The Pediatric Research Equity Act Moves Into Adolescence

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Children continue to be underrepresented as participants in clinical trials, limiting the evidence available to guide treatment decisions. Among new interventional trials registered on ClinicalTrials.gov in 2015, only 6% of 19,239 trials focused on children from birth to 17 years of age, even though this age group comprises about a quarter of the US population. As a result, clinicians frequently use medications tested in adults for the treatment of children and adolescents. In one study, rates of off-label prescribing were estimated to involve 85% of 57,000 hospitalized children nationally. Without adequate evidence to support these interventions, children may be exposed to serious unintended harms. Notable examples include the off-label use of verapamil to treat children with supraventricular tachycardia (associated with hypotension and death) and the antimicrobial chloramphenicol administered to infants (leading to fatal circulatory collapse).

To improve the clinical study of medications in children, Congress passed in 2002 the Best Pharmaceuticals for Children Act, which grants sponsors additional 6 months of market exclusivity in return for voluntarily performing US Food and Drug Administration (FDA)-requested studies in children. The Pediatric Research Equity Act (PREA), passed in 2003, is a complementary, mandatory program that authorizes the FDA to require the study of a new drug or biologic in pediatric populations (defined as <17 years of age). Under PREA, sponsors must submit data that assess the safety and effectiveness of a product in children or that justify the extrapolation of adult data to relevant pediatric subpopulations for the indications under review in adults. The act's requirements apply to new drug applications and biologics license applications, as well as supplements to these, including new indications and formulations. Although these studies are ordinarily required before approval, sponsors can request that the FDA defer or waive their PREA requirements in certain cases (Box).

The Pediatric Research Equity Act has the potential to incentivize timely completion of pediatric studies. Sponsors may request deferrals of their PREA requirements. For example, between 2004 and 2007, deferrals were granted in 55% (338 of 605) of new and supplemental applications. Additionally, these studies can be deferred repeatedly. According to the FDA, as of December 2015, 186 of 332 (56%) deferred studies were granted further extensions. One example is methoxy polyethylene glycol-epoetin beta, an erythropoiesis-stimulating agent approved in 2007 for the treatment of anemia associated with chronic renal failure in adults. The FDA required that the sponsor conduct a dose-finding study to

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Box. Overview of the Pediatric Research Equity Act

Scope

New drug applications, biologics licensing, and supplements to applications must contain data that
- Enable assessment of the safety and effectiveness of the drug or biologic for the claimed indication in all relevant pediatric subpopulations; and
- Support appropriate dosing and administration of the drug or biologic in each relevant pediatric subpopulation; or
- Justify the extrapolation of pediatric effectiveness from studies involving adults, if the disease course or drug action is sufficiently similar between adults and pediatric patients.

Waivers

The act does not apply to products for an indication for which orphan designation has been granted. In addition, the FDA can waive requirements for some or all pediatric age groups if
- Necessary studies would be impossible or highly impracticable because, for example, the disease occurs primarily in adult populations;
- Evidence strongly suggests the drug ineffective or unsafe;
- The drug or biologic does not represent meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients; or
- Reasonable attempts to produce a pediatric formulation have failed.

In addition, sponsors may request an extension of deferrals.

Deferrals

The FDA can grant deferral of submission of required pediatric data if
- The drug or biologic is ready for approval for use in adults before pediatric studies are complete;
- There is evidence to support the delay of pediatric studies until additional safety or effectiveness data have been collected; or
- There is another appropriate reason for deferral.

In addition, sponsors must submit detailed pediatric study plans to the FDA that include
- Necessary studies for orphan indications;
- or deferral requests (eg, evidence indicating that a drug would be ineffective or unsafe in certain pediatric age groups). Despite the public health interest in disclosure of such information, it is unclear if the FDA has the statutory authority to disclose these data. Because it is unlikely to be included in a standard trial protocol, this information may therefore never be publicly available, even if the protocol is eventually posted on ClinicalTrials.gov or as part of a peer-reviewed publication. PREA should be amended to authorize the FDA to provide more detailed information on these pediatric study plans.

If thalidomide to improperly formulated sulfanilamide, the history of drug regulation has been shaped immeasurably by the serious harms to children caused by inadequately tested therapies. The passage of PREA marked an important chapter in efforts to improve clinical study of novel therapeutics in this vulnerable population. Modernizing the PREA program would help ensure continued progress toward equity for children in drug development.

ARTICLE INFORMATION

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Mr Hwang reports prior employment by Blackstone and Bain Capital, which have invested in health care companies. No other disclosures were reported.

REFERENCES


