Rare Disease
Company Coalition

Impact of the Priority Review Voucher Program on Rare Pediatric Disease Drug Development

May 2024

Introduction

The rare pediatric disease (RPD) priority review voucher (PRV) program encourages the development of treatments for rare pediatric diseases. The Rare Disease Company Coalition (RDCC), with support from IQVIA, investigated the history and impact of the rare pediatric disease PRV program. The findings clearly demonstrate that the program delivers substantial value. To date, it has address unmet need across more than 47 distinct indications and benefited more than 200,000 people living with rare disease. However, without Congressional action, the program will begin to expire on September 30, 2024. Preservation of this critical incentive is necessary to further investment in and development of new rare disease treatments.

Key Findings

The rare pediatric disease priority review voucher program **encourages the development** of treatments for rare pediatric diseases, which are associated with **urgent, unmet medical need.**

People with rare pediatric diseases have **limited or no treatment options** due to the **complexities** involved in **developing and delivering** new therapies.

The rare pediatric disease PRV program has led to new innovations that **benefit over 200,000 rare disease patients** and address unmet medical needs across **47 rare pediatric indications.**

More than 90 percent of all priority review vouchers were awarded to therapies for indications with no approved therapy on the market.

The true impact of the program is expanding and still being realized. **More than half of all PRVs** were granted in the last four years alone.

The rare pediatric disease PRV program is a **proven tool** for spurring research & development (R&D) investment for rare pediatric diseases and can help attract critical funding for **small, emerging biopharmaceutical companies.**

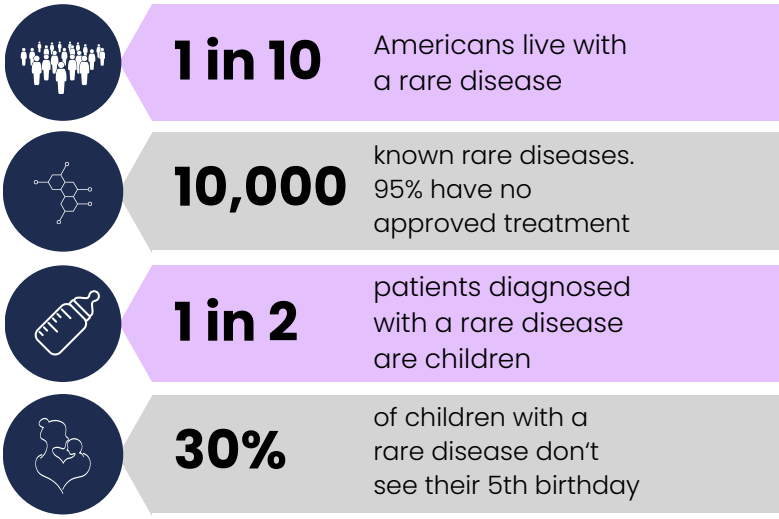
Balancing **financial viability** with the **advancement of medical breakthroughs** remains a challenge for rare disease companies, and a robust incentive system is paramount to counteract these challenges.

A **long-term extension** of the program would provide **stability** to innovators, **encourage investment**, and ultimately **benefit patients** by advancing drug development for rare pediatric diseases.

Unmet need & challenges in rare pediatric disease drug development

Rare diseases present a global health crisis and have an outsized impact in pediatric populations. Approximately 10% of the US population is affected by one of the over 10,000 rare diseases,[1] and only 5% of those rare diseases have a Food and Drug Administration (FDA)-approved treatment.[2] Half of all patients diagnosed with a rare disease are children, and 70% of rare genetic disorders manifest during childhood.[3] Three out of ten children with a rare disease will not survive beyond the age of five.[4] There is tremendous unmet need and at the same time, rare pediatric disease drug development is extraordinarily challenging. These challenges include small patient populations, complex and variable diseases with limited natural history, slow disease progression with often irreversible symptoms, and a lack of defined endpoints and biomarkers.

