Safe and Effective Medicines for Children
Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act

Until recently, most drugs used to treat children had been tested for safety and effectiveness only in adults. In recognition of the resultant dearth of information to guide care for children, in 1997 Congress and the Food and Drug Administration (FDA) created policies to encourage more pediatric studies of drugs.

The policies include the Best Pharmaceuticals for Children Act (BPCA), which provides economic incentives for drug companies to conduct pediatric studies in response to FDA requests, and the Pediatric Research Equity Act (PREA), which allows the FDA to require pediatric studies in certain circumstances. Congress extended BPCA to biologics—drugs derived from human or animal sources, or microorganisms—when it passed the Biologics Price Competition and Innovation Act in 2010.

As directed by Congress, the FDA asked a committee of the Institute of Medicine (IOM) to review aspects of pediatric studies and changes in product labeling that resulted from BPCA and PREA and their predecessor policies. The FDA also asked the IOM to assess the incentives for pediatric studies of biologics and the extent to which biologics had been studied in children. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act presents the IOM study committee’s findings.

Summary of Findings
The committee reached a number of broad conclusions:

Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children. The amount of information var-
ies by medical condition, type of product, and age group. Information from the studies sometimes supports and sometimes counters expectations about a drug’s efficacy and safety among children of different ages. Since the two policies were adopted, the FDA has approved 400 labeling changes related to these policies (see Figure).

Some studies requested under BPCA or required under PREA do not achieve their full potential. Not all studies succeed for a variety of reasons that may include the inability of sponsors to recruit sufficient numbers of children, the use of weak study designs, and the omission of relevant information from drug labels. The FDA has taken steps to respond to many of these problems, according to the IOM committee, although challenges remain, for example, the reluctance of physicians and parents to enroll a child in clinical trials for drugs already approved for use in adults.

More timely planning, initiation, and completion of pediatric studies would benefit children. The FDA encourages companies to submit plans for pediatric studies at the end of Phase II, but this does not always happen. However, in Europe, where companies are required to submit plans for pediatric studies earlier, the timing may be somewhat premature. The committee also notes that delays in sponsors completing FDA-mandated studies warrant further attention.

Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates (infants younger than 28 days), and the long-term safety and effectiveness of medications used by children of all ages. The lack of information about the long-term safety of drugs prescribed for children is a special worry—both for drugs that may be used for decades for chronic conditions and for drugs for which short-term use may be found to harm children’s growth and development months or years later. Many medicines commonly used for premature and sick neonates are older drugs that have not been adequately evaluated in these vulnerable children.

Congress has significantly expanded public access to information from recent pediatric studies conducted under BPCA and PREA and thereby has enhanced the value of these studies. Limitations still exist, however, particularly for older pediatric studies and for drug label revisions involving biologics. Many of the documents that manufac-

**FIGURE: Changes in drug labeling associated with BPCA, PREA, or both, June 1998 to October 2011**

![Figure 7-1](image_url)

**NOTE: The Pediatric Rule preceded PREA.**
turers submit to the FDA are not public. FDA staff reviews of these documents, if released, often are heavily redacted.

The reauthorization processes for BPCA and PREA have improved policies promulgated under both acts, but frequent reauthorizations create uncertainties for industry and the FDA. Congress has done much to strengthen BPCA and PREA, including requiring that information from pediatric studies be added to product labeling in most cases, and that follow-up analyses of adverse events be reported for the first year following a drug label change. Nonetheless, the frequent reauthorizations of the acts—which occur every five years—create uncertainties for manufacturers, especially given the typically long lead time required to plan and conduct studies.

Requirements for pediatric studies of biologics conducted under PREA have generated valuable information, as have other policies. The 2010 expansion of BPCA to cover biologics could further expand knowledge, but it is too early to assess the new law’s effect. Almost 90 percent of biologics investigated by the IOM committee had been studied in children to some extent. Of the dozen that had not been studied in children, most were approved for medical conditions that either are not or rarely are diagnosed in children, such as prostate cancer. Given other long-standing federal policies, such as the 1984 Orphan Drug Act, and the range of existing research, the expansion of BPCA may have a valuable, but more modest, effect in encouraging studies of biologics than it did for conventional drugs.

**Future Options for Improvement**

The committee was not asked to make recommendations to the FDA, except with respect to pediatric studies of biologics. However, the committee did offer possible guidance in several areas. These include suggestions to:

- **Improve public access to information from pediatric studies conducted under BPCA and PREA.** Congress can, for example, make public FDA assessments of drug studies that led to labeling changes before September 2007, and the FDA can explore ways to integrate these assessments into such databases as PubMed and ClinicalTrials.gov.

- **Improve the timeliness of pediatric studies requested under BPCA or required under PREA.** Congress can require submission of pediatric study plans at the end of Phase II trials in adults and permit the FDA more flexibility to impose sanctions for unreasonably delayed studies.

- **Address areas of limited pediatric investigation under BPCA and PREA, including studies in neonates and long-term safety studies.** Congress can expand the BPCA program at the National Institutes of Health to include assessment of more drugs not adequately studied in newborns, and the FDA can use its authority to require long-term pediatric studies of serious safety risks.

- **Strengthen the design and execution of pediatric studies requested under BPCA or required under PREA.** The FDA can expand innovative strate-
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The policies included in BPCA and PREA have helped provide clinicians who care for children with better information about the efficacy, safety, and appropriate prescribing of drugs. Some new pediatric studies found unexpected harm and led to recommendations against a product’s use in children. Others have led to new formulations, like liquids, that are safe and effective for younger children who can’t swallow tablets or capsules. Still, the IOM suggests that more can be done to increase knowledge about drugs used by children and thereby to improve the clinical care, health, and well-being of the nation’s children.

Conclusion

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