce Committee's
Subcommittee on Health
U.S. House of Representatives
Washington, DC 20515

Dear Chair Guthrie and Ranking Member Eshoo:

The Patients & Providers for Medical Nutrition Equity (PPMNE), a national coalition of 45 patient and provider organizations that represent individuals for whom specialized nutrition is medically necessary for treatment of their gastrointestinal (GI) or inherited metabolic disease or disorder, write with support of the Committee's February 29 hearing "Legislative Proposals to Support Patients with Rare Diseases." While the *Medical Nutrition Equity Act (H.R. 6892)* is regrettably not included among the bills subject to the hearing, it is legislation strongly supported by the rare disease community. Specifically, H.R. 6892 ensures that patients with GI or inherited metabolic disorders have access to medically necessary nutrition, which includes specialized foods and formulas, to treat their diseases and disorders.

H.R. 6892 builds on the coverage of medically necessary nutrition Congress passed for TRICARE beneficiaries by extending coverage to other payors.

While the legislation has just been re-introduced this Congress by Representatives McGovern and Rutherford, our community has been advocating for passage of some version of it for over a decade and it secured significant bi-partisan support in the 117th Congress. Nearly all GI and metabolic diseases or conditions included in the *Medical Nutrition Equity Act* are considered rare diseases. Therefore, we hope you will consider H.R. 6892 for future Committee action this Congress.

The 2022 formula shortage highlighted the necessity of specialized formulas for the children and adults who rely on them for both treatment and sustenance. These formulas are not discretionary for patients with these disorders; they are essential to their medical management and survival. We encourage you to visit nutritionequity.org/category/states to read stories from individuals in your states and from across the country which underscore why passage of this legislation is imperative.

The importance of improving access to medically necessary nutrition for patients with GI and metabolic disorders was included in the White House's 2023 National Strategy on Hunger, Nutrition and Health. Congress has also recognized the importance of improving coverage of medically necessary nutrition by including language similar to the *MNEA* in the 2016 *National Defense Authorization Act* for TRICARE beneficiaries. The out-of-pocket costs for specialized formulas and foods to treat GI and metabolic disorders can reach thousands of dollars per month, and, for many patients and families, cost is a barrier to access and treatment. It is time to extend coverage to other insured populations.

Many members of our community are attending Rare Disease Week on Capitol Hill today. We ask that this letter and the attached fact sheet be submitted for the hearing record. We look forward to working with you to advance H.R. 6892 this Congress. Please contact Megan Gordon Don at 202.246.8095 or mgdon@mgdstrategies.com with questions or requests for additional information.

Sincerely,

Patients & Providers for Medical Nutrition Equity Coalition

Innovation in Pediatric Drugs Act of 2023

Children are not just small adults. Drugs work differently in children and must be studied specifically for their use. Yet too often, drug development still leaves children behind. The **Innovation in Pediatric Drugs Act of 2023 (H.R. 6664)**, sponsored by Rep. Anna Eshoo (D-Calif.) and Rep. Mike McCaul (R-Texas), will help speed therapies to children who need them—including children with pediatric cancer and other rare diseases—by making needed changes to the pediatric drug laws.

PEDIATRIC DRUG LAWS: AN OVERVIEW

The Innovation in Pediatric Drugs Act would make needed improvements to the **Best Pharmaceuticals for Children Act (BPCA)** and the **Pediatric Research Equity Act (PREA)**, two laws that encourage and require the study of drugs in children. Data resulting from BPCA and PREA studies are added to drug labels to give parents and providers essential information on the safety and efficacy of drugs used in children.

PREA requires drug companies to study adult drug indications in children when children could benefit from pediatric studies. In 2017, the **Research to Accelerate Cures and Equity** (**RACE) for Children Act** amended PREA so that FDA could require companies to conduct pediatric studies of new adult cancer therapies whose molecular targets are relevant to pediatric cancers. Prior to 2017, PREA in effect excluded most oncology drugs from pediatric testing because cancers were understood by their location in the body.

BPCA is a voluntary incentive for drug companies to conduct FDA-requested pediatric studies—especially for off-label drug uses—in return for an additional six months of marketing exclusivity.

THE INNOVATION IN PEDIATRIC DRUGS ACT

Ensuring Drugs for Rare Diseases are Studied in Children

There are close to 7,000 rare diseases without appropriate treatments, and the vast majority of orphan diseases affect children. Unfortunately, in most cases, FDA is not allowed to require orphan drugs (drugs for rare diseases) to be studied in children under PREA.

Orphan drugs used to account for a small minority of annual drug approvals. Yet today, the majority of drugs approved are orphan drugs, meaning that the majority of newly approved drugs are exempt from pediatric study requirements.

In 2019, FDA released a study on the pediatric research gaps that have resulted from the PREA orphan exemption. It showed that 36% of pediatric-relevant orphan drugs approved since 1999 lacked some or all pediatric data.

Congress previously passed the RACE for Children Act, which lifted the PREA orphan drug exemption to allow studies for some orphan drugs for cancer. The time is now to lift the orphan exemption for all children with rare diseases.

The Innovation in Pediatric Drugs Act would amend PREA to lift its orphan exemption, ensuring that children with rare diseases can benefit fully from the pediatric research requirements.

Providing Equal Accountability for Pediatric Study Requirements

Due dates for PREA studies are typically deferred by FDA until a date after the approval of the drug for adults. Unfortunately, FDA has no effective enforcement tools to ensure that these studies actually get completed on time—or at all.

Congress tried to solve this problem in 2012. It allowed FDA to send "non-compliance letters" to companies that failed to complete their pediatric studies. Disappointingly, this did not fix the problem. According to an analysis conducted by the American Academy of Pediatrics, as of early 2021, 123 PREA non-compliance letters had been issued, yet only 41 (33%) of these instances of non-compliance had been resolved. That left 82 (67%) instances of non-compliance unresolved with studies still late. The average late study was 4.4 years late. Twenty-one studies were between 5-10 years late, 7 were 10-15 years late, and 3 were more than 15 years late.

FDA requirements for postmarket studies in adults can be effectively enforced, but requirements for postmarket studies in children cannot. If a company fails to complete adult postmarket studies, FDA can penalize the company by imposing a fine but it is prohibited, by law, from applying those penalties to pediatric postmarket studies under PREA.

