

## POLICY

# “Creating Hope” and Other Incentives for Drug Development for Children

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Enhancing drug development for pediatric disease is a priority and a public responsibility. The Creating Hope Act of 2010 is important new proposed legislation that adds drugs and biologics for treating rare diseases in children to those for neglected tropical diseases as eligible for a priority review voucher from the U.S. Food and Drug Administration. The Act enhances existing incentive programs through specific financial benefits to companies who seek a pediatric indication for a new drug to treat an orphan disease that occurs specifically in children.

Pediatricians who treat children with serious and life-threatening diseases often find themselves face to face with the inadequacies of pediatric drug development. Despite leaps in biomedical science, the translation of discoveries into products for children continues to fall short. A substantial number of drugs used in children are not approved for pediatric use, and many drugs have not been adequately studied in children (1, 2). In addition, drug development for specific pediatric populations (such as neonates) or for diseases that occur exclusively in children (such as certain childhood cancers, as well as some genetic and metabolic diseases) has been conspicuously lacking. Although a number of challenges exist in pediatric drug development, the lack of financial return on investment (because of a relatively limited market) is recognized as a pervasive limitation to advancing the field (3).

Over the past few decades, incremental progress has been made in stimulating pediatric drug development (4). The most recent “carrot” is the Creating Hope Act of 2010, a priority-review voucher incentive program for new drugs and biologics (such as vaccines and monoclonal antibodies) that are developed exclusively for pediatric indications and designed for prevention or treatment of rare pediatric diseases (Fig. 1). This new legislation builds on an existing incentive for drugs targeting ne-

glected tropical diseases and supplements other pediatric legislative and regulatory programs.

The Orphan Drug Act (1983) built a regulatory foundation for drug development for rare diseases, many of which occur in children. It provides incentives [such as 7 years market exclusivity, assistance from the U.S. Food and Drug Administration (FDA), tax credits, exemption from certain user fees (that is, fees paid by the sponsor to the FDA under the Prescription Drug User Fee Act), and the opportunity for grants] to manufacturers of drugs developed for treatment of rare or orphan diseases (those occurring in <200,000 people in the United States). The Orphan Drug program is managed by FDA’s Office of Orphan Products Development and has been very successful. Since 1983, more than 2000 drugs and biologics have received orphan drug designation, and approximately 358 have been approved by the FDA, ~20% for diseases that occur exclusively in children and ~60% for those occurring in children and adults (5, 6). Critics have suggested that some of these drugs would have been developed anyway and have highlighted examples of “gamesmanship” in manufacturers’ use of the orphan drug process, such as limiting the initial indication to fit the orphan definition and later expanding to more profitable populations. Despite this, the overall medical impact of the Orphan Drug Act has been impressive, and lifesaving drugs for children have been made available through the program (5, 6). But, the Act alone has not solved the drug development gap, given that only about 200 of nearly 7000 rare diseases currently have approved therapy (7). In addition, the least amount of progress has been made in the



**Fig. 1. New hope.** Developing treatments for rare diseases in children is a public health responsibility. The Creating Hope Act of 2010 would provide incentives for companies that develop drugs for treating such diseases.

development of drugs for exclusively pediatric orphan diseases.

Since the 1990s, a series of provisions were put in place to address the need for more data on pediatric drugs. In 1997, passage of the FDA Modernization Act provided manufacturers 6 months of additional market exclusivity as incentive for conducting pediatric studies. The implementation of the Best Pharmaceutical Practices for Children Act (BPPCA; 2002, 2007) extended the exclusivity provisions and included a number of modifications to address the pediatric information gap. BPPCA allowed FDA to request manufacturers to conduct pediatric studies (studies are voluntary) of a drug on the basis of a priority list of marketed drugs published by the National Institutes of Health (NIH) and established a mechanism and funding (~\$200 million annually) for the program, including support for studies that manufacturers did not conduct. Since its implementation, BPPCA has been responsible for a substantial increase in pediatric-relevant drug information, and several hundred pediatric labeling changes have been made as a result (8). Although some of these changes have had little impact on practice,

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many have identified important safety issues, age-related dosing changes, and other practice-relevant data.

