Denise Myshko

Patients

THE LITTLEST

Incentives and mandates have spurred drugmakers to test many products in children and to enhance the pediatric information provided on drug labels. But experts say there is still a long way to go to address this specialty population.

Over the past 15 years, biopharmaceutical companies have made great strides in studying how children respond to medications. Spurred on by laws enacted in the United States and Europe, companies have been successful in bringing new medicines to children.

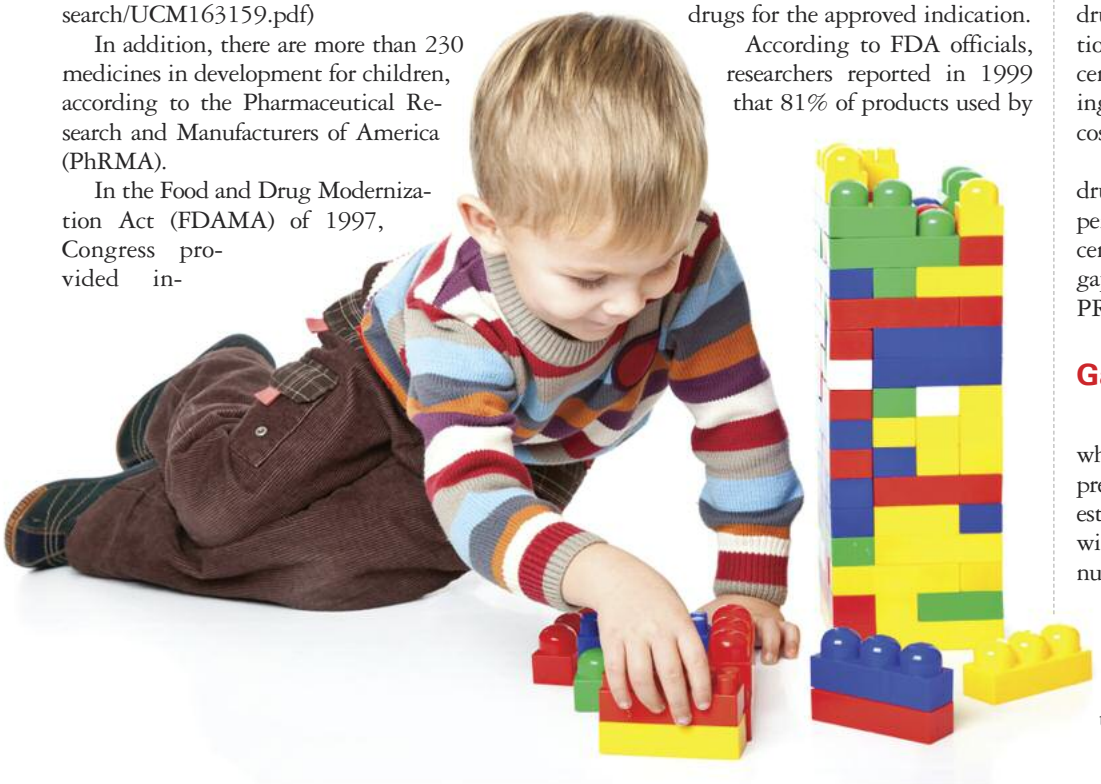
More than 400 drugs have been labeled for pediatric use by hundreds of companies. And, since 2007, 346 pediatric studies have been completed, involving more than 155,000 pediatric patient volunteers, according to the Food and Drug Administration. (For a list of approved pediatric products, please go to http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticResearch/UCM163159.pdf)

In addition, there are more than 230 medicines in development for children, according to the Pharmaceutical Research and Manufacturers of America (PhRMA).

In the Food and Drug Modernization Act (FDAMA) of 1997, Congress provided incentives to encourage manufacturers to conduct pediatric studies of medicines with potential uses for children. This legislation included a provision that granted pharmaceutical firms an additional six-month period of exclusivity.