If FDA is not given additional enforcement tools, not only will these studies required in the past not get completed, but future studies will be in jeopardy too, including pediatric cancer studies required under the RACE for Children Act, which went into effect in 2020.

The Innovation in Pediatric Drugs Act would amend PREA to give FDA the authority it needs to ensure that legally required pediatric studies are completed in a timely way.

Investing in Pediatric Studies of Older Off-Patent Drugs

The FDA incentives and requirements under BPCA and PREA work for many newer drugs, but unfortunately cannot help encourage studies of older drugs.

For this reason, Congress in 2002 authorized a BPCA program at the National Institutes of Health. This program funds NIH to do studies of off-patent drugs used in children that companies cannot be incentivized or required to conduct. To date, 18 pediatric drug labels have been changed through this program.

The BPCA NIH program has been flat-funded at $25 million since its original authorization in 2002. Drug studies are expensive and while the program is an efficient use of scare resources, the $25 million funding level is insufficient to meet the current needs. When accounting for biomedical research inflation, the purchasing power of the program in 2022 was only 56% of what it was in 2002.

The Innovation in Pediatric Drugs Act would address this inequity by amending BPCA to increase the authorization level of this program to $50 million to keep up with the increasing need for and cost of these studies.

For more information, please contact James Baumberger (jbaumberger@aap.org) at the American Academy of Pediatrics.

CONGRESSIONAL BUDGET OFFICE
U.S. Congress
Washington, DC 20515

Phillip L. Swagel, Director

December 21, 2023

Honorable Jodey Arrington
Chairman
Committee on the Budget
U.S. House of Representatives
Washington, DC 20515

Honorable Michael C. Burgess
U.S. House of Representatives
Washington, DC 20515

Re: Additional Information About Drug Price Negotiation and CBO's Simulation Model of Drug Development

Dear Chairman Arrington and Congressman Burgess:

This letter provides additional information that you and your colleagues requested about the Congressional Budget Office's analysis and model related to federal policies that affect the development of new drugs in the United States. In particular, you asked:

- How CBO's estimates of the budgetary effects of prescription drug provisions in the 2022 reconciliation act account for which drugs will be selected for price negotiation and for the effects on prices of competing drugs in the same therapeutic class as those selected for negotiation;

- How CBO's simulation model of drug development assesses potential changes in demand attributable to increases in the initial price of drugs when they come to market;

- Whether CBO's model accounts for changes in the indications (that is, the medical conditions that drugs are used to treat) that companies target when developing new drugs; and

- What changes to the model CBO may consider making to account for several factors, including ongoing trends in investment in early-stage drug development by venture capital firms, the law's effects on companies' decisions about which indications to target, and new research and data that could be used to refine and enhance the model.

Background

Under the 2022 reconciliation act (Public Law 117-169), the Secretary of Health and Human Services will negotiate prices for certain prescription drugs covered under Medicare Part B and Part D. To be selected for negotiation, a Part D drug must be among the 50 top-selling drugs without an approved generic equivalent or biosimilar competition in Part D. When Part B drugs become eligible for negotiation in 2026, those selected must likewise be among the 50 top-selling drugs in Part B. Selected drugs must meet other criteria as well.

CBO estimated that price negotiation will lower average drug prices paid by Medicare and will reduce the budget deficit by $25 billion in 2031.[1] The agency further estimated that average drug prices in 2031 will be 9 percent lower in Part B and 8 percent lower in Part D (net of rebates and discounts) because of negotiation.[2]

The 2022 reconciliation act also requires drug manufacturers to pay an inflation rebate to Medicare for each unit of a drug that is sold to a Medicare beneficiary, if the drug's reference price exceeds its inflation-adjusted benchmark in any given year. (In Part B, the reference price is the drug's average sales price; in Part D, it is the average manufacturer price.) CBO estimated that average net prices of drugs in both Part B and Part D will be 2 percent lower in 2031 than they would have been without the inflation-rebate provisions and that overall, those provisions will reduce the federal budget deficit by $8 billion in that year.

CBO's cost estimate for the 2022 reconciliation act accounts for how the law will affect companies' decisions about whether to develop new drugs. The agency used a simulation model to estimate the law's impact on the number of new drugs coming to market and how legislation could affect that number over time. CBO estimated that over the next 30 years, 13 fewer new drugs (of 1,300 estimated new drugs) will come to market as a result of the law.

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[1] Congressional Budget Office, estimated budgetary effects of Public Law 117-169, an act to provide for reconciliation pursuant to title II of S. Con. Res. 14 (September 7, 2022), www.cbo.gov/publication/58455.

[2] Congressional Budget Office, "How CBO Estimated the Budgetary Impact of Key Prescription Drug Provisions in the 2022 Reconciliation Act" (February 2023), www.cbo.gov/publication/58850.

Additional Information About CBO's Estimates of the Budgetary Effects of Drug Provisions in the 2022 Reconciliation Act

CBO's estimates of the budgetary effects of drug provisions in the 2022 reconciliation act incorporate certain expectations about how the law will be implemented. To date, decisions made by the Centers for Medicare & Medicaid Services (CMS) have been largely consistent with those expectations.

For example, you asked whether the selection of certain drugs for price negotiation—namely, those about to face competition from biosimilar or generic drugs—has changed CBO's assessment of the budgetary effects of the law's drug provisions. CBO's estimates took that factor into account. The agency's assessment of the effects of those provisions incorporates the expectation that some drugs selected for negotiation would never be subjected to price reductions as a result of negotiation, because generic or biosimilar drugs would enter the market before the selected drugs' negotiated prices take effect.

CBO's assessment also incorporates the expectation that CMS will negotiate drug prices on the basis of a drug's active ingredient instead of its trade name or approval date; in practice, that is how CMS has approached negotiations thus far. CBO will continue to monitor the implementation of the 2022 reconciliation act's prescription drug provisions to understand how it may affect the federal budget.

Price and Demand Responses to the Law's Drug Provisions. CBO expects that the prescription drug provisions in the 2022 reconciliation act will affect the prices of drugs in several ways. For example, in the agency's assessment, drug companies will increase the list price of drugs entering the market as a response to the law's inflation-rebate provisions and, to a much lesser extent, its negotiation provision.[3]

Nevertheless, the agency expects that, net of rebates and discounts, drug prices in the commercial and Medicare Part D segments of the market will be affected only slightly, if at all, by those higher list prices. That is because drug manufacturers will raise rebates to offset increases in list prices and maintain net prices to maximize revenues in those market segments. (CBO's estimates of the 2022 reconciliation act's impact on overall drug prices account for that behavior.) Considering the limited

[3] For a more detailed discussion, see Congressional Budget Office, letter to the Honorable Jason Smith providing additional information about prescription drug legislation (August 4, 2022), www.cbo.gov/publication/58355.

changes in net prices of new drugs, CBO expects that the demand for those drugs will be largely unaffected.