A lingering issue for BPCA, however, is the contention that companies with a blockbuster drug on the market may conduct relatively inconsequential pediatric studies to acquire exclusivity, resulting in a big return on (relatively little) investment and delayed entry of competitors (including generic drug manufacturers) into the market. It is clear that continued diligence is needed to assure that the types of studies that qualify for exclusivity provide “value-added” medical information relevant for pediatric practice. With regard to the “cash cow” allegation, studies of the economic return on pediatric exclusivity have documented that most products that have been part of the program have annual sales of less than \$200 million (median \$181 million) and that the economic return for 6 months exclusivity has been variable, with a median net benefit of \$134 million, and range from -\$8.9 million to \$507.9 million (9). Although some companies may benefit disproportionately from exclusivity, many receive only a modest return. It appears that the financial incentive for pediatric exclusivity has gotten the attention of the pharmaceutical industry, and in some part that is a good thing because without industry collaboration, drug development for children will be largely stalled. Vigilance and tracking of the cost of pediatric exclusivity is prudent and may inform the need for refinement of the provision in the future.

In 1999, the FDA implemented the Pediatric Rule, which required manufacturers to provide adequate labeling for pediatric use if an agent would be used by a substantial number of pediatric patients (for example, >50,000) or would provide a meaningful pediatric benefit. Legal challenges to the Pediatric Rule led to the Pediatric Research Equity Act (PREA; 2003, 2007), under which Congress provided FDA with the clear authority to require pediatric studies for drugs and biologics. PREA is triggered when a new indication, active ingredient, or dosing route or regimen is under review. Under PREA, FDA is responsible for reviewing a sponsor's request for a waiver or deferral of the pediatric requirement based on the potential to delay approval for an adult indication, the feasibility of acquiring pediatric data, safety issues, and other factors. Statistics about deferrals and waivers are made available to the public. According

to these data, 524 waivers and 338 deferrals were granted between 2004 and 2007 (10).

Both BPCA and PREA were reauthorized in 2007 (through 2012) and at that time the programs were enhanced, with attention paid to increased transparency, efficiency, development of pediatric formulations, and furthering the role of NIH. Recognizing some limitations, both programs are moving us substantially closer to the goal of filling the pediatric drug development gap. Coincident with the implementation of legislative/regulatory programs, a series of administrative improvements have been added within FDA to strengthen the management and review of orphan and pediatric drug development, including the establishment of the Office of Pediatric Therapeutics, the Pediatric Review Committee, and the Pediatrics Advisory Committee, and most recently the appointment of a new Associate Director for Rare Diseases at the Center for Drug Evaluations and Research. Although legislative and administrative initiatives in the United States have been critically important and are improving, they are less well integrated and somewhat less forceful as compared with parallel initiatives in the European Union. There, regulations are more unified, decisions of their Pediatric Committee are binding, a Pediatric Investigational Plan (PIP) is introduced earlier in the process of drug development, and the PIP is required (unless waived or deferred) for approval of a Marketing Authorization Application (11–13).

The Creating Hope Act of 2010 is the latest of the series of legislative and regulatory attempts to address the deficiencies in drug development of pediatric therapeutics. This Act was introduced to the Senate in August by Senator Brownback of Kansas (along with Senator Brown of Ohio and Senator Franken of Minnesota) and is now being considered in the Health, Education, Labor and Pensions Committee (14). The purpose of this bipartisan bill is to amend the Food, Drug and Cosmetic Act to improve the existing priority review voucher incentive program relating to neglected tropical diseases and expand it to rare pediatric diseases. The Creating Hope Act addresses an important unmet need and has received strong support from advocacy groups (15).

In 2008, the original priority review voucher program was established as a mechanism to incentivize companies to develop drugs for the prevention or treatment of certain tropical diseases. In essence, a

company developing such a drug, if qualified, could obtain a voucher at the time of approval, entitling it to receive priority regulatory review for another product. Priority review decreases the target time for FDA review of New Drug Applications and Biologics License Applications from 10 to 6 months. The opportunity benefit of getting to the market faster for a blockbuster drug may be worth tens to hundreds of millions of dollars (16, 17). A voucher may be desirable for smaller companies without a blockbuster drug as well, because the voucher is transferable upon change of control and can be sold. The overall impact of the original program on the development of drugs for tropical diseases is yet to be fully realized, but at least one company (Novartis, for Coartem, a combination of two drugs for treating malaria) has received a voucher thus far. Recently, a proposal has been advanced for a European program for neglected diseases that accelerates pricing and reimbursement deliberations (a critical step in making drugs available in the European Union) in addition to providing priority review incentives (18).

