Ensuring Treatment for Children with Orphan Diseases:

ENDING EXEMPTIONS FROM THE PEDIATRIC RESEARCH EQUITY ACT (PREA)

ENCOURAGING PEDIATRIC DRUG DEVELOPMENT

Children are often more vulnerable to diseases and the devastating consequences of them. For children to benefit from advances in medicine, pediatric research and development (R&D) is necessary to ensure safety, correct dosing, and formulations for children, who have difficulty swallowing pills or taking bad-tasting medicines. Despite the great need for child-friendly medicines, drug developers are often slow to formulate and test new treatment options for children, especially when the pediatric market is not seen as profitable.

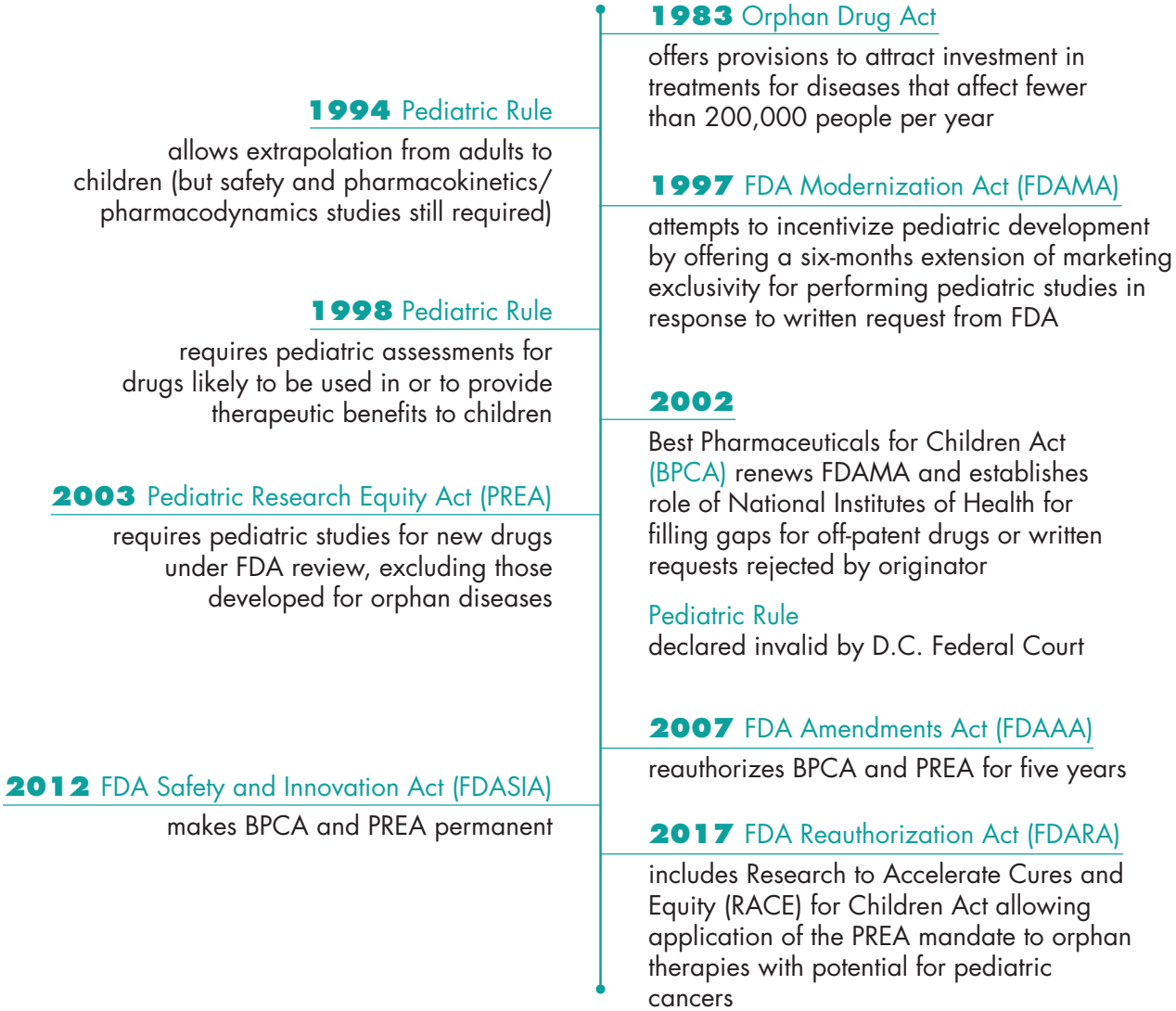
To ensure that studies on safety and dosing in children take place, the Pediatric Research Equity Act (PREA) of 2003 mandates that drug sponsors consider children when developing new drugs with relevance to pediatric populations. In addition, the Best Pharmaceuticals for Children Act (BPCA) of 2002 incentivizes drug developers to conduct voluntary studies in children by offering an additional six months of marketing exclusivity. Under BPCA, the U.S. Food and Drug Administration (FDA) can issue written requests for pediatric studies, but—unlike with PREA's mandate—it is ultimately the choice of the drug sponsors to decide to conduct the requested studies. PREA and BPCA have generated new or revised labeling for use in children for 854 drugs since 2007.[1]

