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ADVANCES IN PEDIATRICS

Advances in Pediatric Pharmacology, Therapeutics, and Toxicology

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Keywords

• Pediatrics • Pharmacology • Pharmacokinetics • Toxicology

Key points

- Pediatric research has expanded in the United States and Europe, largely because of legislation providing a framework for the design and execution of pediatric studies.
- Although much work remains, as a result of greater regulatory guidance more pediatric data are reaching product labels.
- The pharmacokinetic/pharmacodynamic properties of many drugs used to treat children have yet to be characterized.

INTRODUCTION

Significant advancements have been made in pediatric therapeutics over the last 2 years. Of note, the US Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012, making the Best

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Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) permanent for the Food and Drug Administration (FDA), no longer requiring reauthorization every 5 years. BPCA, which was also authorized for the National Institutes of Health (NIH) for the next 5 years, provides a mechanism for off-patent drug development and a pediatric exclusivity incentive, encouraging manufacturers to perform pediatric studies in exchange for an additional 6 months of patent protection. PREA gives the FDA the authority to require that studies be performed if the indication being sought for approval in adults is relevant to child health. As a result of BPCA and PREA, pediatric labeling information has improved, but one analysis reported that as of 2009 only 46% of drugs had some labeling information related to pediatric use, an increase from the 22% estimated in 1975; also, 41% of new molecular entities had pediatric labeling, up from 20% in 1999 [1]. A summary of select labeling changes made by the FDA in 2012 and 2013 is presented in Table 1.

In Europe, the Pediatric Regulation went into effect in 2007 to promote the expansion of pediatric research in this region. The European Medicines Agency (EMA) highlighted successes over the first 5 years of the regulation, and reported that about 400 clinical trials including children (0–18 years) are performed each year. The EMA Pediatric Committee has agreed to more than 600 Pediatric Investigational Plans (PIPs) with pharmaceutical companies, and a large collaboration of pediatric research networks (Enpr-EMA) has been created [2]. More pediatric research has translated into more information in the Summary of Product Characteristics: 221 changes with regard to safety and efficacy, 89 additions of dosing information, and 77 other modifications related to new study data being added [2].

An important requirement in FDASIA and in the EMA Pediatric Regulation is that clinical trials also be performed in neonates when appropriate, because neonates historically have been excluded from drug trials far too often. If neonatal studies are not warranted or cannot be performed for logistical or ethical reasons, sponsors must provide justification. This provision is important, as limited pharmacokinetic (PK) and pharmacodynamic (PD) data are available in this vulnerable population. Between 1997 and 2012 only 31 drug products were studied in neonates, resulting in labeling changes for 27; these figures are relatively small when compared with pediatric studies performed in older age groups for more than 400 drug products [3]. A separate analysis indicated that approximately 54% of neonatal labeling changes resulted in addition of the following statement: ''safety and efficacy have not been established'' [4]. For the remaining 46% (4 human immunodeficiency virus [HIV] drugs, 3 anesthesia drugs, 4 drugs for other indications), an approval for use in neonates was obtained [4]. Therefore there is an overall lack of PK/PD data in neonates, in particular premature infants, and clinical trials are not being performed for widely prescribed medications in this population.

Another concern receiving considerable attention relates to drug shortages. Drug shortages can be problematic because they cause clinicians to alter drug treatment and, in some cases, prescribe less effective or more toxic