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## Drug Research and Children

Recent studies are providing important new information about drug safety and effectiveness for children. Pediatricians say it's about time.

Most drugs prescribed for children have not been tested in children. Before the Food and Drug Administration initiated a pediatric program, only about 20 percent of drugs approved by the FDA were labeled for pediatric use. By necessity, doctors have routinely given drugs to children "off label," which means the drug has not been approved for use in children based on the demonstration of safety and efficacy in adequate, well-controlled clinical trials.

To be well-controlled, a study should have an adequate number of patients who receive the study drug and a control group--people who are similar to the group taking the drug being studied, but who are receiving some different type of treatment, such as another drug or an inactive pill (placebo).

Experts say the historical lack of pediatric drug testing is due to a combination of reasons. The primary reason is that pharmaceutical companies generally have viewed children as a market that would bring only small financial benefits. The drugs that have been adequately studied in children--vaccines, some antibiotics, and some cough and cold medicines--have a large market.

"It's also harder to carry out studies in children," says Dianne Murphy, M.D., director of the FDA's Office of Pediatric Therapeutics. "You need child-friendly environments in every sense, from age-appropriate equipment and medical techniques to pediatric specialists who are sensitive to a child's fear."

Jeffrey Blumer, M.D., Ph.D., chief of pediatric pharmacology at Case Western Reserve University in Cleveland, says technical procedures that seem simple for adults, such as drawing blood or getting a urine sample, can be difficult with children.

The ethical issues are also stickier. For example, while adults can give informed consent to participate in a clinical trial, children can't because "consent" implies full understanding of potential risks and other considerations. Parents are involved in the decision to enroll children in a study, and children ages 7 or older can "assent" or "dissent," meaning they can agree or disagree to participate in a study.

Blumer says, "I've had parents who are enthusiastic about a study and then a 7-year-old who hears everything involved and says, 'No way!'"

## Children Aren't Small Adults

Rather than avoiding pediatric research because of the challenges, experts say it's more important to build the foundation and resources needed to conduct the studies. Without them, children face significant risks.

In the absence of data, doctors use their medical judgment to decide on a particular drug and dose for children. "Some doctors stay away from drugs, which could deny needed treatment," Blumer says. "Generally, we take our best guess based on what's been done before."

A common approach has been to use data from adults and adjust the dose according to a child's weight. Experimenting over the years has taught doctors to use many drugs in children safely and effectively. But this trial-and-error approach has also resulted in tragedy, indicating that adult experiences with a drug aren't always a reliable predictor of how children will react.

For example, in the 1950s, the antibiotic chloramphenicol was widely used in adults to treat infections resistant to penicillin. But many newborn babies died after receiving the drug because their immature livers couldn't break down the antibiotic.

"Experience has shown us that we need to study drugs in children because they aren't small adults," says Ralph Kauffman, M.D., director of medical research at Children's Mercy Hospital in Kansas City, Mo. "It's not just about smaller weight," he says. "There are dynamics of growth and maturation of organs, changes in metabolism throughout infancy and childhood, changes in body proportion, and other developmental changes that affect how drugs are metabolized."

#### Proof Is in the Data

Fortunately, recent legislative changes that provide both a voluntary and a mandatory mechanism to conduct drug studies in children have resulted in a dramatic increase in pediatric drug trials. "There have been more studies conducted in children in the last five years than in the previous 30 years combined," Kauffman says.

The information coming out of those studies has added pediatric information to the drug labeling for more than 80 drugs, and more changes are coming. Drug labeling is the guidance to doctors and other health care providers on how to use a drug. "We knew that we needed science to determine proper dosing for children the same way we do with adults," says Murphy. "Now, we have confirmed it."

Ibuprofen, one of the most common over-the-counter drugs on which parents rely to reduce children's fevers, carried no dosing information for children younger than 2 years old until recently. Now, because of studies in thousands of young infants, the dose considered to be safe and effective for over-the-counter use has been established for children ages 6 months to 2 years.

The labeling has also been changed for Zantac (ranitidine), a drug used to treat gastroesophageal reflux. This condition can be life-threatening in infants. When reflux occurs, the stomach contents can flow up the esophagus and be aspirated into the lungs. This can harm the lungs of infants and result in breathing problems.

Studies have given doctors accurate dosing information for safer and more effective use of the drug to manage reflux in seriously ill infants. Richard Gorman, M.D., chairman of the Committee on Drugs at the American Academy of Pediatrics (AAP), a member of the FDA's Pediatric Advisory Committee, and a pediatrician in Maryland, says, "Now I can use ranitidine with as much information as doctors who use it in adults. I know the dose. I know the dosing interval."

New discoveries have revealed underdosing, overdosing, ineffectiveness, and safety problems. Gorman says, "Even though the best and brightest pediatric minds have helped us establish dosages for children, we're finding out that the dose is different than we thought in some cases. And that probably came as a surprise to most of us."