THE ORPHAN DRUG EXEMPTION FROM PREA NEGLECTS CHILDREN

Unfortunately, the benefits of such legislation do not extend to children in need of treatment for neglected or orphan diseases (those affecting fewer than 200,000 people in the United States per year, including diseases such as tuberculosis, cystic fibrosis, and many pediatric cancers). PREA contains an exemption from pediatric research requirements for drugs for orphan diseases. In a cruel twist of irony, the orphan drug exemption in PREA—intended to further incentivize drug development for orphan diseases—results in severe delays to, or in some cases a complete lack of, research to guide the safe and appropriate use of lifesaving medicines in children. And because fulfilling BPCA requests is optional, and neglected diseases by definition lack developer competition, the exclusivity BPCA offers is unlikely to incentivize pediatric development of orphan drugs. Under the FDA's Rare Pediatric Disease Priority Review Voucher (PRV) program—also intended to incentivize development for serious and life-threatening rare or orphan diseases that primarily affect children—a product sponsor who receives an approval for a drug or biologic for a rare pediatric disease may qualify for a voucher that can be used to expedite FDA review of a subsequent marketing application for a different product. Because the Rare Pediatric Disease PRV program is voluntary and eligibility criteria consists only of diseases that primarily impact children it's adequacy is limited for incentivizing pediatric R&D for rare diseases that affect adults but are also present in children.

In the absence of FDA authority to require pediatric investigations of products for orphan diseases, and without adequate incentives to stimulate voluntary investments from sponsors, the burden of closing the research gap to inform safe use of medicines in children then falls on publicly funded research institutions, delaying access and costing U.S. taxpayers money. In the resultant long span between availabilities of new products for adults and for children, pediatricians, parents, and caregivers must cut, crush, and mix bitter medicines, coax already sick and uncomfortable children to take them, and hope that the children under their care are receiving a safe and effective dose. The dangerous position this puts clinicians, caregivers, and children in has been addressed for certain pediatric cancers—the Research to Accelerate Cures and Equity (RACE) for Children Act allows the FDA to apply PREA requirements to drugs developed for orphan cancers that have molecular targets similar to those in children.[2]

FIGURE 1. EVOLVING LEGISLATION FOR PEDIATRIC RESEARCH LEAVES BEHIND CHILDREN WITH NEGLECTED DISEASES



ORPHANED BY THE ORPHAN DRUG EXEMPTION: TUBERCULOSIS IN CHILDREN

A stark example of the harm of this exemption is tuberculosis (TB). The leading infectious killer globally, TB sickens 1 million children each year, including 500 children in the United States. TB is devastating to children—who are particularly vulnerable to TB and for whom available diagnosis, prevention, and treatment options are inadequate[3]—and their families who support them in their struggle. Existing medicines, especially those used to treat multidrug-resistant tuberculosis (MDR-TB), have severe side effects, such as permanent hearing loss and painful nerve damage. Some MDR-TB medicines can be administered only by painful injection. In the absence of optimized treatment for children, TB treatment requires six months to two years of coaxing children to accept toxic medicines. R&D is critical to improve TB treatment for children in the United States and around the world.

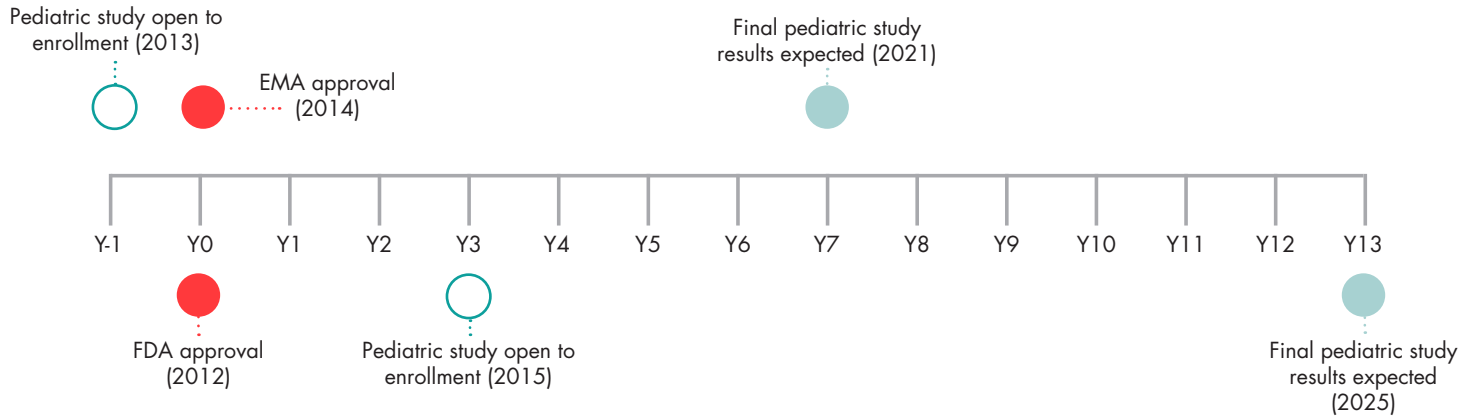
Exciting recent developments in the availability of two new TB options—bedaquiline and delamanid—comparatively demonstrate the impact of exempting treatments for orphan diseases from pediatric studies. In 2012, the FDA approved Janssen's bedaquiline for use in adults—the first TB medicine from a new drug class in 50 years. Bedaquiline is safer, better tolerated, and more effective than many existing medicines for MDR-TB. A landmark study found that people who received bedaquiline had a 41 percent increase in treatment success and were three times less likely to die during treatment than those whose treatment did not include bedaquiline, even though the former were often sicker at the start of treatment.[4] Globally, bedaquiline is now a core element of adult MDR-TB treatment and replaces painful injectable medicines that cause hearing loss.

