Two thirds of required pediatric post-marketing drug studies are missing

19 November 2018

The FDA requires clinical studies of new drugs in pediatric populations, since many drugs developed for use in adults are also used in children. These studies are often requested after the drug is approved in adults, as "post-marketing" trials. However, a study from Boston Children's Hospital finds that only about a third of these mandatory trials were completed within an average of seven years. As a result, most new drug labels continue to lack information needed for use in children, and most FDA-approved medications remain untested in children.

The findings, published November 19 in *JAMA Pediatrics*, constitute an audit of the main policy responsible for ensuring that child-specific drug information is available to clinicians and patients.

"More than 50 percent of all drugs approved by the FDA lack information on how to safely and effectively use the drug in children," says Florence Bourgeois, MD, MPH, of the Pediatric Therapeutics and Regulatory Science Initiative at Boston Children's Hospital (pedrx.org). "As a clinician, I was struck early on by how little evidence we often have to guide medication use in children. Although the FDA has an established process to ensure medicines are safe and effective in adults, this has historically been lacking for children."

Mandated studies in children

In 2003, Congress passed the Pediatric Research Equity Act (PREA) to increase pediatric drug research. It authorized the FDA to mandate clinical studies in pediatric populations to assess drug safety and effectiveness and provide information on appropriate dosing and administration in different pediatric age groups.

When it was passed, PREA allowed manufacturers to seek deferrals from pediatric studies in certain cases, allowing them to complete the studies after the drug was approved. Over time, implementation has relied heavily on deferrals and in 2007, when PREA was renewed, it was decided to make all deferred studies post-marketing trial requirements.

Study findings

In the *JAMA Pediatrics* study, Bourgeois and colleagues assessed the implementation of these post-marketing studies from 2007 to 2014, including both new drugs and new indications for already-approved drugs. During that time frame, the FDA approved 114 new drugs and new indications subject to pediatric study requirements under PREA. A total of 222 pediatric post-marketing studies were required for these drug approvals.

As of December, 2017, only 34 percent of pediatric studies were completed. Of those completed, 45 percent had results were reported in a journal.

At the time of approval, only 16 percent of drugs approved with post-marketing studies had any information on pediatric efficacy, safety or dosing in their labels. This increased to only 41 percent after a median follow-up of seven years.

Perpetuating off-label prescribing

"We have a powerful legislation in place that sets the standard that all drugs relevant to pediatric health hit the market with some information on their safety and efficacy in children," says Bourgeois, who is also an associate professor of pediatrics at Harvard Medical School and a member of the Computational Health Informatics Program at Boston Children's Hospital. "Unfortunately, we are still seeing long delays between the approval of a drug and the availability of pediatric information. This perpetuates off-label drug use that may be unsafe or ineffective."

Bourgeois says that PREA requirements apply only to drugs that are deemed relevant to pediatric

conditions. Drugs with orphan indications are exempt from any pediatric study requirements. "But we feel that pediatric studies should also be performed for orphan drugs on a case-by-case basis, since many orphan diseases start in childhood," says Bourgeois.

She notes that PREA was broadened in 2017 to apply to all oncology products, even if they have received an orphan drug designation. This type of amendment to PREA might benefit other pediatric conditions as well, she says.

Strengthening PREA?

The team suggests additional FDA oversight and use of enforcement tools to ensure completion of pediatric studies. They also recommend reevaluation of the deferral process to identify trials that could be required to be finished sooner, and additional examination of the barriers to trial completion.

"Our goal is to strengthen the PREA legislation," says Bourgeois. "This will require not only a careful examination of how the legislation has been implemented, but also consideration of the challenges that industry is likely encountering when trying to complete these trials. We may need additional conversations to better understand how to maximize our resources and obtain pediatric data for the drugs that are most likely to impact children's health."

More information: TJ Hwang, et al. Completion and Reporting of Mandatory Pediatric Post-Marketing Trials under the Pediatric Research Equity Act. *JAMA Pediatrics* 2018 Nov 19.

Provided by Children's Hospital Boston