Congress reauthorized these provisions in the Best Pharmaceuticals for Children Act (BPCA) in 2002 and again in 2007 as part of the Food and Drug Administration Amendments Act (FDAAA). There are also provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if a sponsor submits pediatric studies as a result of a written request from the FDA. Furthermore, the Pediatric Research Equity Act (PREA) gives the FDA the authority to require studies of drugs for the approved indication.

According to FDA officials, researchers reported in 1999 that 81% of products used by children lacked sufficient information or labeling regarding pediatric use.



"Before the advent of PREA in 2003, new drugs marketed for an adult indication were not being studied in children in a systematic way," says Michelle Roth-Cline, M.D., Ph.D., pediatric ethicist, Office of Pediatric Therapeutics at the FDA. "Legislation has gone a long way to change the process."

She says before PREA was established in 2003, sponsors were not required to study new drugs entering the market for an adult indication in children. Before 1997, there was no incentive to study drugs in children unless labeling of the product in pediatrics was inherently cost-effective, which is rarely true.

While these laws have done much to ensure drugs are tested labeled for use in children, experts caution there is a need for additional incentives and guidance to meet some of the gaps not addressed by the laws. BPCA and PREA are scheduled to sunset in 2012.

Gaps in the Process

Industry experts say there are several areas where pediatric drug development efforts and prescribing protocols fall outside the range of established guidelines. One of those areas is with off-patent drugs or generics, which in a number of cases are used to treat children without a complete data set to support their use.

Robert Nelson, M.D., Ph.D., senior pediatric ethicist, Office of Pediatric Therapeutics at the FDA, says the only time the agency can require a pediatric

study is if a sponsor wants to pursue a new indication, a new formulation, a new dosing regimen, or a new ingredient.

"When a company comes in with a new application to extend the use of a drug, we can attach a pediatric requirement to that application," he says

Roger Garceau, M.D., senior VP and chief medical officer of NPS Pharmaceuticals, says there need to be incentives for companies to conduct pediatric studies. This is especially true for older drugs for which there are multiple competitors or generics available.

"We're talking about basic science and clinical studies to tell physicians about the safety and efficacy of drugs in various childhood populations," he says. "For NPS, any additional product would have to fit with our pipeline and strategy."

Dr. Garceau says he would like to see additional guidelines on pediatric trial endpoints.

"There has been a lot of discussion about endpoints in adult trials and how to translate these data to a patient benefit, either into patient-reported outcomes or quality of life," he says. "For children, it's hard to measure many of the outcomes, especially patient-reported ones. Children are not a single group, but rather a spectrum with a wide range of ways that they communicate. An infant certainly communicates differently from a 2-year-old, and a 2-year-old differently from an adolescent."

The National Institutes of Health is trying to address this gap. In fact, the original BPCA asked the National Institute of Child Health & Human Development (NICHD) to evaluate off-patent drugs for use in children and to conduct research that contributes to labeling.

Dr. Nelson says another gap that is poorly addressed by current legislation is drugs used to treat neonates, many of which are off-patent.

"It's challenging to do neonatal studies," he says. "Often we may have not extended studies to that age group until we have more safety and efficacy information in older age groups. Another challenge is that neonatal diseases are not the same as in older children or adults."

Experts also point to the challenge of harmonizing efforts for European and U.S. studies in children.

Dr. Nelson says the timing for submitting a pediatric plan is different for both regulatory bodies. For example, in the United States, the requirement is for a pediatric plan to be submitted at the time of the submission of the adult application. In Europe, the requirement for the pediatric plan to be submitted is at the end of Phase I.

"The best time to talk about doing a pediatric study is at the end of Phase II," Dr. Nelson says. "This is the timing we encourage sponsors to adhere to, but this is not formal language written into our legislation. We and regulators at the European Medicines Agency are aware of this timing issue."

The FDA, he says, has been sharing product development information with the EMA through monthly teleconferences.

