MACROSCOPY

Future of Pediatric Therapeutics: Reauthorization of BPCA and PREA

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Two companion pieces of legislation critical to pediatric therapeutics are scheduled to sunset (automatically terminate) on 1 October 2007 unless reauthorized by Congress. The Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003, along with the preceding pediatric provisions of the FDA Modernization Act (FDAMA) of 1997, have had an unprecedented impact on pediatric medicine over the past 8 years. It is essential that Congress renew the provisions of these statutes to ensure availability of safe and effective therapies for children in the coming decades. The importance of this legislation to the future of children's health can be appreciated only in the context of the history of limited new drug development for children over the past 40 years before the enactment of these two pieces of legislation.

Development and marketing of drugs for human consumption in the United States has been predominantly regulated for the past 40 years by the 1962 amendments to the Food, Drug, and Cosmetic (FD&C) Act, the so-called Kefauver-Harris amendments. These amendments, when implemented in 1966, introduced several new regulatory mandates, including the requirement to prove efficacy as well as safety of a drug by conducting scientifically rigorous, well-controlled clinical trials before marketing approval. In addition, pharmaceutical companies were for the first time prohibited from making efficacy claims for a new drug that were not supported by scientific evidence and included in the official label approved by the FDA. It is clear from a review of the legislative history of the 1962 amendments that Congress intended for children to be included in the protections provided under the amended FD&C Act. However, this was not the case in practice. In the absence of specific requirements for studies in all age groups who would benefit from a new drug, children were largely excluded from clinical trials and drugs were labeled only for adults with a disclaimer that safety and efficacy in children had not been established. In 1968, merely 2 years after implementation of the 1962 amendments, Dr. Harry Shirkey, then chair of the American Academy of Pediatrics Committee on Drugs, called attention to the exclusion of children and coined the term "therapeutic orphan." Dr. Shirkey went on to point out the irony that, although passage of the 1962 FD&C amendments was precipitated by the thalidomide phocomelia tragedy affecting thousands of children, children were now being systematically excluded from studies to establish safety and efficacy of new drugs. Several published surveys between 1975 and 1999 have consistently documented that approximately 80% of prescription medicines are approved and labeled for adults with no pediatric safety or prescribing information and a disclaimer regarding use in children. The result has been routine and widespread "off-label" use of medications in infants and children in the absence of adequate safety, efficacy, and dosing information with the ever-present risk of adverse outcomes due to underdosing, overdosing, or unanticipated adverse events unique to children and not predicted from experience in adults. This situation has prevailed for the past 40 years.

Reasons for excluding children from new drug development are complex. Among those most commonly mentioned are ethical constraints, medical-legal risks, technical and logistical difficulties, and economic disincentives. However, the ultimate rate-limiting factor has been the economics of drug development in children, given the small market for most drugs in the pediatric age group relative to the adult market size. Ethical guidelines for conducting clinical studies involving children have been available for nearly 30 years. In 1974 the American Academy of Pediatrics first published "Guidelines for the Evaluation of Drugs to Be Approved for Use During Pregnancy and for Treatment of Infants and Children". This was followed by publication in 1977 of "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," which were revised in 1995. Federal regulations for protections for children involved as subjects in research were published in 1983 and subsequently incorporated into the "Common Rule" codified in CFR 45 Part 46, subparts A–D. In 2000, similar

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protections were included in the ICH E11 guidelines. Likewise, technical challenges for conducting studies in children have been largely addressed, and there is little precedent in trial law to support the concern that medical-legal liability is greater when involving children in clinical research than it is with adults.

The turning point for pediatric drug development came with a 3-day workshop on Drug Development and Pediatric Populations, convened in 1990 by the Forum on Drug Development of the Institute of Medicine, National Academy of Sciences. Representatives from pediatric medicine, academia, industry, the FDA, and the NIH made the following recommendations:

The FDA should develop regulatory changes to facilitate inclusion of pediatric information in drug labeling.

Congress should draft and pass legislation to address economic constraints.

The pharmaceutical industry should take a proactive stance in pediatric drug development.

The NIH should take the lead in providing infrastructure funding to foster pediatric research in a more efficient, innovative, and effective manner.

During the ensuing decade, each of these recommendations was addressed. The FDA promulgated regulations to facilitate and encourage pediatric studies and labeling; the NIH introduced several initiatives to increase pediatric research, including establishing study networks such as the Pediatric Pharmacology Research Units Network, the Research Units for Pediatric Psychopharmacology Network, the Neonatal Network, and the Obstetrics and Perinatology Research Units Network; leaders in the pharmaceutical industry developed pediatric research programs; and Congress passed legislation both to provide economic incentives for companies to engage in pediatric drug development and to require pediatric studies of new drugs.

