Differences in the physiology of adults and children can produce significant differences in the way they respond to drugs and vaccines. Without adequate data on pediatric safety and efficacy of many products, physicians until recently had to make decisions on their use in pediatric patients based upon labeling that only addressed use in adults.

To correct this situation, the US Food and Drug Administration (FDA) has created regulations and Congress has passed a series of laws to ensure that marketed drugs will be evaluated for safety and efficacy in infants, children and adolescents. Initially, voluntary processes and incentives were implemented, but these did not lead to enough products being studied in pediatric patients. From 1998–2003, FDA developed additional processes that made it mandatory to address the use of a product in pediatric patients prior to approval for use in adults, in many cases requiring that studies be done in pediatric patients. The most recent law, the Food and Drug Administration Amendments Act of 2007, extended these incentives and requirements, introduced increased transparency to the process, and improved the review process for studies in pediatric patients.
Early Attempts to Encourage Pediatric Studies

In order to encourage manufacturers to generate data on the use of their products in pediatric patients, in 1979 FDA issued the Pediatric Extrapolation Regulation. This regulation allowed drugs and biologics approved for adults to be labeled for the same indication for pediatric patients on the basis of safety and dosing studies in the appropriate age groups. In 1994, FDA issued the Pediatric Rule, permitting products to be labeled for pediatric use based upon extrapolation from adult efficacy data to efficacy in pediatric patients, if the illness and its course were sufficiently similar in adults and children. The 1994 Pediatric Rule permitted extrapolation only for efficacy data and not for data regarding the product’s safety or for data from studies designed to select the appropriate dose.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) provided an incentive of six months of patent extension (if the patent were still active) or six months of market exclusivity extension (see below) to manufacturers that conduct studies to evaluate safety and efficacy in pediatric patients, if their products are expected to be used extensively in pediatric populations. The six months of market exclusivity functioned by delaying for six months the approval of any application for a generic version or for a closely related drug. This marketing exclusivity could only be granted as an extension to a period of exclusivity that had already been obtained for the product through another FDA-regulated mechanism. To qualify for the additional six months of market exclusivity, a Proposed Pediatric Study Request (PPSR) had to be submitted by the manufacturer. If FDA agreed with the PPSR, the agency then issued a Written Request that the study be conducted and included a timeframe for completion of the study. If the study were completed according to the plan and if the reports were submitted on time, six months of patent extension and/or six months of additional marketing exclusivity would be granted.

FDAMA also instructed FDA to develop a list of previously approved drugs for which data on usage in pediatric patients could be beneficial. FDA was authorized to issue a Written Request for pediatric studies to the manufacturers of each of the drugs on this list; if the request were refused for any reason, FDA was instructed to work with the National Institutes of Health to publish requests for contract proposals to try to obtain the pediatric data from other sources.

Nevertheless, until 1998, studies of safety and efficacy in pediatric patients were still voluntary, and the exclusivity incentive offered by FDAMA did not increase the number of studies in pediatric patients as much as FDA had hoped. Therefore, in 1998 FDA issued a regulation (the Pediatric Rule) that required the safety and effectiveness of products to be evaluated in pediatric patients if they were intended for use by a substantial number of children or provided meaningful therapeutic benefit to pediatric patients compared to existing treatments. This rule was suspended in 2002 by a court determination that it exceeded FDA’s statutory authority.

Two Subsequent Laws Regarding Pediatric Studies

The Best Pharmaceuticals for Children Act (BPCA), which took effect in January 2002, implemented a number of measures to improve data on the use of drugs and vaccines in pediatric patients. It provided the opportunity for sponsors to obtain six months of extension of exclusivity as an incentive for doing pediatric studies in response to a Written Request from FDA, and it defined the types of studies that could be done to obtain exclusivity. It required FDA to award contracts to have pediatric studies conducted for certain products that were already on the market. It also required the agency to ensure the inclusion of ethnic and racial minorities in pediatric studies and to give priority review to applications that sought to add pediatric indications. It authorized the creation of an office to coordinate FDA activities related to safety and ethical issues of studies in pediatric patients.

The Pediatric Research Equity Act (PREA) was passed in 2003, giving FDA clear authority to require pediatric studies for products that would be used in pediatric patients. It required that age-appropriate formulations be tested for each pediatric age group in which the product might be used, although extrapolation from one pediatric age group to another could be accepted in certain situations. However, orphan drugs and generic drugs were exempt from the PREA requirements.

PREA allowed FDA to defer or waive the requirement for studies in pediatric patients, either on its own initiative or on the basis of a request from the manufacturer. Acceptable reasons for deferral were defined as situations in which:

- waiting for studies in pediatric patients would delay availability of the product for adult patients
- concern about the safety of the product
in pediatric patients would make it advisable to review studies in adults further before permitting studies in pediatric patients to begin.

Acceptable reasons for a waiver of pediatric studies were defined as:

- pediatric studies were impossible or highly impractical (e.g., the number of pediatric patients with the disease is very small or patients are geographically dispersed)
- there was evidence that the product would be ineffective or unsafe in a pediatric age group
- the product was not likely to be used in a substantial number of pediatric patients
- an age-appropriate formulation could not be made

The waivers could be limited to one or more pediatric age groups; for instance, a waiver could be granted only for studies in infants on the grounds that it is not possible to develop an infant formulation for the product.

