Review Article

The Pediatric Studies Initiative: After 15 Years Have We Reached the Limits of the Law?

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ABSTRACT

Background: Despite considerable disincentives for conducting drug studies in children, 15 years ago the Food and Drug Administration, pediatric health advocates and congressional sponsors created a carrot-and-stick policy approach of voluntary and mandatory programs to encourage the pharmaceutical industry to include children in the drug development process. After several rounds of reauthorization of the laws on a temporary basis, the enabling statutes have been made permanent.

Objective: The purpose of this analysis is to review the advances that resulted from the law and the areas where further progress is needed.

Methods: A brief review of the history and results of the pediatric studies initiative was conducted by the authors and a determination made about the accomplishments of the law and remaining challenges.

Results: Indicators of the changes that resulted from this pediatric studies initiative are both indirect, such as the increase in the number of indication supplements for new populations, and direct, such as the decrease in the percentage of medicines used off-label in children. Although the pediatric studies initiative has significantly improved therapeutic options for children, concern still exists that drug companies are reluctant to include children in drug development unless continuously incentivized, whether positively or negatively. Two challenges are particularly problematic: neonatal studies and child-friendly formulations.

Conclusion: Although the latest round of legislation should provide opportunities to address these problems, significantly more effort will be needed to achieve real culture change. Ultimately, the solution will require full program implementation by the Food and Drug Administration and close collaboration by many key stakeholders to ensure that pediatric studies become a routine part of the drug development process. (*Clin Ther.* 2014;36:156–162) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: carrot and stick, incentives, neonates, pediatric formulations, pediatrics, research and development.

INTRODUCTION

There are considerable disincentives that make the prospect of studying pediatric indications a daunting one, especially if the drug was primarily developed for the adult market. Among these are liability and ethical concerns, limited patient populations for certain diseases, the practical difficulties of conducting trials in children, a limited scientific basis for determining dose, the lack of accepted end points and validated pediatric assessment tools, and the limited marketing potential compared with adults. Because of these circumstances, until 15 years ago, 50% to 80% of medicines being used in children in the United States, Europe, and

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Japan, the major loci of drug development worldwide, were being used off-label without sufficient dosage, tolerability, and efficacy data or appropriate formulations being available.[1]

What happened 15 years ago was the result of frustration among the Food and Drug Administration (FDA) and pediatric health advocates at the lack of success of regulatory policies to encourage the pharmaceutical industry to include children in the drug development process. Although the FDA prepared a pediatric assessment regulation with enforcement provisions for newly developed drugs, congressional sponsors considered options for incentivizing pediatric clinical trials for already marketed drugs. In late 1997, the FDA Modernization Act was passed, and among its many provisions was an incentive program for the pharmaceutical industry to conduct pediatric studies in exchange for an additional 6 months of market protection against generic competition for all the products that contained the active ingredient studied (referred to as *pediatric exclusivity*). This provision was reauthorized in January 2002 as the Best Pharmaceuticals for Children Act (BPCA) and was reauthorized again in September 2007 as part of the Food and Drug Administration Amendment Act. Meanwhile, the FDA issued a regulation in late 1998 that mandated pediatric assessment of new drugs (or already marketed drugs under certain circumstances), which was later codified as the Pediatric Research Equity Act of 2003 (PREA) and also reauthorized in 2007 under the Food and Drug Administration Amendment Act. Thus, the BPCA and PREA, or the carrot-and-stick approach, relied on both positive and negative incentives and became the driver for pediatric studies in the United States. The BPCA and PREA were subsequently expanded to include biological products under the Biologics Price Competition and Innovation Act, which was signed into law as part of the Patient Protection and Affordable Care Act, now more commonly known as the Affordable Care Act, in March 2010. Ultimately, PREA and BPCA were made permanent under the FDA Safety and Innovation Act of 2012, also known as Prescription Drug User Fee Act (PDUFA) V because it is the fifth iteration of a law that has been the statutory stalwart of biopharmaceutical regulation and policy since 1992 but required reauthorization every 5 years. So now, after 15 years and 5 PDUFAs, it seems an appropriate vantage point for looking both backward and forward at the pediatric studies initiative.

WHAT HAS BEEN ACCOMPLISHED UNDER THE BPCA AND PREA?

Indicators of the change engendered by the BPCA and PREA come from many directions, both indirect and direct. For example, indirect evidence of the initiative's effect on increasing the number of drugs labeled for pediatric indications comes from a recent review of supplemental new drug applications approved by the FDA in 1998 to 2011. The study reports that of approximately 1000 supplements approved for new indications, 26.7% were for new populations, which are considered to be almost exclusively pediatric supplements. In fact, these supplements increased from the early study period (1998–2004) during which they comprised a quarter of all indication supplements to a third of all such supplements during the latter part of the study period (2005–2011) at a time when the overall number of supplements remained fairly constant.[2] More indirect evidence can be inferred by noting that changes

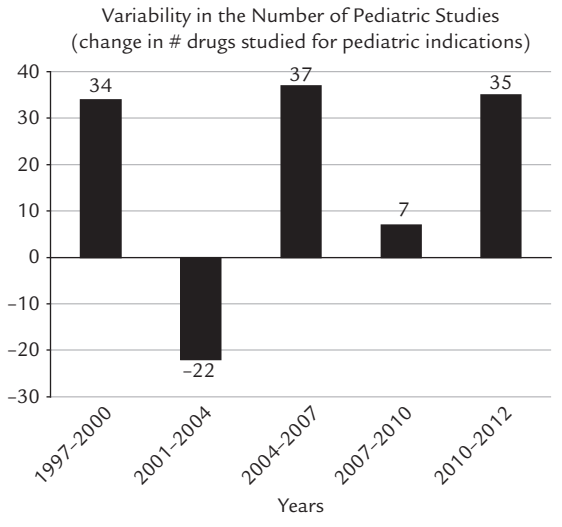

Figure. By reviewing the number of medicines listed in the reports available for various years on Medicines in Development for Children from the Pharmaceutical Research and Manufacturers of America website (http://www.phrma.org/research/medicines-development-children), changes were noted during certain periods that appeared to correspond to changes in the status of the incentive laws.

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