Enhancing the Pediatric Drug Development Framework to Deliver Better Pediatric Therapies Tomorrow

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ABSTRACT

Health care professionals involved in the clinical management of children have long appreciated the limited number of therapies suitably evaluated for their optimal use in the pediatric population. In the past century, advances in regulatory policy significantly evolved adult drug evaluation. The scarcity of available patient populations, practical complexities of drug development research, and minimal financial returns have hampered pharmaceutical investment in the study of therapies for children. More recently, pediatric policy and legislation in the United States and Europe have instituted a system of obligations and incentives to stimulate investment in pediatric drug development. These initiatives, in conjunction with a more sophisticated process of drug discovery and development, have led to significant advancements in the labeling of drugs for pediatric use. Facilitated by the emergence of new targets, precision medicine, and innovations in regulatory science, there is now a subtle shift in focus toward drug development research for children rather than simply in children. Although there has been an increase in pediatric studies of investigational agents and labeling of pediatric information for use, there have been unintended consequences of existing policies. As a result, limited progress has been made in certain therapeutic areas and for off-patent therapies. Future policy reform to enhance the availability and accessibility of pediatric medicines should not only reflect an understanding not only of the successes of existing policy and legislative initiatives but also constructively address failures and unintended consequences. Taken together, policy reform, global cooperation, and innovation in regulatory science will more ably deliver better pediatric therapies tomorrow. (*Clin Ther.* 2017;39:1920–1932)

Key words: drug development, innovation, pediatric, policy.

INTRODUCTION

Children are subject to many of the same diseases as adults, often leading to clinical treatment that uses the same drugs and biological products. Although the level of relevant research has been increasing, only a fraction of the available therapies in adults have been adequately evaluated in pediatric populations to assess age-appropriate dosing, tolerability, and efficacy.[1–3] Because pediatric patients can differ markedly from adults in how medicines are absorbed, metabolized, and excreted, it is not always appropriate to rely on available adult information for use in children. Moreover, numerous diseases in children differ from the adult equivalent or have no adult equivalent disease on which to base assumptions to characterize the potential response to treatment.

Historically, studies that included children and pregnant women had been conducted with limited regulatory oversight. In some instances, unanticipated mortality (elixir sulfanilamide) and significant developmental toxic effects (thalidomide) resulted.[4,5] These tragedies led to significant policy change governing the testing and marketing of new drugs in the 20th century. This included passage of the 1938 Food, Drug, and Cosmetics (FD&C) Act, which gave the US Food and Drug Administration (FDA) power to monitor the safety profiles of new drugs, and the 1962 Kefauver-Harris Amendments to the FD&C Act, which imposed strict guidelines for the process of drug approval, requiring a drug be tolerable and effective before approval and marketing.[6]

Although the policies contained protections that were not limited to adults, the tragedies leading to the

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new legislation had so shocked the societal conscience that the absence of specific requirements to include children led to their routine exclusion from clinical trials. With no pediatric tolerability and efficacy data being generated, children were now exposed to new risks through off-label exposure to drugs as part of clinical practice. In a 1968 *Journal of Pediatrics* editorial, Harry Shirkey[7] wrote about this disparity. He highlighted the juxtaposition of pediatric adverse events (AEs) driving new regulatory mandates to strengthen adult drug approval requirements and the absence of adequate labeling for pediatric use, leaving the pediatric population at increased risk for underdosing or overdosing and unanticipated AEs unique to children.

During the past 2 decades, governments have been addressing the inadequacy of drug testing and insufficient information for use in product labels for children through the introduction of policies intended to stimulate investment in pediatric drug development.[8,9] Among the various policies introduced, laws to provide economic incentives and obligations to require pediatric studies of new drugs in the United States and Europe have had the greatest measurable effect. This review provides a summary of existing pediatric policy initiatives, describes their effect on the availability of new therapies for pediatric use, explains their applicability to today's drug development portfolios, and introduces considerations for pediatric policy evolution in the years ahead.

PEDIATRIC POLICY AND LEGISLATIVE CHANGE

United States

To improve the licensing and labeling of products and the availability of age-appropriate formulations for pediatric use, the United States introduced a series of pioneering pediatric regulations and laws (**Table I**). In 1979, the FDA introduced a pediatric use subsection to the label template. However, manufacturers had little incentive to study pediatric patients because the population affected by the intended use was often limited, yielding a relatively small market. In 1994, the FDA published a final pediatric labeling rule to expand pediatric labeling provisions to require manufacturers of marketed products to review existing data and assess whether it could support pediatric labeling extensions.[10] The rule introduced the concept of extrapolation of adult data for pediatric use but did not mandate the conduct of pediatric studies. Although the rule led to the submission of pediatric labeling supplements for a fraction of approved products, the supplements received by the FDA did not substantially improve pediatric use information, failing to adequately address the problem.[11]

In 1997, US Congress passed the Food and Drug Administration Modernization Act, which created §505A of the FD&C Act, establishing an incentive that granted manufacturers an additional 6 months of marketing exclusivity if they voluntarily performed pediatric studies agreed on under a written request (WR) issued by the FDA.[12] One year later, the Pediatric Rule was published as a companion rule designed to require manufacturers of certain new drugs to conduct pediatric studies to support pediatric use for the claimed indication.[13] Both §505A and the Pediatric Rule were intended to work in conjunction to drive the pediatric study of drugs. However, in 2002, the Federal Court in the District of Columbia invalidated the Pediatric Rule, noting that it exceeded the FDA's statutory authority. Later that year, the Best Pharmaceuticals for Children Act (BPCA) was enacted, reauthorizing the pediatric exclusivity incentive and establishing a National Institutes of Health process to study off-patent drugs for pediatric use when manufacturers declined to do so.[14] In 2003, the US Congress passed the Pediatric Research Equity Act (PREA), which adopted many of the principles that had been introduced under the Pediatric Rule and added a provision that exempted products from the pediatric study requirement when the product had been granted an orphan designation.[15] Because the laws had sunset provisions, BPCA and PREA required reauthorization under the FDA Amendments Act in 2007. Under the FDA Amendments Act, the National Institutes of Health process was expanded to allow the National Institutes of Health to draft a proposed pediatric study request for on-patent drugs that the FDA could extend as a WR to sponsors.[16] In 2010, pediatric incentives were also made applicable for extension of exclusivity only for biologics under the Biologics Price and Competition Innovations Act.[17]

Under these policies, modest revenue increases resulted from pediatric labeling extensions. However, the BPCA had proven to be an important stimulus for some blockbuster products whose manufacturers had