CBO's estimates of the budgetary effects of the 2022 reconciliation act also account for the impact of the law's negotiation provision on the prices of drugs that are therapeutic competitors to those chosen for price negotiation. The agency expects that prices will decrease for drugs that do not have negotiated prices but that are therapeutic competitors to those selected for negotiation. The savings from those reduced prices account for less than 5 percent of the estimated budgetary savings attributable to the law's negotiation policy.

Effects of the Law's Drug Provisions on Drug Availability and Health Outcomes. A key factor in CBO's estimate of the number of new drugs that would come to market is the projected size of the law's effect on companies' expected revenues. In the case of the 2022 reconciliation act, the agency estimated that global revenues from sales of new drugs would fall by 1 percent to 3 percent. The effect on revenues reflects three key factors: first, that manufacturers can adjust their pricing strategy for future drugs to account for the law's provisions governing price negotiation and the inflation rebate; second, that reductions in prices attributable to the negotiation provision would occur only after a drug has been on the market for about a decade; and third, that the negotiation provision applies only to drugs in the Medicare program.

Although CBO's estimates of the effects of the law's drug provisions account for how companies make broad decisions about whether to develop new drugs, the agency has not assessed how the provisions might affect companies' strategies for developing specific drugs or which indications are targeted for a given drug. CBO has also not assessed how those strategies or choices would affect the timing of drugs' availability or patients' health outcomes.

Trends in Venture Capital Investment in Drug Development

Using data from the business-information provider Crunchbase, CBO has examined how the share of venture capital firms' investment that goes to pharmaceutical companies has changed since the 2022 reconciliation act became law in August of that year. (The available data from Crunchbase relate to firms' overall investment in pharmaceutical companies rather than their specific investment in early-stage drug development.)

Although investments vary from month to month, there is currently no evidence of a systematic decrease in the percentage of venture capital

flowing to pharmaceutical companies after August 2022—or in the period immediately preceding the law's enactment (when there was probably some public awareness of its provisions). In fact, the share of venture capital reaching pharmaceutical companies has been trending upward (see Figure 1 on page 7). That trend is consistent with estimates developed using CBO's current model, as is other recent evidence on industry-wide behavior since the 2022 reconciliation act became law.[4] CBO will continue to work to understand how investments in drug development may evolve and will update its model on the basis of any new evidence.

CBO's Transparency Efforts and Planned Future Work

Transparency is a top priority for CBO. The agency's initial version of its simulation model of drug development was described in a technical paper published on its website in August 2021.[5] CBO revised the model after receiving feedback from various stakeholders, including Congressional staff, representatives from the pharmaceutical industry, and academic experts. The revisions, which included a change in the way the model accounts for the effects of federal policies on early-stage drug development, are described in a slide deck that the agency published in January 2022.[6]

In addition to publishing that working paper and slide deck, CBO has presented and described its drug development model at an annual conference of the American Society of Health Economists, the Dartmouth Institute for Health Policy & Clinical Practice, and a health economics seminar cosponsored by Boston University, Harvard University, and the Massachusetts Institute of Technology.[7]

CBO will continue to improve its simulation model of new drug development. For example, the agency will explore ways to expand the model to estimate how the effects of policies may vary for drugs with different characteristics, such as small- or large-molecule drugs or those

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[4] See Richard G. Frank and Ro W. Huang, "Early Claims and M&A Behavior Following Enactment of the Drug Provisions in the IRA" (Brookings Institution, August 23, 2023), http://tinyurl.com/2bzx8r5x; and ATI Advisory, *Pharmaceutical Innovation and the Inflation Reduction Act: What Can We Learn From the First Half of 2023?* (November 2023), http://tinyurl.com/3fyr9knr.

[5] Christopher Adams, *CBO's Simulation Model of New Drug Development*, Working Paper 2021-09 (Congressional Budget Office, August 2021), www.cbo.gov/publication/57010.

[6] Christopher Adams, "CBO's Model of New Drug Development" (presentation to the Dartmouth Institute for Health Policy & Clinical Practice, January 13, 2022), www.cbo.gov/publication/57450.

[7] Christopher Adams, "CBO's Model of New Drug Development" (presentation to the Health Economics Seminar cosponsored by Boston University, Harvard University, and the Massachusetts Institute of Technology, February 2, 2022), www.cbo.gov/publication/57449.

that target certain diseases or patient populations (such as the elderly). As part of those efforts, the agency will also explore the possibility of expanding the model to allow for indication-specific estimates of drug development, as evidence permits.

Moreover, CBO continues to request and receive feedback to help inform potential refinements and improvements to its drug development model and its estimates of the budgetary effects of legislation that would affect the development of new drugs. The agency recently published a blog post highlighting its work in that area and calling for new research to further enhance that work.[8]

I hope this information is useful to you. Please contact me directly if you have further questions.