The impact of rare diseases extends beyond health implications. Rare disease patients incur substantially higher medical costs compared to those with non-rare conditions, placing a heavy financial strain on affected people, their families and health care systems.[6] However, the availability of treatments mitigates the economic impact. Recent studies reveal that the per-patient-per-year (PPPY) costs associated with rare diseases far exceed those of high-prevalence diseases (e.g., diabetes, cardiovascular disease).[7] Recent studies have shown that in the United States alone, the costs related to 373 rare diseases range from $1 trillion dollars to $2.2 trillion annually, and the societal responsibility for all known rare diseases may reach an astonishing $7.2 trillion to $8.6 trillion dollars per year. [8, 9] Regulatory and commercial hurdles add further uncertainty to rare disease drug development.



Regulators grapple with disease heterogeneity, limited natural history data, and a lack of regulatory precedent. Longer development timelines (orphan drug development can take up to 15.1 years [10, 11]) and higher costs (clinical development of orphan drugs can cost up to $291 million dollars[12]) exacerbate the challenges. Commercially, small market sizes pose high risks for biopharmaceutical companies and investors. These challenges are further compounded when working with pediatric populations.

Given these substantial obstacles, it is critical to encourage rare disease drug development. Landmark policies like the Orphan Drug Act of 1983 have been incredibly successful in transforming the rare disease ecosystem and spurring innovation. However, recent trends indicate that the United States' robust incentive ecosystem is in jeopardy. It is imperative to preserve key incentives like the rare pediatric disease PRV program to encourage innovation and provide treatment options for people living with a rare disease.

History of the rare pediatric disease priority review voucher program and its utilization

The rare pediatric disease PRV program was created in 2012 and subsequently reauthorized with bipartisan support in 2016 and 2020. The program encourages drug development for rare pediatric diseases by expediting the regulatory process for qualifying products.

Companies can obtain a PRV by initiating a development program for a rare pediatric disease and submitting a PRV request to the FDA during New Drug Application (NDA) or Biologics License Application (BLA) submission. If a sponsor's drug or biologic receives approval for a rare pediatric disease and the PRV request is granted, a PRV is awarded. Sponsors can redeem vouchers for priority review (reducing the review time from 10 months to 6 months) of a future NDA or BLA submitted to the FDA, or transfer or sell to another biopharmaceutical company to expedite review of another drug or biologic.

While the program's primary goal remains incentivizing the development of treatments for rare pediatric diseases, the program also speeds the approval of additional therapies, which could be indicated for higher-prevalence diseases, granting more patients quicker access to innovative treatments.[13]

Impact of the priority review voucher program on rare pediatric disease drug development

The rare pediatric disease priority review voucher program has led to new innovations benefiting over 200,000 patients and addressing high unmet needs across 47 rare pediatric indications.[14]

Since its inception, the FDA has awarded 53 PRVs. Our study finds that these PRVs treat 39 diseases, corresponding to 47 novel indications. Even in cases where PRVs were awarded for diseases where a previous FDA-approved product existed, many of the new therapies target distinct subpopulations that would not be served by existing therapies and would otherwise continue to have unmet medical need. This underscores the program's effectiveness in spurring the development of innovative treatments for rare pediatric diseases that previously lacked targeted therapies.[15] Importantly, by supporting the development of the first approved treatment for a given rare disease, regulatory precedent is established which can help to catalyze future drug development in that disease area. This is particularly critical for rare diseases that include extremely rare subpopulations, each of which may have its own uniquely indicated therapy.

Developing a rare pediatric drug from "bench to bedside" is a complex and time-consuming process that can span up to 15 years.[16,17] The journey involves pre-clinical research, clinical trials (including phases 1, 2, and 3), regulatory review, and post-marketing surveillance. As the program has only been operational for 12 years - shorter than the potential development cycle for a rare disease therapy - the impact of the program is still being realized. Over 50% of all PRVs were granted in the last four years alone.[18] This reflects the continued and expanding positive influence of the program on the development of rare pediatric disease drugs and biologics.