**The Food and Drug Administration Amendments Act of 2007**

The Food and Drug Administration Amendments Act of 2007 (FDAAA)\(^{12}\) reauthorized and updated both BPCA and PREA, and required that data to support safety and effectiveness in all pediatric age groups be submitted in all future applications. However, it permitted FDA to accept findings extrapolated from studies in adults, or from one pediatric age group to another, accompanied by pharmacokinetic studies, if deemed appropriate, and it permitted deferrals and waivers of studies when appropriate.

FDAAA emphasized the need for transparency in evaluating products in pediatric patients. It required that all pediatric findings be described in the product labeling (package insert) even if the results were negative or inconclusive. It required that the number of pediatric studies, types of studies, number of patients studied, labeling changes resulting from the studies and FDA reviews of the pediatric studies be posted on the FDA website. The progress of deferred pediatric studies and the details of waivers of pediatric studies were required to be posted on the FDA website, as well. FDAAA also required all pediatric Written Requests, and selected pediatric studies, to be reviewed by FDA’s pediatric review committee as well as by the agency’s subject-specific reviewing divisions.

FDAAA instructed FDA to contract with the Institute of Medicine to evaluate pediatric studies conducted under this law and its precursors since 1997, and to evaluate the resulting labeling changes. This evaluation also had to include assessment of the process of extrapolation of indications and recommendations for pediatric patients from data obtained in adults or in other pediatric ages, the use of alternative endpoints for pediatric studies, the number and types of adverse events in pediatric studies, and relevant ethical issues.

FDAAA also ended a practice by which manufacturers obtained *de facto* exclusivity for pediatric usage without obtaining an explicit award of exclusivity from FDA. This practice involved filing pediatric study results with the agency just before the termination of other marketing exclusivity, since FDA could not review competitors’ applications during the period of review. Under FDAAA, applicants are eligible for pediatric exclusivity only if the pediatric study reports are submitted to FDA at least nine months prior to the expiration of the product’s existing marketing exclusivity.

**Relevant European Regulations**

Concerns about the safety of medications for children led to regulations in Europe for similar goals that went into effect 26 July 2007\(^{13,14}\), although a discussion of these is beyond the scope of this article.

**Effectiveness**

These laws and regulations, which were intended to result in evidence-based labeling for pediatric
use and pediatric dosage of drugs that are likely to be used to treat pediatric patients, have had a clear impact. Over the approximately six years since the enactment of BPCA and PREA, FDA issued 369 Written Requests specifying 882 studies (as of 31 March 2009). As of 19 December 2008, 159 labeling changes had been made based on the pediatric studies performed in response to Written Requests. Thus, the impact of BPCA is evident by this large number of Written Requests issued by FDA and the resulting labeling changes. PREA, on the other hand, also has resulted in a very large number of additional pediatric studies being conducted as a result of manufacturers complying with the PREA requirements for pediatric assessments for all drugs that might be used in pediatric patients, even when the manufacturer was not seeking pediatric exclusivity.

References
1. Although the age ranges of the pediatric age subcategories are not defined in the laws related to studies in pediatric patients, and although different age ranges have been used at times by different FDA centers, the agency has generally defined these age ranges as listed below, for instance in the Federal Register announcement of the Pediatric Rule of 1994 (accessible at www.fda.gov/cder/pediatric/pediatric_rule1994.htm) and (with slight variation) in Guidance for Industry: General Consideration for Pediatric Pharmacokinetic Studies for Drugs and Biological Products; Draft Guidance, November 1998 (accessible at www.fda.gov/cder/guidance/1970dft.pdf):
   - Neonates birth to 1 month
   - Infants* 1 month to 2 years
   - Children* 2 to 11 years
   - Adolescents 12 to 16 years

* Neither of these FDA documents specified the demarcation between “infants” and “children” such as saying that infants are “≤2 years” and children are “>2 years,” although that was presumably intended.
4. The patent extension and marketing exclusivity that originally were authorized by FDAMA for a five-year period were re-authorized for two successive five-year periods by the Best Pharmaceuticals for Children Act of 2002 and the FDA Amendments Act of 2007.
5. FDA considers the term “substantial number of patients and/or extensive use” to mean 50,000 pediatric patients in the US with the disease or condition for which the drug or biological product is indicated. This cut-off could have been derived from the definition of an orphan disease as one with fewer than 200,000 patients in the US, and the assumption that 25% of any US population is less than or equal to 16 years of age.
6. Ibid.
7. “Meaningful Therapeutic Benefit” is defined in FDAAA as follows:
   - “The drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease compared with marketed products labeled for that use in the relevant pediatric population;” or
   - “The drug or biological product is in a class of products or for an indication for which there is a need for additional options”
9. BPCA defined the pediatric studies that should be submitted in response to a Written Request as efficacy or pharmacokinetic studies in some or all pediatric age groups. Studies that were not conducted by the applicant (for instance, studies appearing in the published literature), also can be submitted in response to a Written Request, but these do not qualify the product for pediatric exclusivity.

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