"As a result of this legislation and other developments, we've become more proactive and transparent with communications because studies, in particular pediatric studies, are multinational in nature," Dr. Roth-Cline says.

Pediatric Trial Challenges

Industry experts say there are many barriers to conducting trials with children, including ethical, economic, logistical, and technical barriers. One challenge, our experts say, is that "pediatrics" is not one group of patients.

Cynthia Jackson, D.O., VP and global head of the pediatric center of excellence at Quintiles, says she would like to see harmonization of European and U.S. requirements around the age groupings for children.

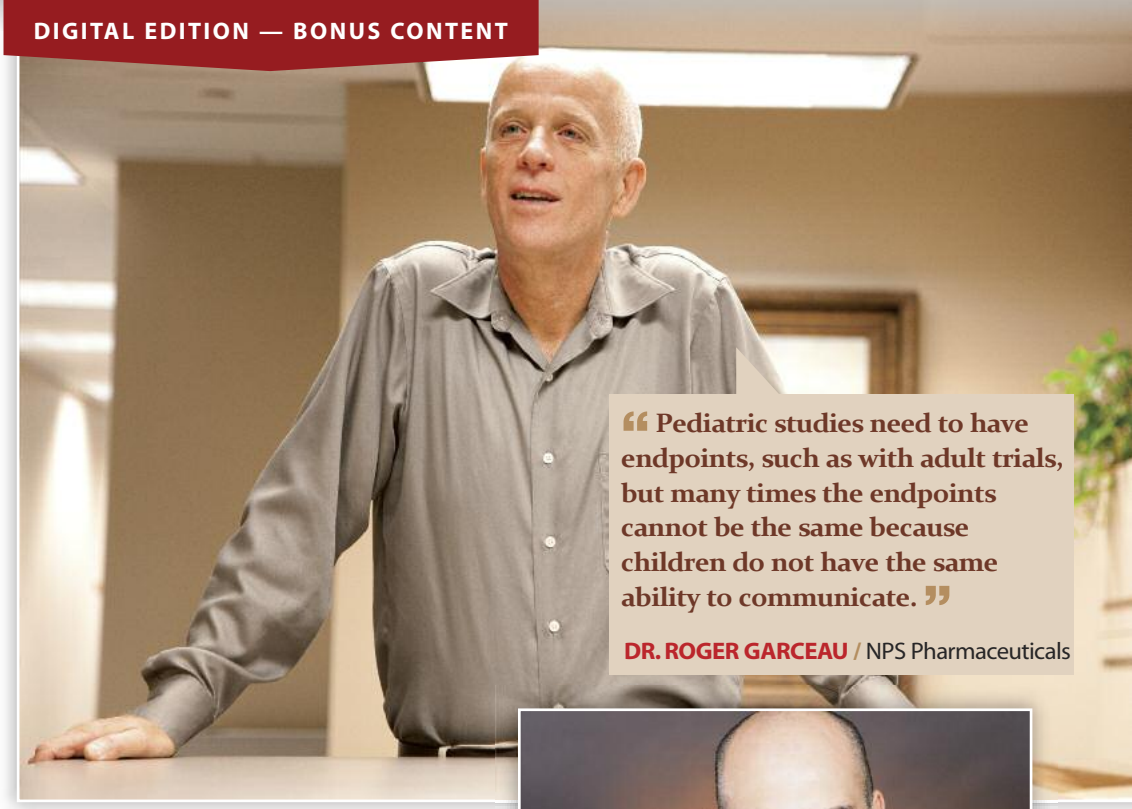
"In the EU, the pediatric age group is defined as anyone between birth and 18 years," she says. "In the United States, we break it down to neonates, infants, child, older child, and adolescents through 17 years of age."

Jon Bruss, M.D., VP of infectious disease at Medpace, says conducting trials with children is often complex because children are changing physiologically and developmentally throughout their growth to adulthood.