Impact of the rare pediatric disease priority review voucher program on pediatric, adult, rare and prevalent drug development

Redeemed vouchers continue to benefit both pediatric and adult orphan and non-orphan communities by providing first-in-class or best-in-class therapies. Of the 53 PRVs awarded to date, 29 have been sold by the original recipients to other companies. 22 PRVs have been redeemed, and of those vouchers, 6 were for products addressing orphan indications, while 16 were for non-orphan indications. Notably, 9 out of the 16 non-orphan products were considered first-in-class and/or best-in-class therapies, benefitting 40 million patients with new and better treatment options.[19]

Rare Pediatric Disease (RPD) Priority Review Vouchers (PRVs) Awarded

- Since the implementation of this program, **53 vouchers have been awarded :**
  - To 43 different pharmaceutical companies
  - Across 39 diseases, encompassing 47 different RP indications
- More than 50% of all RPD PRV designations, awards and redemptions occurred in the last four years
- This trend is expected to continue as programs continue to move through the development process (with average time from bench to bedside of 15 years)

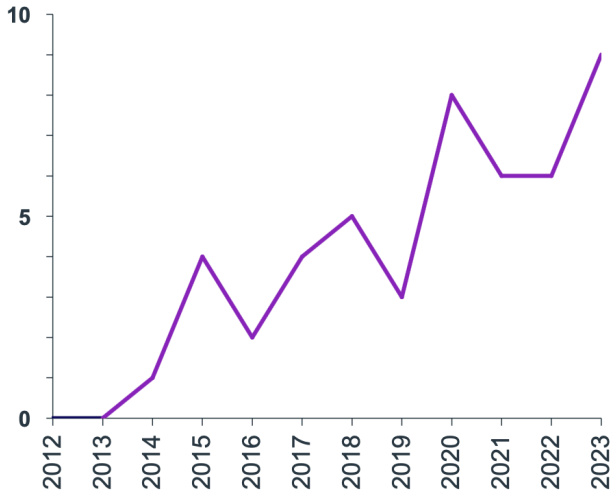


Figure 1: The number of rare pediatric disease priority review vouchers awarded from the program's creation in 2012 through 2023.