The Creating Hope Act of 2010 updates and improves the original law and adds drugs and biologics for pediatric rare diseases to the list of conditions that qualify for a priority review voucher. In addition, the Act provides several improvements to the original bill, including (i) closing certain loopholes (for example, under this act, the law would no longer apply to a drug that was previously approved outside the United States), (ii) specifying that the voucher is transferable more than once, (iii) adding a provision for getting the FDA opinion that a program qualifies for a voucher before final drug approval, and (iv) adding a requirement for a good-faith marketing statement and follow-up reporting (Table 1). Drugs qualifying for a voucher must be innovative (new) and for human use. Drugs for the prevention or treatment of a pediatric disease must (i) be targeted to a rare disease, (ii) be eligible for priority review, (iii) be exclusively for a pediatric indication (and the company is not seeking an adult indication), and (iv) be supported by data from studies in children and doses intended for pediatric use. The owner of a voucher issued for a neglected tropical disease or rare pediatric disease must notify the FDA in advance of intent to use the voucher; user fees apply. The latter provisions are included to allow the agency time

**Table 1. Improvements to the “Priority Voucher for Neglected Diseases Program” through the “Creating Hope Act of 2010”**

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| Adds rare pediatric diseases to the bill   |
| Adds Chagas disease to the list of tropical diseases   |
| Prevents issuance of the voucher for a drug for treating tropical diseases that has been approved by another government agency outside the United States for more than 24 months |
| Places no limit on the number of times the voucher can be transferred before its use   |
| Requires the sponsor to write a plan to market the product in the United States  |
| Requires good-faith intent by the sponsor to market the product  |
| Requires submission of a report about the disease or indication and the product to FDA within 5 years after product approval   |

and resources to address the time demands of priority review.

Although BPCA and PREA represent prime motivators of pediatric drug development, most of their productivity has been related to assuring pediatric data for drugs that are also developed for adults. The Orphan Disease Act has been quite productive, but to date, a minority (~20%) of orphan drugs are for diseases that occur exclusively in children. In pediatric-specific cancers and other areas, new drug development has been slow. Nancy Goodman of the Kids Vs Cancer Foundation, a strong proponent of the Creating Hope Act, points out that only one drug for a pediatric indication has been approved in cancer in the past 20 years (15). The pending bill would enhance incentives for drug development in rare pediatric diseases that are typically serious and life-threatening illnesses, with an otherwise small return on financial investment but with big medical impact. Recently, Kesselheim reviewed the pros and “collateral effects” of incentive programs to promote pharmaceutical research and development, identified a number of potential unintended consequences of these programs (such as additional cost to patients/public and potential for misuse), and provided some insights into improvements that link incentives to the desired public health outcome (19). These are relevant considerations; clearly, incentive initiatives need to be transparent and include the ability to measure impact (for tracking and assessment). For pediatric incentive and regulatory programs, there is progress in this regard. The 2007 re-authorization of BPCA and PREA provide added transparency and continued outcome reporting. Although there is room for improvement, there is evidence that refinements of these programs in re-authorization are moving

in the right direction. The pending Creating Hope Act goes further and includes reporting requirements for market distribution of the product for which a voucher was issued and provides that the drug is used exclusively for a pediatric indication, thus targeting the desired outcome.

In assessing incentive programs, the costs as well as the medical and public health impact need consideration. We certainly need to strive to optimize the balance of government/taxpayer contribution, effects on the adult community through increased drug costs, delayed access to generic drugs, incentives to the pharmaceutical industry, and other factors. It has been suggested that the government can do more to support drug development for children and rare diseases. In fact, some newer initiatives do just that, including BPCA and Orphan Drug Act grant programs and the new Therapeutics for Rare and Neglected Diseases program at the NIH. The latter provides NIH in-house drug development support to academic investigators working on rare and neglected diseases. Nevertheless, successful drug development also requires the interplay between government and industry. Although government funding can help “de-risk” candidate pediatric drugs by enabling early safety and proof-of-principle studies, industry is a necessary partner in later clinical development, manufacturing, distribution, and other components of the process. Although government support is critical, it is not sufficient to produce products that are available for use in children. Incentive programs are a key catalytic element.

The development of drugs for the treatment of children with serious disease is a public health responsibility that must be shouldered by the community at large; children certainly are not able to pay. During

the past few decades, we have made substantial progress in advancing our knowledge about how drugs are used in children and in stimulating drug development for children through existing programs. The Creating Hope Act of 2010 provides specific incentives for innovative new drug development that targets rare childhood diseases, and incorporates a number of measures that help us evaluate and manage potential collateral risks. It appears to represent an important addition to the armamentarium in pediatric drug development. BPCA and PREA will require reauthorization in 2012, and a report on their progress will be instructive in making any needed improvements to these laws. On a broader scale, this may also be the right time to take a comprehensive look at how we can better integrate the various pieces of U.S. pediatric legislative and regulatory initiatives into a robust program in order to assure that children’s interests are optimally addressed in the drug development process and to bolster the mandate for pediatric data.

Our investment in biomedical research is providing returns, and we need to assure that children, including the most vulnerable, benefit from this investment. There will be a financial cost for this assurance, but doing otherwise is unacceptable.

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