Sincerely,

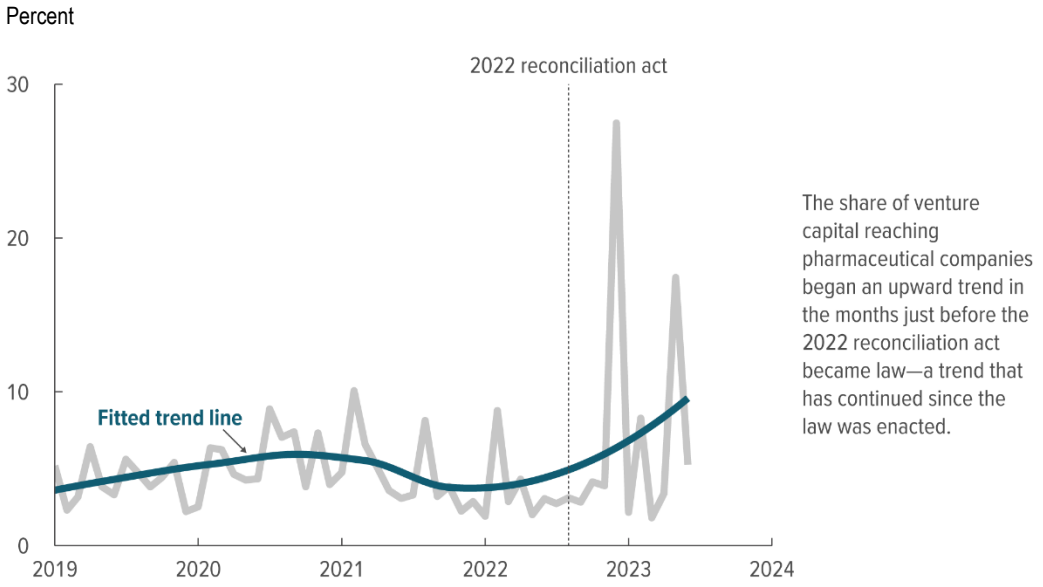
Phillip L. Swagel
Director

cc: Honorable Brendan Boyle, Ranking Member, Committee on the Budget; Honorable Earl L. "Buddy" Carter; Honorable A. Drew Ferguson IV; Honorable Blake D. Moore; Honorable Chip Roy; Honorable Lloyd Smucker; Honorable Rudy Yakym III

[8] Congressional Budget Office, "A Call for New Research in the Area of New Drug Development," *CBO Blog* (December 20, 2023), www.cbo.gov/publication/59818.

Figure 1.

Share of Venture Capital Flowing to Pharmaceutical Companies



Data source: Congressional Budget Office, using monthly data from the business-information provider Crunchbase.

Mease *et al.*
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Orphanet Journal of Rare Diseases

RESEARCH

Open Access

Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development

Catherine Mease[1*], Kathleen L. Miller[1], Lewis J. Fermaglich[1], Jeanine Best[2], Gumei Liu[3] and Erika Torjusen[1]

Abstract

Background The Rare Pediatric Disease (RPD) Priority Review Voucher (PRV) Program was enacted in 2012 to support the development of new products for children. Prior to requesting a voucher, applicants can request RPD designation, which confirms their product treats or prevents a rare disease in which the serious manifestations primarily affect children. This study describes the trends and characteristics of these designations. Details of RPD designations are not publicly disclosable; this research represents the first analysis of the RPD designation component of the program.

Results We used an internal US Food and Drug Administration database to analyze all RPD designations between 2013 and 2022. Multiple characteristics were analyzed, including the diseases targeted by RPD designation, whether the product targeted a neonatal disease, product type (drug/biologic), and the level of evidence (preclinical/clinical) to support designation. There were 569 RPD designations during the study period. The top therapeutic areas were neurology (26%, n = 149), metabolism (23%, n = 131), oncology (18%, n = 105). The top diseases targeted by RPD designation were Duchenne muscular dystrophy, neuroblastoma, and sickle cell disease. Neonatology products represented 6% (n = 33), over half were for drug products and 38% were supported by clinical data.

Conclusions The RPD PRV program was created to encourage development of new products for children. The results of this study establish that a wide range of diseases have seen development—from rare pediatric cancers to rare genetic disorders. Continued support of product development for children with rare diseases is needed to find treatments for all children with unmet needs.

Keywords Rare pediatric diseases, Food and Drug Administration, Children, Designations, Drug development

*Correspondence:
Catherine Mease
catherine.mease@fda.hhs.gov
[1] Office of Orphan Products Development, Office of the Commissioner, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA
[2] Office of Pediatric Therapeutics, Office of the Commissioner, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA
[3] Office of Therapeutic Products, Center for Biologics Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA

Introduction

Product development for pediatric populations faces numerous challenges. These include difficulties in patient enrollment and retention, dosing and safety challenges, and ethical considerations [1–4]. Additionally, the market for therapeutics in pediatric populations is smaller than for the adult population and therefore may be less attractive to for-profit developers [5]. As a result, there is a significant dearth in the number of approved drugs and biologics for pediatric use [6, 7]. While financial incentive programs exist, such as those created by the

Orphan Drug Act, these challenges are especially acute in rare pediatric diseases [8]. One way to address this unmet need is through the provision of additional financial incentives for companies to pursue pediatric product development.

Over the decades, U.S. Congress has passed numerous laws to encourage or require the development of therapeutics for children [9]. These include the Best Pharmaceuticals for Children Act (BPCA) of 2002 (which provides incentives to drug developers who voluntarily complete pediatric studies for their product) and the Pediatric Research Equity Act (PREA) of 2003 (which allows the US Food and Drug Administration [FDA] to require pediatric studies for certain products) [10–12]. However, products for rare diseases with orphan drug designation, exclusive of pediatric cancers, are exempt from the requirements of PREA [13, 14]. Therefore, an additional incentive program specific to rare diseases in children, the Rare Pediatric Disease (RPD) Priority Review Voucher (PRV) Program, was established in 2012 with enactment of the Food and Drug Administration Safety and Innovation Act [15–17].

PRVs are financial incentives to drug and biologic development, which are also awarded for approval of certain marketing applications for tropical diseases and medical countermeasures [16, 18, 19]. For RPD, companies may be awarded an RPD PRV when their rare pediatric disease product application is approved by the FDA [16]. The PRV can be redeemed for a priority review (a goal of six months of regulatory review time) instead of a standard review (a goal of ten months of regulatory review time) for a subsequent product application submitted for FDA approval or can be transferred to a third party [20]. The reported purchase prices of PRVs to third parties averages about $100 million (range $67.5 million to $350 million) [21, 22].

Prior to companies receiving an RPD PRV, a determination must be made that a drug or biologic is for a rare pediatric disease. Although RPD designation is not required prior to requesting an RPD PRV, the FDA strongly encourages companies to submit a request for RPD designation prior to submission of a potential rare pediatric disease product application. All applicants must document in their voucher request how their application meets RPD PRV eligibility criteria, including support that their drug or biologic is for the prevention or treatment of a rare pediatric disease, which may be established by RPD designation [16, 23].

To be granted RPD designation, an applicant must submit a request that includes data supporting the proposed mechanism of action of the drug or biologic (e.g., clinical, preclinical: in vivo, and preclinical: in vitro). Additionally, the applicant must demonstrate that the disease is a "rare pediatric disease," defined as a life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, and the total prevalence of the disease, including adults and children, affects fewer than 200,000 people [16, 23]. The RPD designation portion of the RPD PRV program is administered by the Office of Orphan Products Development in collaboration with the Office of Pediatric Therapeutics within the Office of the Commissioner at the FDA.