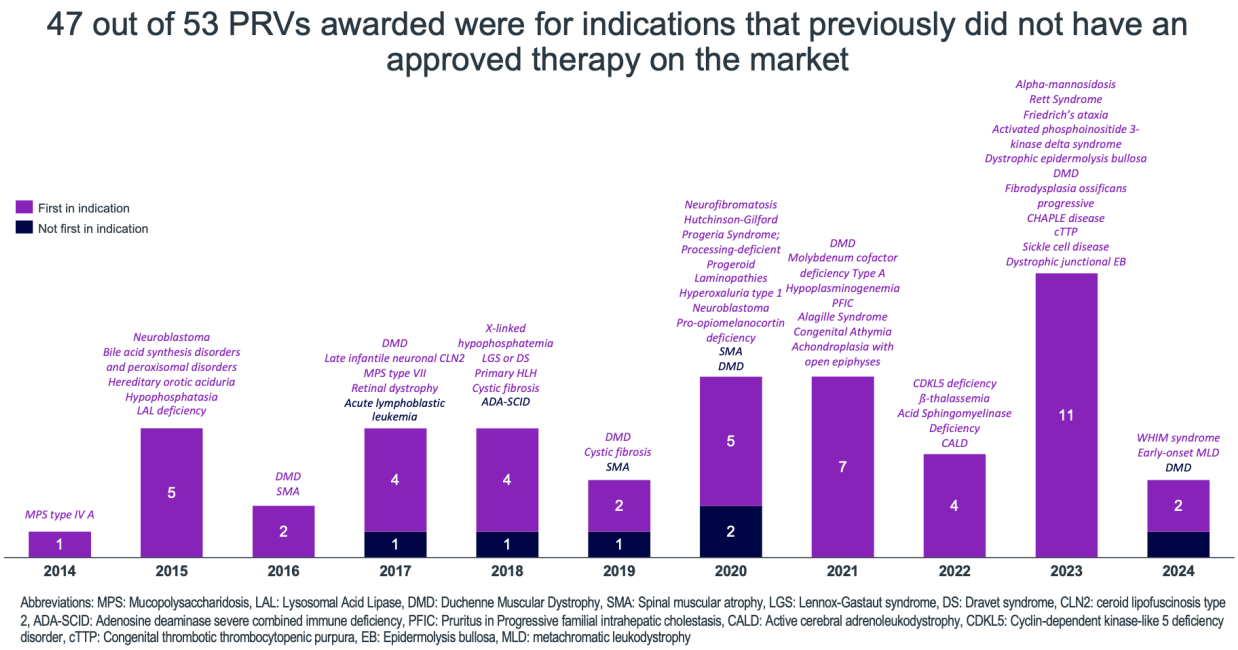


Figure 2: The breakdown of PRVs awarded for first in indication and not first in indication, from 2014 through present.

Rare disease stakeholder perception of the rare pediatric disease PRV program

Our research collected insights from key stakeholders across the rare disease community. We focused on understanding if and how these stakeholders consider the program as a factor in their investment strategies and long-term R&D decisions. We conducted one-on-one interviews with:

1. Biopharmaceutical representatives who have applied for priority review vouchers;
2. Institutional investors experienced in funding orphan drug development program;
3. Patient organizations representing therapy areas that have benefited from PRVs; and
4. Health economists.

Investors and industry experts alike recognize the program's value in incentivizing R&D investment for rare pediatric diseases.

Many report that the PRV program is critical to their decision-making processes (e.g., the transition of a program between research, pre-clinical, and clinical development). However, some stakeholders noted that the program requires more time to fully demonstrate its benefits.

Across all stakeholder groups, the sunset provision of the rare pediatric disease PRV program has raised critical concerns. Industry stakeholders worry that this provision will continue to add uncertainty in their pipeline of rare pediatric disease drugs, and potentially impact future development of innovative therapies for children with rare diseases. Investors observe that the uncertainty surrounding reauthorization cycles affects the financial calculus for funding orphan drug

programs. They anticipate that a failure to reauthorize will lead to reduced funding and limiting available capital for R&D. Diminished investment could delay future breakthroughs, affecting patient outcomes and potentially leaving children without effective treatments.

The rare pediatric disease PRV program directly benefits patients who might not otherwise receive treatment for their condition. Moreover, the program enables a future therapy to come to market more swiftly, ultimately benefiting an even larger population of patients.

PRV program impact on continued innovation

The rare pediatric disease PRV program has had a significant impact on the number of rare pediatric disease products in development. The recent increase in the number of products granted Rare Pediatric Disease (RPD) designation - a designation that confirms that a product is intended to treat or prevent a rare disease that primarily impacts children - illustrates this trend. In total, the FDA has granted RPD designation to 569 products, with a surge of 350 designations occurring between 2020 and 2022 alone. [20] This marked increase is a testament to the continuous R&D investment in this critical area since the adoption of the PRV program. The substantial rise in the number of products granted RPD designation, including over the past three years, is a clear indication of the program's success. The program has been instrumental in encouraging companies to invest in R&D for rare pediatric diseases and has resulted in a significant increase in the number of potential treatments for these diseases.

