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HHS Public Access

Author manuscript

JAMA Pediatr. Author manuscript; available in PMC 2016 February 04.

Published in final edited form as:

JAMA Pediatr. 2014 October ; 168(10): 879–880. doi:10.1001/jamapediatrics.2014.904.

New Regulatory Paradigms for Innovative Drugs to Treat Pediatric Diseases

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The development of safe and effective pediatric drugs continues to fall short.[1] The paucity of new therapies is particularly stark for rare diseases, which disproportionately affect children and collectively affect an estimated 25 million people in the United States and 30 million in Europe.[2] Since the 1980s, US policymakers have enacted a range of policies to stimulate drug development for *rare diseases*, defined as those affecting fewer than 200 000 individuals in the United States. The most notable policy is the 1983 Orphan Drug Act, which grants 7 years of marketing exclusivity as well as subsidies and tax credits to pharmaceutical companies bringing a drug for a rare disease to market. While the Orphan Drug Act has been credited with stimulating product development for rare diseases, only one-quarter of orphan drugs were approved explicitly for pediatric indications between 2000 and 2009.[3]

To incentivize the development of novel therapeutics for children, US Congress established the Rare Pediatric Disease Priority Review Voucher (PRV) program, passed as part of the Food and Drug Administration (FDA) Safety and Innovation Act. To qualify for the program, the new drug or biologic must be indicated to treat a *rare pediatric disease*, defined as a disease that either affects fewer than 200 000 individuals primarily aged 0 to 18 years in the United States or affects more than 200 000 individuals aged 0 to 18 years of age but for which there is no reasonable expectation that the cost of developing and making the drug available will be recovered from sales in the United States. Once approved, the sponsor of the drug is issued a voucher that can be freely transferred or sold and entitles the holder to a priority FDA review of any new drug or biologic application, with the expedited review accelerating market entry by up to 6 months.

There are a number of important differences between the pediatric PRV program and the Orphan Drug Act, with more stringent requirements applying to the PRV program (Table).[4] For example, to gain pediatric PRV approval, the rare pediatric disease product cannot contain an active ingredient (or an ester or salt of the active ingredient) of a previously

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Conflict of Interest Disclosures: None reported.

approved agent. In addition, the FDA can revoke the pediatric PRV if the product for which the voucher was awarded is not marketed within a year of approval. The program is also subject to a sunset provision, which will be effective 1 year after the first 3 vouchers are granted unless the program is reauthorized by Congress.

Owing to its novelty and limited track record, there are important unanswered questions about the pediatric PRV program. As the FDA develops final guidance for the industry and as policymakers and clinicians review emerging evidence from drugs approved through this new pathway, it is critical to consider the impact of the program in light of several key factors. First, manufacturers can qualify for the pediatric PRV even if their product is intended to treat a nonrare condition, as long as there is no reasonable a priori expectation of recouping costs. However, the statute is silent on whether the FDA can withdraw a pediatric PRV if the patient population is later found to be larger than the threshold. A claw-back provision has precedent in pharmaceutical regulation and could ensure that products receiving PRV designation are truly intended to treat unmet medical needs. For example, in the Humanitarian Device Exemption Program—the device analogue to the orphan drug program—the FDA withdrew marketing authorization in 2006 for 2 devices treating a condition later determined to be significantly larger than the statutory limit for a rare disease.[5]

Second, the accessibility of these new therapeutics to patients remains a source of controversy. On February 14, 2014, the FDA approved the first drug through the pediatric PRV program, elosulfase alfa (Vimizim; BioMarin Pharmaceutical), an enzyme replacement therapy for the treatment of mucopolysaccaridosis IV, or Morquio A syndrome, which affects approximately 800 individuals in the United States and has no existing treatment options. The company subsequently announced that the annual net cost of therapy is expected to be $380 000 per patient after spending approximately $300 million on the development program.[6] Based on equity research analyst estimates, gross revenues from the drug are projected to surpass this investment within just 3 years, raising questions about whether participation in the program should be contingent on certain limitations to the costs passed on to patients. Companies should ensure that access programs reach patients who cannot afford treatment, either because of insufficient or lack of insurance coverage.

Finally, policymakers should revisit the program as the sunset provision approaches with a view toward continuing programs that maximize innovation, benefit vulnerable populations, and minimize costs to taxpayers and public payers. There may be valuable lessons from other pharmaceutical incentive programs for the PRV program. For example, in 2007, a similar voucher program was established to award priority review vouchers for manufacturers developing drugs for neglected tropical diseases. Although there were some initial concerns that the tropical disease PRV would be misused to bring inadequately reviewed drugs more quickly to market,[7] only 1 drug has been submitted for approval through this pathway, by Novartis for canakinumab in 2011, which did not ultimately lead to the drug’s approval. As the pediatric PRV program attracts greater attention, it will be important to test whether and how the PRV influences the research and development priorities of companies and the approval of other drugs.

The creation of the pediatric PRV program and the recent approval of the first drug via this mechanism mark a new chapter in regulatory efforts to address and correct the significant unmet medical needs of diseases affecting children. Close monitoring of the program's implementation and impact should serve to guide refinements in future renewals and ensure that the program meets its intended purpose of rewarding innovation and increased availability of safe and effective therapies for underserved populations and conditions.

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Table

Key Federal Incentives for the Development of Pediatric Drugs

Incentive Program	Incentive	Year Enacted	Key Provisions		
			Novelty	**Withdrawal**	**Program Duration**
Pediatric Priority Review Voucher	Transferable voucher for priority review of any drug	2012	Must be *novel*, defined as not containing an active ingredient (or an ester or salt of the active ingredient) of a previously approved agent	Can be revoked if the product for which the voucher was awarded is not marketed within a year of approval	No further vouchers can be awarded after the last day of the 1-y period that begins on the date that the third voucher is granted
Best Pharmaceuticals for Children Act	6 mo of additional marketing exclusivity[a]	2002	Applies to products with patent life or exclusivity remaining	No specific withdrawal provision	Extended indefinitely under the FDA Safety and Innovation Act of 2012
Orphan Drug Act	7 y of additional marketing exclusivity, tax credits, and clinical research subsidies	1983	No specific novelty requirement	Can only be revoked if the request for orphan drug designation contained untrue information; cannot be revoked if the prevalence of the disease exceeds 200 000 after the designation is granted	Indefinite duration

Abbreviation: FDA, Food and Drug Administration.

[a]The 6 additional months of marketing exclusivity for sponsors conducting pediatric clinical trials were first codified under Section 505A of the US Food and Drug Administration Modernization Act of 1997 and later extended in the Best Pharmaceuticals for Children Act of 2002.

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