# Mechanisms to Provide Safe and Effective Drugs for Children

Children are therapeutic orphans. The majority of drugs used in children are "off label"; that is, the data regarding dose, safety, or efficacy (and often all 3) are not deemed sufficient by the US Food and Drug Administration (FDA) for inclusion on the product label. Not surprisingly, off-label drug use increases the risk of adverse events. To address the knowledge gap leading to such use, the US government has enacted multiple laws to stimulate increased drug research and labeling for children. One such law is known as "pediatric exclusivity," first passed in 1997 and most recently made permanent in 2012 under the FDA Safety and Innovation Act. Pediatric exclusivity grants pharmaceutical companies a 6-month patent extension if they study a product under a written request from the FDA. For so-called blockbuster drugs, those with ≥$1 billion in sales per year, the incentive is substantial.

In this issue of *Pediatrics*, Wharton et al[1] review the labeling changes related to pediatric exclusivity. These 3 items are worth additional consideration. First, although the FDA issued 401 written requests, pharmaceutical companies chose to respond to fewer than half. Of these, the majority resulted in at least some type of label change, even if the label change was "negative" (ie, a safety concern or efficacy was not established). Second, the majority of written requests were for infectious disease, oncology, and endocrine drugs. It is not surprising that infectious disease drugs were among the most common. Infectious disease therapeutics benefit from extrapolation; extrapolation of efficacy is used by the FDA if the disease process is similar and if there are known pharmacodynamic end points (eg, area under the curve, minimum inhibitory concentrations) that are reproducible and predict therapeutic success. Dosing and safety trials are still required under the process of extrapolation, but multiple large trials can be waived, which results in an approval process that is less time-consuming and often feasible. Third, we have shown that the most common determinant of success or failure of pediatric trials relates to the strength and rigor of the clinical pharmacology used in establishing the dose-response relationship.[2,3]

Although the authors chose to examine drugs under pediatric exclusivity (ie, newer drugs), many drugs used in children are now off-patent (usually older drugs). In these cases, pediatric exclusivity does not apply. Fortunately, the federal government has provided other mechanisms for studying these drugs, such as the Best Pharmaceuticals for Children Act off-patent program. In 2010, a contract was awarded to establish the Pediatric Trials Network, which was tasked with studying off-patent and off-label prioritized drugs (and devices). To date, data for 6 drugs have been submitted to the FDA, and it is likely that these data will result in label changes.

In conclusion, when pharmaceutical companies respond to a written request under the Pediatric Exclusivity Program, important information is typically added to the FDA label, thus improving the health of children.

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**KEY WORDS**

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**ABBREVIATION**

FDA—Food and Drug Administration

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It would be optimal if all of the labeling changes were for efficacy, but this is not always the case. Conducting pediatric trials, particularly those in the youngest children (especially neonates), is challenging because of low consent rates, a small target population (most children are healthy, and children represent a small fraction of the total population), lack of validated end points, and limited pediatric clinical pharmacology expertise. Despite these shortcomings, innovative stimuli from the federal government for the study of all drugs used in children lead to increases in the number of safe and effective medications for children.

Finally, the authors assert that "positive and negative outcomes continue to inform the construct of future pediatric trials." We agree that it is possible that further analyses of the characteristics of successful and failed trials will lead to improved trial design and increased success of efficacy. However, substantial improvements will only come to fruition if all individual patient data collected during the trials are released into the public domain. The release of pediatric data into the public domain is uniquely possible due to ethical mandates (children cannot provide informed consent) and because most pediatric drug development is considered "precompetitive space," that is, the market is so small that pharmaceutical companies risk little if individual patient data are made public.

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