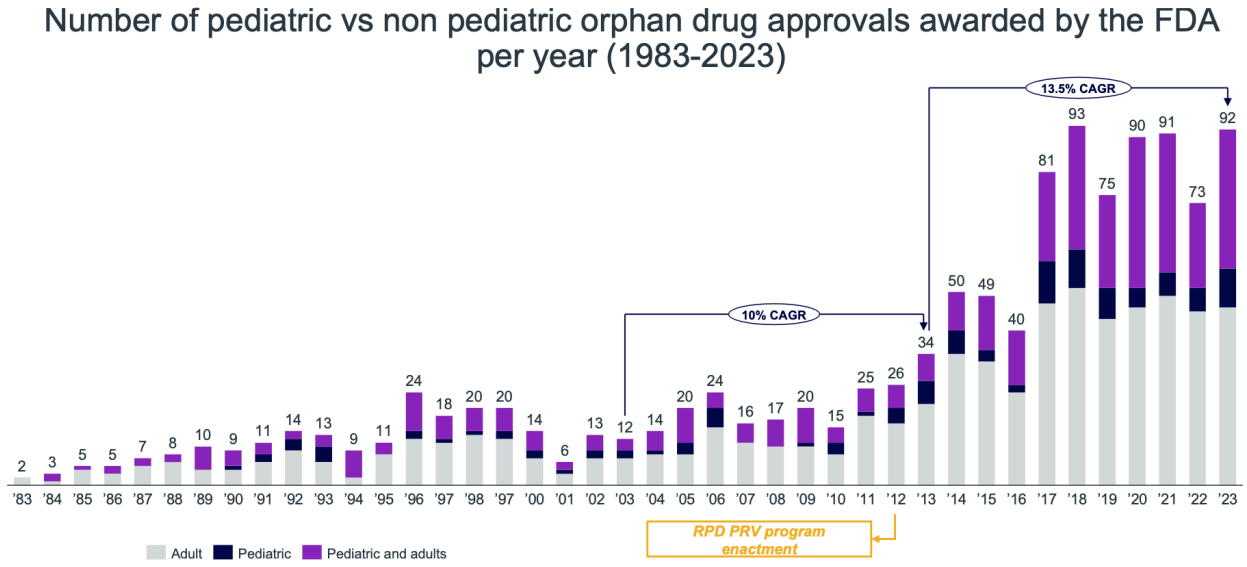
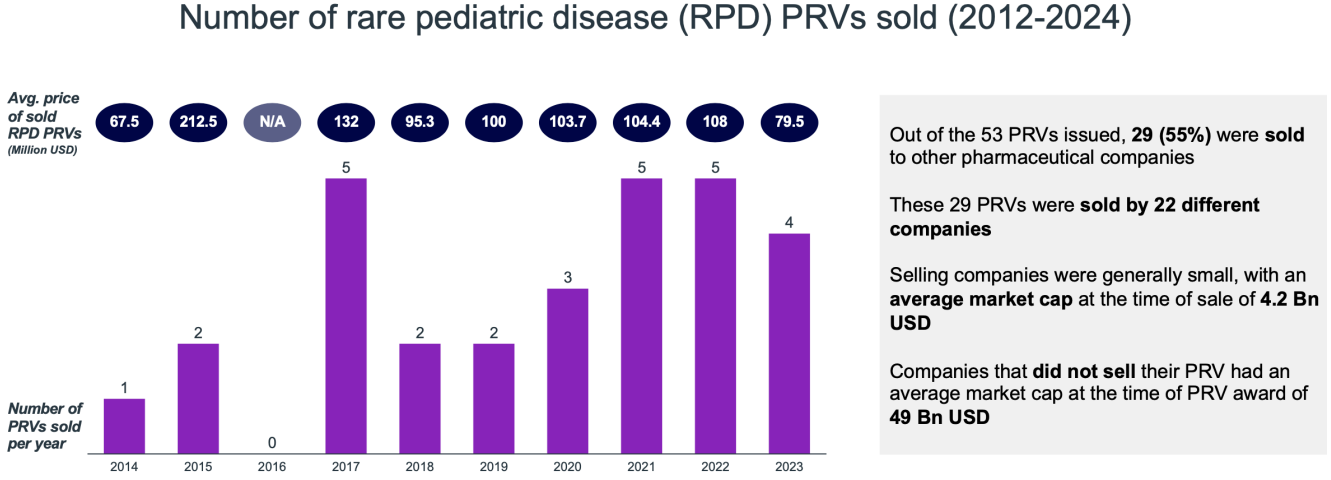


Figure 3: The breakdown of pediatric and non-pediatric orphan drug approvals awarded by the FDA over 40 years, from 1983-2023. Includes average Compound Annual Growth Rate (CAGR) over the past two decades, from 2003-2023.