The primary objective of this study was to provide a 10-year retrospective analysis of RPD designations from the program initiation in 2013. This is the first time this data is being made available as RPD designations are not publicly disclosable. An analysis of the first decade of RPD designations provides important information for stakeholders, as limited information is available in the public domain and the RPD PRV program is due to sunset in 2024 if Congressional action is not taken to renew it. This retrospective analysis additionally builds on previous research that investigates the impact of legislation on rare pediatric product development [15, 24].

Methods

We used an internal FDA database to analyze all RPD designations, from 2013 to 2022. The dataset included: (1) date of designation; (2) product name; (3) disease description; (4) approval; and (5) voucher status.

The dataset also included whether the product was therapeutic, preventative, or diagnostic for management. Per FDA's RPD PRV guidance: "[a]n application may qualify as a rare pediatric disease product application if it is for a drug or biologic that is a diagnostic for the management of a disease or condition. We note, however, that such diagnostic products must be the subject of a NDA [new drug application] or BLA [biologic license application] to qualify as a rare pediatric disease product application, as diagnostic products that are the subject of medical device applications are not eligible for a rare pediatric disease[s] priority review voucher. An application for a drug for the initial diagnosis of a disease or condition will not qualify as a rare pediatric disease product application" [16].

Finally, the dataset included whether the designation was subject to the 60-day statutory review deadline or not. A designation request receives a 60-day FDA review clock when it is submitted concurrently with a request for fast-track designation or orphan drug designation [8, 25]. Those requests submitted without either additional designation request do not have a statutory review goal date, but FDA aims to respond to such requests in a timely manner.

Using this initial dataset, we constructed multiple additional variables for analysis. We assigned a therapeutic area to each designation, which was based primarily upon the general disease process (e.g., oncology, infectious disease) and secondarily, the most affected organ system [26].

All RPD disease descriptions were converted from longer phrases (e.g., "For the treatment of Angelman syndrome") to simplified disease terms (e.g., Angelman syndrome) to allow for aggregation across designations. To confirm that each disease term was a recognized and described disease or condition, we used a uniform system of disease terminology ("Mondo") created to facilitate integration and consistency of disease nomenclature across various ontology resources [27].

Additionally, we created a dichotomous variable to identify designations for neonatology conditions. Neonatology conditions were defined as disorders in children up to 44 weeks post-menstrual age that were: (1) conditions related to prematurity and physiologic immaturity, or (2) conditions in which the serious or life-threatening manifestations primarily affect neonates or typically present during the neonatal period and the time to intervene occurs during the neonatal period [28]. Metabolic diseases that require lifelong treatment were not included in the neonatology definition.

For drug and biologic descriptions, a product type category was constructed by determining whether the designated products were biologic or drug products. Within the biologic product type category, we further identified all vaccines, monoclonal antibodies, cell therapies, and gene therapies. We also identified all antisense oligonucleotide products within the drug product type category.

We constructed a variable to investigate the level of scientific evidence used to support the request for RPD designation. Designations were categorized into those that utilized clinical data, preclinical in vivo data, or preclinical in vitro data, all of which are acceptable to support designation. Clinical evidence was further classified into applicant-derived clinical data, clinical trial data cited from the literature ("cited clinical trial"), or a case study cited from the literature ("cited case study").

Lastly, we gathered data on annual counts and therapeutic areas of the RPD PRVs that have been awarded based on the approval of a product for a rare pediatric disease.

Results

There have been 569 RPD designations since the inception of the RPD PRV program through December 31, 2022 (Fig. 1). Annual designation frequency was relatively constant over this period with the exception of

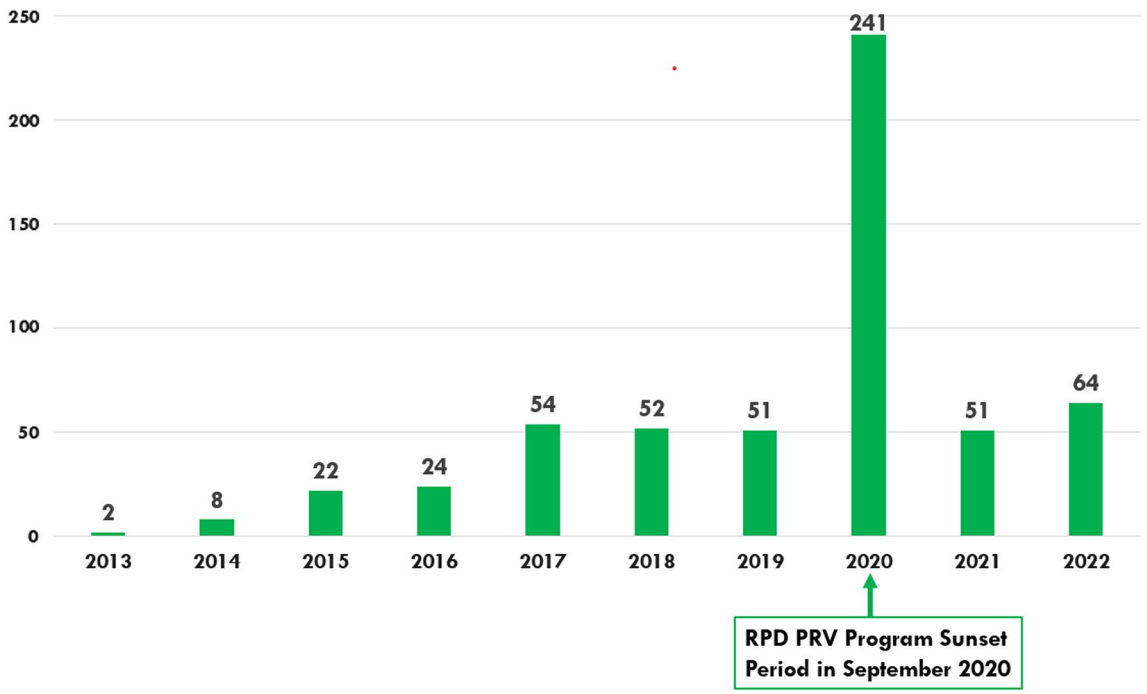

Fig. 1 Number of RPD designations per year, 2013–2022 (n = 569). On December 27, 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended. Under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the product, and that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers

2020 (the year the program was set to begin sunsetting), during which a nearly five-fold increase was observed. This single year accounted for 42% (n = 241) of the total designations.