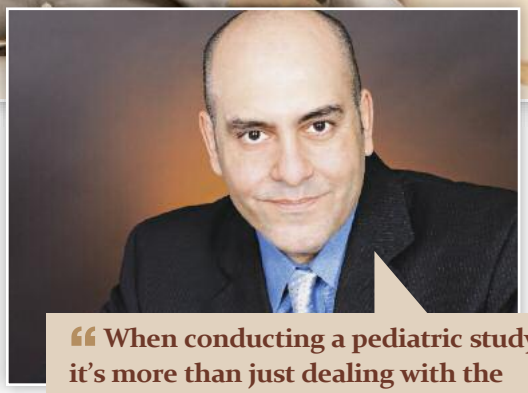
"The physiology of a 20-year-old is similar to that of a 30-year-old," Dr. Garceau says.

He says studies need to be directed in a targeted way at the different populations.

"Appropriate ages that represent all of the patients who will use the drug must be stud-



> "Pediatric studies need to have endpoints, such as with adult trials, but many times the endpoints cannot be the same because children do not have the same ability to communicate."
>
> **DR. ROGER GARCEAU** / NPS Pharmaceuticals



> "When conducting a pediatric study, it's more than just dealing with the patient; we have to consider the family and the whole ecosystem around the child."
>
> **CHRIS GARABEDIAN** / AVI BioPharma

> "There are significant similarities as well as differences in the FDA and EMA pediatric trials laws, which makes harmonization of a pediatric development plan sometimes quite complicated."
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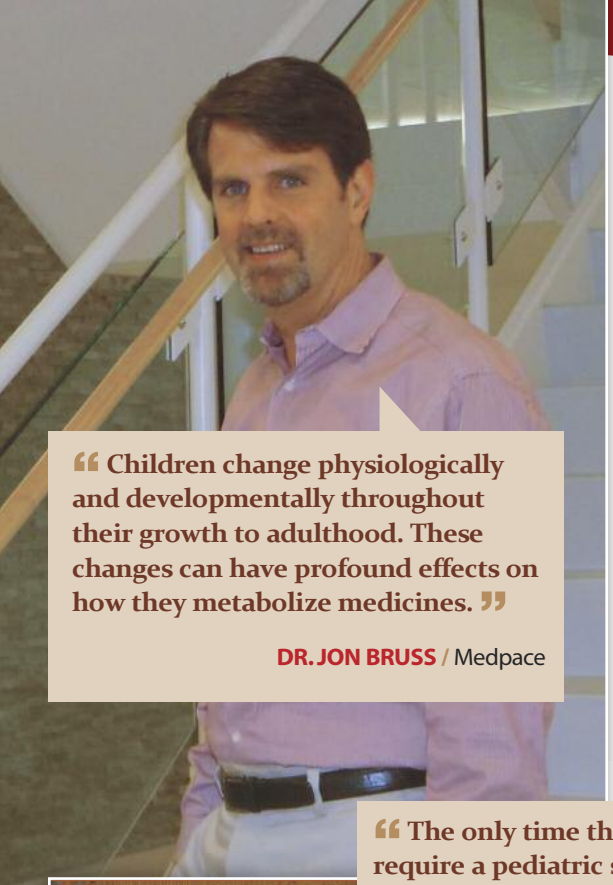
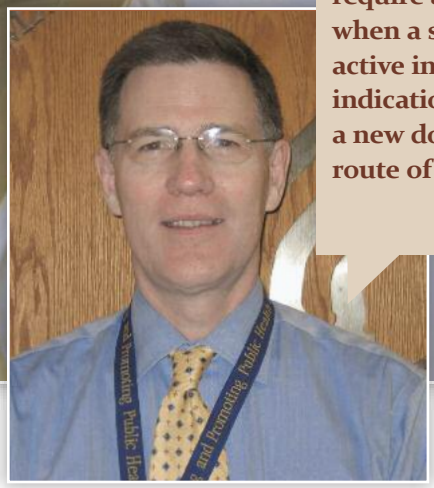
> **DR. CYNTHIA JACKSON** / Quintiles