Among the various initiatives over the past decade, legislation to provide economic incentives and require pediatric studies of new drugs has had the greatest measurable impact on pediatric drug development. The FDAMA stimulated a marked increase in pediatric studies of drugs by providing an incentive of a 6-month extension of market exclusivity for all products containing the active moiety, in return for studies that conform to the details of a Written Request issued by the FDA. When the FDAMA sunset in 2002 with 28 label changes, it was succeeded by the BPCA, which maintained the exclusivity extension. In addition, the BPCA established an office of pediatric therapeutics at the FDA and required careful evaluation and public discussion of all significant new safety data received during the first year of marketing of a drug following receipt of exclusivity. The impact of these incentive programs has been enormous (**Table 1**).

Table 1 Outcomes of pediatric studies requested through the FDAMA and the BPCA: 22 November 1997 through 30 October 2006

Written Requests issued by FDA	326
Requested studies (efficacy, safety, kinetics, etc.)	761 (one Written Request may require several specific studies)
FDA divisions involved in pediatric studies	15
Exclusivity determinations	129
Active moieties granted exclusivity	123
Labels with revised pediatric prescribing information	118

The increase in pediatric studies of drugs leading to labeling has begun to correct the deficit in pediatric pharmacology research that has accrued since 1962. In addition, the BPCA has been complemented since 2003 by the PREA, which requires new drugs be studied in pediatric patients for the indications for which the sponsors are seeking approval in adults, unless the requirement is waived or deferred by the FDA.

Of note is the revision of 118 drug labels to add or expand pediatric information. Examples of important pediatric labeling changes based on studies conducted under the BPCA with practical and direct therapeutic impact include:

- Ondansetron: Patients <18 years of age have a higher clearance and shorter half-life than adults, except for infants 1–4 months of age, in whom the half-life is 2.5 times longer than children 4–24 months of age.
- Benazepril: Clearance is significantly higher in children, with a half-life one-third that of adults.
- Gabapentin: Higher doses are required in children <5 years of age, and neurobehavioral adverse events were identified in young children.
- Fluvoxamine: Higher doses are required in adolescents, but dosage is decreased in females 8–11 years of age as compared with males or older adolescents.

Equally important is the expansion of pediatric research into therapeutic areas previously largely ignored. These include addiction, analgesia, cardiovascular/renal, dermatology, endocrinology/metabolism, gastroenterology, immunomodulators, medical imaging, neurology, behavior/psychiatry, ophthalmology, and pulmonary.

As we look forward to reauthorization of the BPCA and the PREA during the current session of Congress, we must consider the potential incremental cost due to a 6-month delay of drugs reaching the less expensive generic market. The estimated cost of these incentive programs must be weighed against the gains in cost and quality of health care for children. One of the primary goals of the FDAMA and the BPCA was to improve pediatric drug therapy through systematic study that would reduce adverse events through better prescribing information. Cost savings to the health-care system solely from a modest 2% reduction in adverse events for children have been estimated to be in the range of US$152–$708 million annually, based on overall annual cost of adverse events and the incidence of adverse events in children.

Another cause for concern is the perception by some that clinical research is inherently risky, associated with

reluctance to expose children to such risk. However, a significant body of literature has documented that a child being treated under protocol in a well-designed, carefully conducted study with appropriate institutional review board oversight, generally has a better outcome than comparable patients receiving "standard care." This raises the question of which is safer and more ethical: treatment of a child participant in a clinical trial or with "off-label" treatment in which the child is an experiment of one without collection of data? In the former situation, there is the intent that new generalizable knowledge will be derived that will not only potentially benefit the child subject but also benefit other children. In the latter, the child will receive treatment based on the prescriber's experience, recommendations of peers, or limited clinical series of patients without systematic collection of data that can be generalized and publicized for the benefit of larger populations of children.

In conclusion, as stated clearly by the American Academy of Pediatrics in their guidelines *Ethical Conduct of Studies Involving Children*, "There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents."[1] The FDAMA and the BPCA have provided the only successful stimulus for the study of drugs in pediatric populations in the past 40 years. However, the work has just begun. New drugs that provide improvements in treatment for adults are very likely to be used to treat children. Renewal of the BPCA and the PREA is critical to ensure that our nation's children receive therapies based on well-controlled studies conducted in a similar pediatric population. To do less compromises the quality of their health care and relegates them to therapeutic second-class citizenhood.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

1. American Association of Physicians, Committee on Clinical Research Involving Children, Board on Health Sciences Policy. *Ethical Conduct of Research Involving Children*. Field, M.J. & Behrman, R.E., eds.. (National Academies Press, Washington, DC, 2004).