Fifty-four percent (n = 305) of the designations had a statutory FDA review clock of 60 days and 46% (n = 264) of the designations did not have a review clock. The number of designation requests with a 60-day FDA review clock has steadily increased over the years suggesting that more RPD designation requests are being submitted concurrently with a request for fast-track or orphan drug designation.

Treatments, prophylactics, and diagnostics for management

Virtually all RPD designations were for treatments (95%, n = 538). Diagnostics for management of diseases comprised 3% (n = 19) of designations and prophylactic products 2% of designations (n = 12).

Therapeutic areas

The top five therapeutic areas were neurology (26%, n = 149), metabolism (23%, n = 131), oncology (18%, n = 105), hematology (6%, n = 32), and immunology (4%, n = 25) (Table 1). Metabolism had the greatest number of diseases represented with 70 unique diseases targeted by RPD-designated products.

Diseases targeted by RPD designations

A total of 245 diseases were represented in the RPD designations granted in the ten-year period between 2013 and 2022. There were 26 diseases with five or more associated RPD designations, which, in total, accounted for 41% of all RPD designations (n = 233) (Table 2). Diseases

Table 1 RPD designations by therapeutic areas, 2013–2022

Therapeutic area	Number of RPD designations	Percentage of total RPD designations (%)	Number of diseases associated with at least 1 RPD designation within therapeutic area	Number of RPD designations per disease within therapeutic area
Neurology	149	26	63	2.4
Metabolism	131	23	70	1.9
Oncology	105	18	22	4.8
Hematology	32	6	8	4
Immunology	25	4	16	1.6
Ophthalmology	22	4	16	1.4
Dermatology	21	4	10	2.1
Pulmonary	15	3	6	2.5
Orthopedics	15	3	6	2.5
Endocrinology	12	2	6	2
Gastroenterology	12	2	7	1.7
Cardiology	9	2	5	1.8
Infectious diseases	9	2	6	1.5
Otorhinolaryngology	5	1	2	2.5
Nephrology/urology	4	1	3	1.3
Transplant	2	< 1	2	1
Pharmacology/toxicology/poisoning/chelators	1	< 1	1	1

Table 2 Distribution of RPD designations per disease

Disease breakdown	Number of diseases	Percentage of total diseases (n = 245) (%)	Percentage of total RPD designations (n = 569) (%)
Number of diseases associated with 1 RPD designation	152	62	27
Number of diseases associated with 2 RPD designations	32	13	11
Number of diseases associated with 3 RPD designations	18	7	9
Number of diseases associated with 4 RPD designations	17	7	12
Number of diseases associated with 5 or more RPD designations	26	11	41

associated with only one designated product accounted for 62% (n = 152) of total diseases targeted by RPD designation. The remaining 38% (n = 93) of diseases were associated with two to four RPD designations.

Table 3 presents diseases associated with the most RPD designations. Three of the top five diseases targeted by RPD designation were cancers: neuroblastoma, diffuse intrinsic pontine glioma, and osteosarcoma.

Neonatology

Products designated to treat neonatal conditions represented 6% (n = 33) of the RPD designations. Four neonatal conditions (neonatal seizures, bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy of prematurity) are each associated with four RPD designations. These four neonatal conditions comprise nearly half of the neonatology products designated.

Product type

Figure 2 represents the breakdown of drugs versus biologics among the RPD designations. A majority (56%, n = 319) of the designations were for drugs and 44% (n = 250) were for biologic products. There was no change in the relative proportion of drugs versus biologic products over time. Six percent (n = 22) of drugs were antisense oligonucleotides. Sixty-four percent (n = 161) of biologics were gene therapies.

Level of evidence

The majority of RPD designations, 54% (n = 306), supported their request for designation with preclinical in vivo evidence, followed by 38% (n = 217) providing clinical evidence (Fig. 3). The use of clinical evidence remained relatively stable over time. The majority (51%, n = 111) of clinical evidence originated from

Table 3 Diseases associated with at least five RPD designated products (n = 26)

Most designated diseases	Number of RPD designations	Percentage of total RPD designations	Therapeutic area
Duchenne muscular dystrophy	30	5	Neurology
Neuroblastoma	21	4	Oncology
Sickle cell disease	18	3	Hematology
Diffuse intrinsic pontine glioma*	16	3	Oncology
Osteosarcoma	15	3	Oncology
Acute lymphoblastic leukemia	10	2	Oncology
Cystic fibrosis	8	1	Pulmonary
Epidermolysis bullosa	8	1	Dermatology
Congenital isolated hyperinsulinism	7	1	Endocrinology
Dravet syndrome	7	1	Neurology
Ewing sarcoma	7	1	Oncology
Friedreich ataxia	7	1	Neurology
GM2 gangliosidosis[#]	7	1	Metabolism
B-thalassemia	6	1	Hematology
Medulloblastoma	6	1	Oncology
Mucopolysaccharidosis type 1	6	1	Metabolism
Propionic acidemia	6	1	Metabolism
Spinal muscular atrophy	6	1	Neurology
Angelman syndrome	5	1	Neurology
Gaucher disease	5	1	Metabolism
Krabbe disease	5	1	Neurology
Lennox-Gastaut syndrome	5	1	Neurology
Mucopolysaccharidosis type 2	5	1	Metabolism
Netherton syndrome	5	1	Dermatology
Rett syndrome	5	1	Neurology
Rhabdomyosarcoma	5	1	Oncology

*Diffuse intrinsic pontine glioma has also been classified as pediatric-type diffuse high-grade gliomas

[#] GM2 gangliosidosis includes both Tay-Sachs and Sandhoff diseases

21 USC 360bb(a)(2) defines a "rare disease or condition" as: "any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 [sic] in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

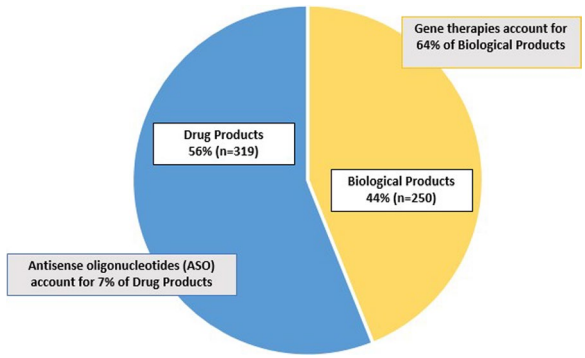

Fig. 2 Product type of RPD designations, 2013–2022 (n = 569)

applicant-conducted clinical trials. The remaining designations supported by clinical evidence was split between applicants using cited clinical trials (29%, n = 63) and case studies (20%, n = 43).

