Development of Drug Therapies for Newborns and Children

The Scientific and Regulatory Imperatives

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KEYWORDS

• Pediatric • Neonatal • Research • Extrapolation • Dosing • Regulations

KEY POINTS

- Pediatric drug development laws have improved labeling of products, including off-patent products, for use in pediatric patients.
- Extrapolation of efficacy data from adults relies on the understanding of the disease and response to therapy in adults and application to pediatric patients.
- Dose selection in pediatric patients, including neonates, should be based on understanding the influence of growth and development on pharmacokinetics and pharmacodynamics.
- Data on age- and disease-appropriate biomarkers in pediatric patients are critically lacking.
- Tremendous strides are being made in establishing consortia and clinical research infrastructure to facilitate drug development in pediatric patients, including neonates.

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INTRODUCTION

Pediatric advocacy and legislative initiatives have propelled pediatric drug development forward. There still remain significant challenges, including lack of basic science knowledge of disease mechanism for some conditions affecting neonates and children, application of extrapolation and dose-ranging studies to pediatric populations, and incorporation of Good Clinical Practice guidance into clinical trials. This paper will discuss these and other topics from a regulatory, industry, and academic/NIH point of view.

PEDIATRIC LEGISLATION AND IMPACT

For new medications to be marketed in the United States, they must be approved under the Food, Drug, and Cosmetic (FD&C) Act. Under the FD&C Act, drug manufacturers must demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies to obtain marketing approval. During the review of the marking application, the US Food and Drug Administration (FDA) must assess whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks. Pediatric disasters such as the sulfanilamide tragedy (where sulfanilamide was dissolved in an elixir flavored with diethylene glycol and resulted in 100 fatalities) prompted many of the FDA's current regulations that require drugs to be safe and effective, as well as pure. Despite this, in 1968 Dr Harry Shirkey published an editorial in the *Journal of Pediatrics* in which he stated, "By an odd and unfortunate twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans."[1] His editorial noted that most drugs approved by FDA, including drugs that were commonly used in infants and children, were not approved for children and product labeling contained no information about the efficacy or safety of the drug when used in children.

Indeed, many pharmaceutical manufacturers were reluctant to study drugs in children owing to ethical and financial constraints or trial design challenges. Medications were often administered to children empirically, assuming that they were "little adults." This simplistic and often erroneous assumption resulted in pediatric dosing recommendations derived solely as fractions of adult dosing rather than on intrinsic factors based on known differences in growth and development (eg, volume of distribution and maturation of the metabolic and excretory pathways). Safety and efficacy were also simply assumed to be the same in the pediatric and the adult populations, and did not take into account both known and potential safety and efficacy differences that may be present in a growing and developing pediatric patient.[2]

Efforts to increase the availability of clinical data to support evidence of efficacy and safety of drugs used in infants and children were made over the next 20 years, but it was not until congress passed the first incentives for conducting pediatric studies in the Food and Drug Modernization Act of 1997 that drug development began to include children more consistently. This provision allowed the FDA to issue a Written Request outlining the studies needed on a specific drug for 1 or more conditions or indications, including indications not approved in adults. The FDA can grant 6 months of marketing exclusivity to sponsors who complete the voluntary pediatric studies included in a Written Request. The incentives first authorized under the Food and Drug Modernization Act of 1997 were reauthorized in 2002 in the Best Pharmaceuticals for Children Act (BPCA). BPCA was permanently reauthorized for FDA in 2012 under the FDA Safety and Innovation Act. Additionally, the ability to obtain pediatric exclusivity was extended to biologic products under the Patient Protection and Affordable Care Act of 2010. The BPCA also established a partnership between the FDA and the National Institutes of Health (NIH) to conduct studies on older drugs (eg, off-patent products) used in children for which pediatric information is lacking.