However, these advancements in the global standard of care for MDR-TB have not yet extended to children, as pediatric investigations of bedaquiline lag woefully behind. Expert consensus is that pediatric studies should begin as soon as safety and signs of efficacy have been established in adults;[5] in TB, this is after phase IIb studies. Pediatric studies for bedaquiline thus should have started in 2011. But without PREA's mandate, pediatric studies of bedaquiline were left to Janssen's discretion. The pediatric study of bedaquiline began only in 2015, and final results are not expected until 2025, leaving at least a 13-year gap from when this lifesaving medicine became available for adults and when its safety and dose for children will be known. Although the FDA never issued a written request for pediatric studies of bedaquiline,[6] the additional marketing exclusivity offered to companies under BPCA is unlikely to have been a sufficient incentive for pediatric development of bedaquiline, given the small market for MDR-TB and the resulting lack of competition.

In contrast, timely generation of evidence to support the use of orphan drugs for children occurs when pediatric development is mandatory. For example, the world's second new TB drug, Otsuka's delamanid, was approved in 2014 by the European Medicines Agency (EMA). The EMA maintains pediatric development requirements as a condition of approval even for orphan diseases like TB. Otsuka's pediatric investigations of delamanid have already finished in most age groups, with final results expected in 2021; delamanid has been recommended for use in children by the World Health Organization since 2016.[7] Delamanid's case demonstrates that rapid pediatric drug development for orphan diseases is feasible when facilitated by regulatory requirements. An FDA requirement for pediatric studies of treatments for orphan diseases is essential to ensuring the timely collection of data to support safe and appropriate use in children.

FIGURE 2. YEARS FROM APPROVAL IN ADULTS TO PEDIATRIC RESEARCH RESULTS WITH AND WITHOUT REGULATORY REQUIREMENTS

DELAMANID (EMA REQUIRES PEDIATRIC RESEARCH)



BEDAQUILINE (FDA DOES NOT REQUIRE PEDIATRIC RESEARCH)

A WAY FORWARD

Closing the gap between development of new medicines for adults and for children is vital. The existing FDA authority to urge developers to close this gap is limited, especially for orphan diseases.[8] Currently, the FDA can issue written requests for voluntary pediatric studies of treatments for orphan diseases and provides guidance to companies regarding safety considerations and regulatory expectations for pediatric drug development.[9,10,11] The FDA has also closed an important loophole, no longer allowing sponsors to use a pediatric subpopulation designation for a non-orphan disease in adults to exempt themselves from requirements under PREA, but the orphan disease exemption from PREA remains.[12] As the world's leading regulatory authority, the FDA should be empowered to hold pharmaceutical companies accountable for collecting data necessary to inform the safe and appropriate use of orphan disease products for children, as is the case for products for all other diseases. This empowerment can happen only through legislative authority. The reapplication of PREA to orphan diseases would narrow the gap between when adults and children are able to access new treatments, both in the United States and around the world, as many countries and global organizations rely on the FDA's regulatory decisions to inform and guide their own. Through the use of waivers and/or deferrals when relevant, the FDA has the ability to ensure that pediatric research requirements for orphan diseases don't delay or discourage the development of new treatments for adults.

Congress has already demonstrated a willingness to make policies that ensure children with certain forms of orphan diseases can benefit from expedited research. The RACE for Children Act allows the FDA to apply PREA requirements to drugs developed for orphan cancers that have molecular targets similar to those in children.[13] The precedent set by the RACE for Children Act should be expanded to other neglected and orphan diseases to ensure that all children are able to share the benefits of the best available treatments sooner.

END NOTES

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