Priority review vouchers

There were 38 RPD PRVs awarded from 2014 to 2022 (Table 4). The therapeutic areas with the most awarded PRVs were neurology (n = 13) and metabolism (n = 12), accounting for two thirds of all vouchers. The highest number of RPD PRVs awarded in a single year occurred in 2020 with seven.

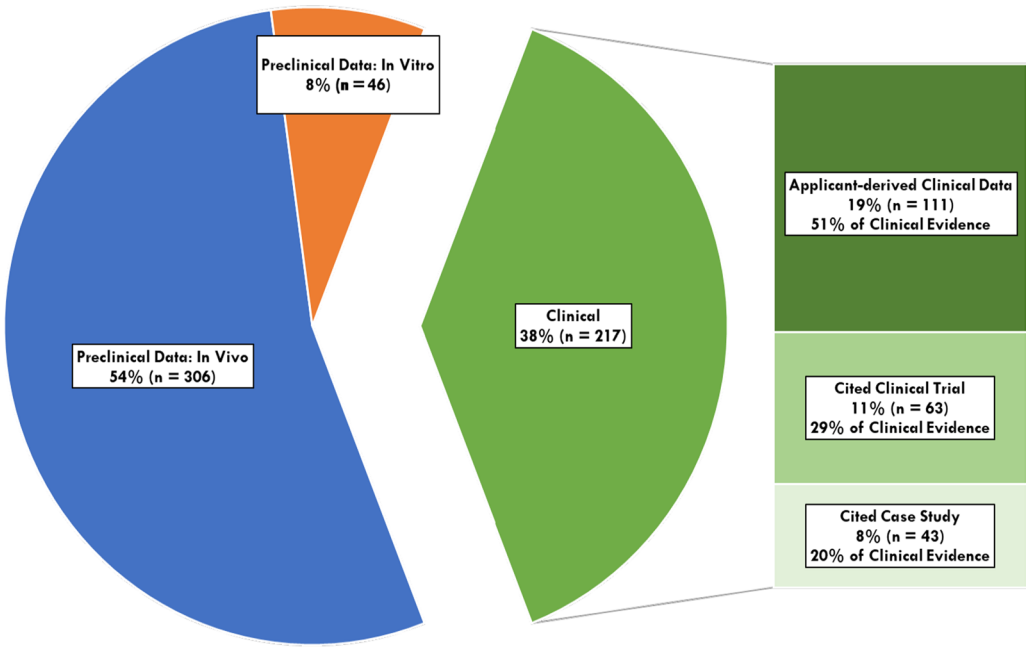

Fig. 3 Types of evidence used by applicants to support scientific rationale for RPD designation (n = 569)

Table 4 Summary of awarded RPD priority review vouchers, 2014–2022 (n = 38)

	Number of RPD priority review vouchers awarded	Therapeutic area (s)
2014	1	Metabolism (1)
2015	5	Metabolism (4); Oncology (1)
2016	2	Neurology (2)
2017	5	Neurology (2); Metabolism (1); Oncology (1); Ophthalmology (1)
2018	5	Immunology (2); Metabolism (1); Neurology (1); Pulmonary (1)
2019	3	Neurology (2); Pulmonary (1)
2020	7	Metabolism (3); Neurology (3); Oncology (1)
2021	6	Gastroenterology (1); Metabolism (1); Neurology (1); Ophthalmology (1); Orthopedics (1); Pulmonary (1)
2022	4	Neurology (2); Hematology (1); Metabolism (1)

Per Sect. 505 (b)(1) of the FD&C Act or Sect. 351 of the Public Health Service (PHS) Act, the PRV can be redeemed for a priority review instead of a standard review for another drug or biologic submitted for FDA approval after the date of approval of the rare pediatric disease product

Discussion

Supporting product development for children is a critical public health initiative, given the substantial unmet need. A Congressional Research Service Report explains that: "drug manufacturers are reluctant to test drugs in children because of economic, ethical, legal, and other obstacles. Market forces alone have not provided manufacturers with sufficient incentives to overcome these obstacles." [29] The RPD PRV program seeks to encourage product development for the pediatric population by providing a financial incentive for companies developing drugs and biologics specifically for children with rare diseases.

In the decade since the RPD PRV Program was introduced, 569 RPD designations were granted for products targeting 245 unique rare pediatric diseases. Almost half (42%) of these designations occurred in one year, 2020. We surmise that this extreme spike occurred because the RPD PRV program was going to begin sunsetting on September 30, 2020. Companies needed to receive their RPD designation before that date to maintain their eligibility for a future PRV. If the program had indeed terminated, no further RPD PRVs would have been granted after September 30, 2022. While this same phenomenon was not seen in 2016 when the RPD PRV program was previously due to sunset, we believe a spike did not occur at that time because the Congressional language in place at the time did not include a date by which designation was required. Spikes in designation activity like that experienced in 2020 may continue in the future if Congressional language includes a date by which designation is required, and if early action is not taken to renew the program resulting in potential uncertainty for sponsors.

Today, the RPD PRV program has not been permanently reauthorized by Congress—it must be renewed periodically by legislative action. This need for continued reauthorization creates unpredictability in long-term planning and resource allocation for companies developing these drugs and biologics, which could potentially lead to less product development in this space.

Our conclusions are fourfold. First, there was a wide range of rare pediatric diseases for which product development has been occurring. There were 245 unique diseases targeted by RPD-designation, and there was no single disease that was the focus of most of the development. Additionally, while four of the top ten diseases most often associated with RPD designated products were cancers, this is congruent with the trends seen in the adult rare cancer space, which have experienced increased development [30].