Balancing financial viability and advancing medical breakthroughs remains a critical challenge for rare disease companies. Only one-third of commercial-stage rare disease companies with revenues over $100 million per year are profitable, compared to more than half of comparable non-rare commercial stage companies. These rare disease companies invest over 40% of their revenue into research and development, while non-rare companies allocate a comparatively lower 17%.[21] Given these financial challenges, the ability to obtain and transfer rare pediatric disease PRVs has proven to be a catalyst for raising funds, especially for pre-clinical and small- to mid-sized companies with more constrained revenue streams.[22] Our research finds that companies who sold their PRVs had a significantly lower market capitalization than those who did not. This finding suggests that the dual-pronged approach of using or selling a voucher has been particularly advantageous for pre-clinical and small- to mid-sized companies. The program provides these companies with a valuable source of capital that companies can use to fund R&D programs in the absence of revenue.

Overall, the rare pediatric disease PRV program has not only been successful in incentivizing R&D investment for rare pediatric diseases, but has also provided much-needed financial support for smaller companies. The ability to obtain and transfer PRVs has allowed these companies to access funding they may not have had otherwise, ultimately contributing to the continued development of new treatments for rare pediatric diseases.



Smaller companies are utilizing PRVs as additional sources of income, to keep their company afloat, pay off development cost of products and to fund ongoing and future R&D

Figure 4: The spread of PRVs sold per year and the average price of sold PRVs (in millions USD).

Industry experts confirmed that smaller biopharmaceutical companies that are focused on treating low-prevalence rare disease populations are the primary beneficiaries of the rare pediatric disease PRV program. For these companies, the rare pediatric disease PRV plays a pivotal role in the decision-making process for developing rare disease drugs, given the small patient populations and limited revenue opportunities.[23] Investors consider the PRV program a significant factor in their investment decisions. The average value per voucher is around $100 million USD, making voucher eligibility a key incentive for investment in the rare pediatric disease space.[24] However, the sunset provision continually re-introduces uncertainty, affects market dynamics, disrupts strategic planning, adds investment risk, and hampers long-term investment.

Conclusion

The rare pediatric disease priority review voucher program is a proven incentive that has spurred the development of new innovations that benefit more than 200,000 patients across 47 rare pediatric indications. While there remains an urgent unmet medical need for new treatments for rare pediatric diseases, the future of this vital tool is uncertain. The PRV program will begin to expire on September 30, 2024 unless Congress takes action. Expiration of this critical program would result in reduced incentives for the discovery of new treatments, jeopardize programs already under development, and destabilize investment in new treatments. The RDCC applauds Congress for the significant progress in improving the lives of children with rare disease through the creation and subsequent reauthorization of the Rare Pediatric Disease PRV program in 2012, 2016 and 2020, respectively. A long-term extension of the PRV program will support the stability of research & development and ultimately lead to new treatment advances for rare pediatric diseases.

The Rare Disease Company Coalition urges Congress to reauthorize the rare pediatric disease priority review voucher program through fiscal year 2030.

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Rare Disease Company Coalition

We are dedicated to being a reliable and trusted resource for our leaders in Congress and the Administration, and a productive partner to rare disease-minded industry, academic and patient groups, by educating on the issues and opportunities that affect rare disease companies and advancing our shared mission to improve the lives of people living with rare diseases.

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