The FDA is working with the AAP to educate pediatricians about new physician labeling changes through an online continuing medical education program called PediaLink.

### What's Spurring the Research?

The FDA has taken a carrot-and-stick approach to encourage pediatric studies, says William Rodriguez, M.D., the FDA's science director for pediatrics. The carrot is the voluntary pediatric exclusivity provision of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which was reauthorized in January 2002 and extended through 2007 as the Best Pharmaceuticals for Children Act (BPCA). The stick is the Pediatric Research Equity Act (PREA), which allows the FDA to require pediatric studies. Here's an overview of each initiative:

The Pediatric Exclusivity Provision of the BPCA. The pediatric exclusivity provision has done more to spur pediatric studies than any other regulatory or legislative initiative so far. The provision allows companies to qualify for an additional six months of marketing exclusivity if they do the studies in children as requested by the FDA.

Patents protect a company's investment by giving it the sole right to sell a drug while the patent is in effect. When patents or other periods of exclusive marketing for brand-name drugs are close to expiring, other drug companies can apply to the FDA to sell generic versions, without having to repeat the original developer's clinical trials. So the trade-off is that by companies qualifying for an additional six months of exclusivity, there is a delay in the availability of lower-cost generic drugs.

The FDA has interpreted the provision so that the six months of exclusivity isn't added only to the drug that was studied in the pediatric population, but also to any of the drug company's formulations, dosage forms, and indications that contain the same active part of a molecule (moiety) and have existing marketing exclusivity or patent life. So if a company markets an oral formulation and a topical cream containing the same moiety, the six months of marketing exclusivity will be added to any existing exclusivity or patent protection for both products.

The process can be initiated either by a drug company or the FDA. A drug company may submit a proposal to the FDA to conduct pediatric studies. If the FDA agrees that studying a drug may produce

health benefits for children, the agency will issue a "Written Request" addressing the type of studies to be conducted, study design and goals, and the age groups to be studied. Or the agency may issue a Written Request on its own initiative when it identifies a need for pediatric data. No matter how the studies are initiated, if the FDA determines that the data submitted fairly respond to the Written Request, then the company will be granted six months of pediatric exclusivity.

More than 100 drugs have been granted exclusivity so far. As of Dec. 31, 2004, 691 studies had been requested and 298 Written Requests issued. The FDA estimates that about 80 percent of the studies outlined in Written Requests will be conducted.

Kauffman says the exclusivity is proof that economics plays a large role in the lack of pediatric studies. "Once the economic disincentive was removed," he says, "the dam broke completely open."

Since the incentive under FDAMA did not apply to old antibiotics and other drugs that lack marketing exclusivity or patent protection, some categories of drugs have remained inadequately studied. For these products, BPCA provides a contract mechanism through the NIH to fund pediatric studies. In addition, if a company that has a drug with existing exclusivity or patent protection chooses not to conduct the requested pediatric studies, the FDA can refer the Written Request to the Foundation for the National Institutes of Health to award grants so that third parties can conduct the needed studies.

The NIH, in consultation with the FDA and other pediatric experts, publishes an annual List of Drugs for Which Additional Pediatric Studies Are Needed in the Federal Register. Since BPCA went into effect, the FDA has issued 11 Written Requests for off-patent drugs and the NIH has published four requests for contracts.

PREA. In the early 1990s, the FDA implemented voluntary measures to encourage pediatric studies, but they were mostly unsuccessful. In 1997, the FDA published a proposed regulation that for the first time required manufacturers of new drug and biological products to conduct pediatric studies in some circumstances. The rule was finalized in 1998, and the first studies were required to be submitted starting December 2000.

The rule, however, had its critics. In December 2000, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert filed a lawsuit against the pediatric rule, challenging the FDA's legal authority to require pediatric studies. And in October 2002, a federal district court concluded the FDA did not have that authority and the rule could not be enforced.

Former HHS Secretary Tommy G. Thompson responded in mid-December 2002 by announcing that his department would push for rapid passage of legislation that would give the FDA authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on drugs.

"The fastest and most decisive route for establishing clear authority in this area is to work with Congress for new legislation," Thompson said in a prepared statement. "Children need to have access to drugs

that can benefit them, and these drugs need to be properly tested for pediatric use, not prescribed and sold without testing. Congress alone can speak clearly on the authority that FDA needs ..."

On Dec. 3, 2003, President George W. Bush signed the PREA into law. This act basically mimics the old pediatric rule with a few additional provisions.

As was true with the pediatric rule, the PREA will address some of the gaps left by the pediatric exclusivity provision. Unlike the exclusivity provision, the new act requires pediatric studies and covers both drugs and biologics--medical products derived from living sources, such as vaccines, blood, and blood derivatives.