> **“Children change physiologically and developmentally throughout their growth to adulthood. These changes can have profound effects on how they metabolize medicines.”**
>
> **DR. JON BRUSS** / Medpace



> **“The only time the FDA can require a pediatric study is when a sponsor asks for a new active ingredient, a new indication, a new formulation, a new dosing regimen, or a route of administration.”**
>
> **DR. ROBERT NELSON** / FDA

ied,” Dr. Garceau says. “In pediatric studies, there are two possible levels of agreement that need to be obtained: informed consent from the parents and assent from older children. Investigators have to make sure the child understands what is going to happen in the trial. IRBs and investigators are careful in making sure children are protected.”

Dr. Jackson says researchers have to think about how different populations of children metabolize drugs.

“Not only do we have to be concerned about what a drug might be doing for a patient’s disease, but we also have to be concerned about what it might be doing to a child’s developmental and growth process, which isn’t something that we think about in adults,” she says.

Best Practices

Jon Bruss, M.D., VP of medical affairs, infectious disease at Medpace, says planning for pediatric drug development early in the process is absolutely essential. These changes may affect the absorption, excretion, and metabolism of medicines as well as dosage requirements.

“Understanding when to initiate the pediatric program is critical, “ he says. “Knowing when pediatric drug development issues need to be addressed and where pediatric studies fit into the overall development of a compound is an important part of the regulatory strategy. Some companies move forward with their development program for adults and then have to play catch-up. As a result, they may lose the opportunity for exclusivity extension, but more importantly, valuable scientific information of a compound’s use in children may not make it to pediatric caregivers.”

Another critical component of a pediatric study, experts point to are the trial sites.

Dr. Jackson says the biggest difference between the sites for adults and pediatric studies is the need for continuous involvement with the principal investigator.

“Investigators have to explain to the parent why they believe a child would be a good candidate for the study, why they believe the child wouldn’t be harmed by being part of the study, and what all of the procedures are for the clinical trial,” Dr. Jackson says “It is crucial that the whole study center is committed to the pursuit of the pediatric clinical trial.”

Chris Garabedian, CEO and president of AVI BioPharma, says it’s important to work with therapeutic centers of excellence.

“With pediatric diseases, it’s very important to identify the right center for selecting patients,” he says. “Sometimes the standard of care can vary from center to center; and with a pediatric condition, oftentimes, those differences can be much more acute.” PV

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EXPERTS

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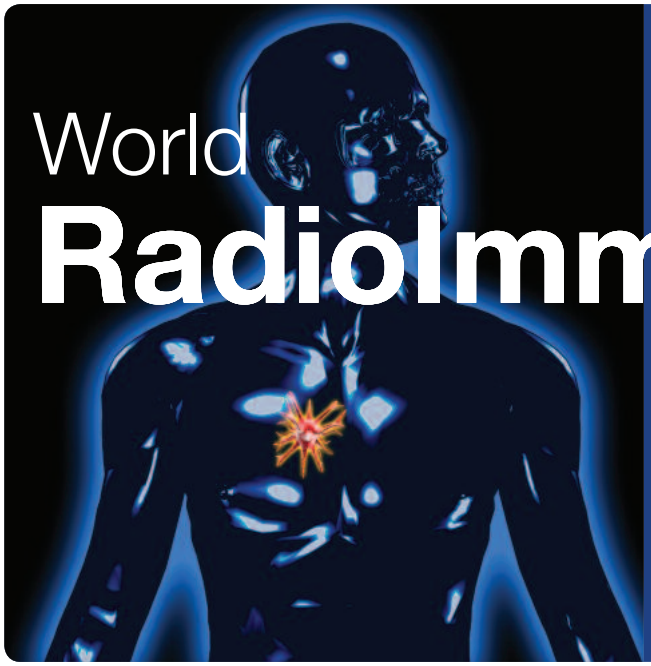

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