Second, we find that drugs and biologics intended for use in the neonatal population represent a surprisingly small proportion of all RPD designations (6%). However, it is notable that within this subpopulation, the more frequently encountered diseases are represented in the designations granted. This could indicate the most well studied neonatal diseases are those that see the most translation into product development. The difficulties with developing new drugs and biologics for neonatal patients have been well documented, including: (1) few appropriate animal models; (2) challenging trial designs; and (3) high rates of co-morbidities [31, 32]. To address some of these concerns encountered by neonatal product developers and to encourage product development in this vulnerable population, FDA published a guidance in 2022 to assist product developers who are planning to conduct clinical pharmacology studies in neonatal populations, but more progress must be made in this field [33]. FDA also published a guidance in 2023 to support innovators in approaching neurodevelopment safety studies in neonates [34].

Third, we find that gene therapy products represent more than a quarter (28%) of all designations. As it has been estimated that more than 70% of rare diseases have a genetic etiology and these diseases disproportionately affect children, it is not surprising that this technology type is a frequent RPD designation target [35]. High-profile approvals of gene therapies for pediatric-onset diseases like spinal muscular atrophy and RPE65-related retinal disease could potentially pave the way for gene therapies as a model for both therapeutic and market viability [36, 37].

Finally, we find that a substantial number of designations are supported by clinical data. Nearly 40% of all RPD designations were granted based on clinical evidence. This is important because it suggests that the preliminary results for these products show potential promise and are further along in development than those supported only by preclinical data. Additionally, the proportion of RPD designations supported by clinical evidence is relatively stable over time, indicating that this result is not a legacy from program initiation (i.e., clinical development programs that already existed when the program began).

Studies of the RPD PRV program have found mixed results in discerning whether the program has stimulated development for these diseases [15]. While this study cannot determine any causal relationships, it contributes a more detailed description of the landscape of product development for rare pediatric diseases. The results indicate that while the program has supported the award of 38 PRVs (for products that are approved for the prevention or treatment of a rare pediatric disease) in its first ten years, this represents only 7% of the RPD-designated products that are not yet approved. However, we also acknowledge that the development of new drugs

and biologics can take more than a decade and most are ultimately not approved [38]. Therefore, it is expected that drug and biologic approvals would lag behind RPD designations, and approvals being a less common event, would only represent a fraction of the total number of designations.

Future research is needed to assess the overall impact of the RPD PRV program to evaluate other important outcomes (beyond product approvals) such as progression through clinical trials, the impact for developers to secure additional funding (i.e., venture capital and angel funding, grants), and the initiation of natural history studies. For rare pediatric diseases not currently represented in the RPD designation program, additional research is needed to understand the potential barriers to product development to effectively shape future initiatives to address these urgent needs.

Limitations

While this study analyzes all RPD designations, it may not capture the entire product development pipeline for this population. For example, nonprofits, such as academic researchers, may have little awareness or incentive to apply for this designation, and therefore their research will not be represented in the results. This may limit the generalizability of our study.

Second, while we attempted to make the disease categorization as consistent as possible by using a respective disease ontology and reviewing categorization decisions with all of the study authors, there is inherent subjectiveness in classifying unique diseases.

Conclusion

The RPD PRV program was created to stimulate the development of new therapies for this historically neglected patient population–children. Prior to receiving a PRV, companies can elect to first receive RPD designation for their product. This research publishes, for the first time, a retrospective assessment of the RPD designation portion of the RPD PRV program. While a wide variety of rare pediatric diseases are represented, most designations are focused in the neurologic, metabolic, and oncologic therapeutic areas. More than a quarter of RPD designations are for gene therapies, and over a third of RPD designations are supported by clinical data. Additional research is needed to evaluate the full impact of the RPD PRV program that extends beyond product approvals. Augmented support for rare pediatric disease product development is needed to address the healthcare inequity facing one of our most vulnerable populations.

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Author contributions
CM designed the study, collected data, carried out the data analysis, drafted the initial manuscript and critically reviewed and revised the manuscript. KLM conceptualized and designed the study, collected data, carried out the data analysis, and drafted the initial manuscript. LJF, JB, and GL designed the study, collected data, carried out the data analysis, and critically reviewed and revised the manuscript. ET conceptualized and designed the study, interpreted the data, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not listed on any public FDA databases.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

The Honorable Doris O. Matsui
2311 Rayburn House Office Building
House of Representatives United States
Washington, DC 20515

The Honorable Neal Dunn
466 Canon Office Building United States
House of Representatives
Washington, DC 20515

The Honorable Mike Kelly
1707 Longworth House Office Building
United States House of Representatives
Washington, DC 20515

The Honorable Mike Thompson
268 Cannon House Office Building
United States House of Representatives
Washington, DC 20515

October 26, 2023

RE: PROTECT Rare Act

Dear Representatives Matsui, Dunn, Thompson, and Kelly:

We are writing to express our appreciation for your leadership in advancing the **Providing Realistic Opportunity to Equal and Comparable Treatment ("PROTECT Rare") Act.** We stand ready to amplify your work to ensure that individuals with very rare conditions have the sameintended benefit of health coverage as individuals with more common conditions – access to treatments our physicians know to be the standard of care for our medical conditions.

The bill will build on existing criteria for medically necessary care so that Medicare and Medicaid will be able to consider clinical guidelines and peer-reviewed literature to assess coverage of rare disease treatments. The bill aligns coverage of rare disease treatments to whatCongress previously mandated in terms of Medicare coverage for cancer treatments.
Importantly, the bill does not provide 'special treatment' for rare diseases; rather, it levels the

playing field for access to those living with more common conditions.

It will also require private payers to create an expedited review pathway for formulary exception, reconsideration, and/or appeal of any denial of coverage for a drug or biologicalprescribed for a patient with a rare disorder.

Again, we appreciate your leadership in improving access to the treatments prescribed for rareand ultra-rare patients by their doctors. We appreciate the opportunity to support this important legislation and look forward to working with you to pass the PROTECT Act this year.

Respectfully,

5P Minus Society
Alpha-1 Foundation
American Brian Coalition
Arachnoiditis Chronic Meningitis Research Network
Association for Creatine Deficiencies
Autoinflammatory Alliance
Barth Syndrome Foundation
Biomarker Collaborative
Cares Foundation
Children's PSC Foundation
Choroideremia Research Foundation
CLL Society
CSNK2A1 Foundation
CRI DU CHAT Research Foundation
Cutaneous Lymphoma Foundation
Danny's Dose
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