Under the PREA, the FDA can require pediatric studies of a drug submitted in a new drug application if the FDA determines the product is likely to be used in a substantial number of pediatric patients, or if the product would provide a meaningful benefit in the pediatric population over existing treatments. At the same time, the PREA does not delay the availability of drugs for adults.

"The BPCA and PREA have worked in tandem," says Murphy. "We have told sponsors who submit a new drug application and who are required under PREA to conduct pediatric studies that they also may qualify for pediatric exclusivity."

#### Building the Foundation

"There was no infrastructure for the research before," says Floyd R. Sallee, M.D., Ph.D., a child psychiatrist and director of the pediatric pharmacology research unit at Cincinnati Children's Hospital Medical Center. "I see the culture changing in industry and at FDA," he says. "Drug companies have hired pediatric experts and there is a larger network of expertise to draw from."

Sallee's center is part of the Pediatric Pharmacology Research Unit (PPRU) Network, a group of centers that conduct pediatric drug trials with support from the National Institute of Child Health and Human Development (NICHD). The network was established in 1994 and now includes 13 PPRUs.

Shirley Murphy, M.D., (no relation to Dianne Murphy), joined the FDA in September 2002, as director of the Division of Pediatric Drug Development. She says linkages between the FDA, NICHD, AAP, and other organizations have been important for building a foundation for pediatric research, and children are getting more and better drugs as a result.

"What it means for parents is that they can feel more secure knowing that their children are being treated appropriately," Shirley Murphy says. "FDA remains committed to keeping pediatric drug research a high priority."

Several areas that will continue to receive the agency's attention include the ethics involved with studying drugs in children. The FDA's Pediatric Advisory Subcommittee has concluded that, generally,

pediatric studies should be conducted in subjects who may benefit from participation in the trial. This means the subject has or is susceptible to the disease under study.

Shirley Murphy cites pediatric oncology as another important area for the agency. "The development of cancer drugs needs special consideration," she says. Differences in the biology of tumors in children and adults usually make it difficult to prescribe children drugs based on adult data. And it has been typical for new cancer drugs to reach children late--only after they have been tested in adults.

As a result of pediatric initiatives, there have been about 30 studies initiated on cancer drugs, which will help researchers gain access to potential new cancer therapies for children.

While it may be challenging to enroll children in clinical trials for some diseases, that's not the case with cancer. Most children receive their cancer therapy as part of a clinical trial. "Parents are desperate to have their children in these studies," says Patrick Reynolds, M.D., Ph.D., a pediatric oncologist with Children's Hospital Los Angeles. "They know very well what the odds are and they want to take a chance to find life-saving treatment. They also want to help other children. They don't want to do nothing."

Reynolds is a member of the FDA's Pediatric Oncology Subcommittee, a group of outside experts who have met several times since 2000 to advise the agency on such questions as: In what phase of a drug development program should pediatric cancer studies begin? What trial designs should be used? How may data from adult studies be used in pediatric studies? How should adult and pediatric studies be coordinated when studying life-threatening diseases?

Reynolds calls both the pediatric rule and the exclusivity provision essential. "Children don't have a voice in this," he says. "Somebody has to stand up for them."

### Changing Drug Labels

Recent pediatric drug studies have resulted in the addition of pediatric information to the labeling for more than 80 drugs. The drug labeling provides guidance for doctors and other health care providers on how to use a drug. Here are examples of several changes that are considered significant for dosing and risk:

Claritin (loratadine) syrup. Used to treat allergy and hives. Patients ages 2 to 5 years require a lower dose (5 milligrams) compared to a 10-milligram dose in older children and adolescents.

Duragesic (fentanyl) transdermal patch. Used to manage chronic pain. It is now only to be used in patients older than 2 years who have been on opioids and are used to them. This medication is administered through a patch placed on the skin.

Luvox (fluvoxamine maleate) tablets. Treats obsessive-compulsive disorder. The dose of the drug may need to be increased to the recommended adult dose in adolescents, but girls ages 8 to 11 years may need lower than the recommended dose.

Midazolam hydrochloride syrup and injection. Used as a sedative. The drug was shown to have a higher risk of serious and life-threatening adverse events for children with congenital heart disease and pulmonary hypertension. Research identified the need to begin therapy with doses at the lower end of the dosing range to prevent respiratory problems in this special pediatric population.

Neurontin (gabapentin) capsules, tablets, and oral solution. Used as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 3 to 12 years. Neuropsychiatric adverse events were identified in 3- to 12-year-olds.

Pepcid (famotidine) tablets, injection, and oral suspension. Used to treat gastroesophageal reflux disease. Patients up to 3 months of age require a lower dose because their ability to get rid of the drug is less than that of older children and adults.

Ultane (sevoflurane) volatile liquid for inhalation. Used in general anesthesia. Pediatric studies revealed rare reports of seizures in pediatric patients given this drug.