BY DENISE MYSHKO

The Trials of Youth

BRINGING CHILDREN INTO CLINICAL RESEARCH

After the fall of the pediatric rule, Congress is moving forward to provide the Food and Drug Administration with the authority to mandate the testing of prescription drugs in children.

The memories of childhood often include long summer days, longer school days, skinned knees, and broken hearts. These images are seldom associated with long treks to clinics, waiting to see doctors, and taking experimental medicines. But for seriously ill children participating in clinical research, these experiences are all too real.

Once considered unethical to conduct clinical studies of new medications in children, now it is considered unethical — and some even say immoral — to offer medical treatment to a vulnerable population with inadequate information about how those patients will respond.

From a pharmacotherapeutic perspective, developmental variations clearly indicate that a child should not be treated simply as a smaller version of an adult, according to a Kalorama Information report, The Worldwide Market for Prescription Pediatric Drugs. Children of different ages absorb, distribute, metabolize, and excrete drugs in different ways.

Knowing more about the effects of medicine in children has distinct benefits. Pediatric labeling on medications would provide cost savings to the healthcare system by reducing medical errors and adverse reactions, analysts say. Those savings are estimated to be 50 cents on every $100 spent on prescription drugs, according to Kalorama.

Currently, there is not enough information regarding the pediatric use of about 75% of prescription medicines. Physicians may have to guess at dosages for children, which can be dangerous and result in underdosing or overdosing.

"In essence, without data, every child who is administered drugs is part of a clinical trial because there isn't enough information to give the physician appropriate guidelines for how to dose the drug in children," says James R. Hildebrand III, Pharm.D., director of Clinical Pharmacology at The Alfred I. duPont Hospital for Children. "Physicians are doing their own research in their own offices."

Data that are collected from one group of people cannot apply to a different group of people, be that gender or age — adults or children, Dr. Hildebrand says.

"Different organ systems mature at different rates and drugs behave differently in children than they do in adults," he explains.

The FDA does a very good job of making sure that companies are doing the right studies if, in fact, a product would have an indication for children. I don't think it has to be a mandate in order to have the FDA doing the right thing.

DR. CHRISTY SHAFFER

"Physicians need to know how children are going to handle a drug, from a safety and efficacy perspective."

LEGISLATIVE PATH

Late in July, the Senate passed S. 650, The Pediatric Research Equity Act of 2003. The legislation will provide the FDA with additional authority to require pediatric studies of pharmaceutical products when they are needed to ensure their safe and effective use in children.

The legislation would apply to all new drugs and biologics and would require companies to assess the safety and effectiveness "for the claimed indications in all relevant pediatric subpopulations; and to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective."

Submission of some or all assessments could be deferred if the drug or biological product is ready to be approved for use in adults before pediatric studies are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. Companies also can apply for a waiver if they can demonstrate that the studies are impossible or impracticable or there is evidence suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.

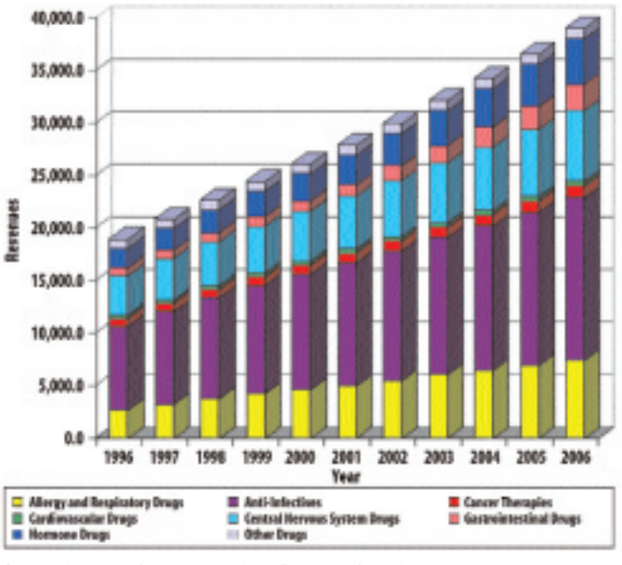
Also in July, the House introduced similar legislation, H.R. 2857. This bill was introduced by Rep. James. C. Greenwood of Pennsylvania and has been referred to the House Committee on Energy and Commerce.

"We support the act," says Cameron Durrant, M.D., MBA, president of PediaMed Pharmaceuticals Inc. "We think it is a very important step forward. Adult medicines can't be automatically transferred for dosing in children. It's very important that adequate testing be done. We should insist that the same rigorous standards apply to children as currently apply to adults."

Regulatory authorities and legislators, however, have tried several times to address the issue of pediatrics studies. For example, under the Food and Drug Modernization Act of 1997 (FDAMA), a provision

WORLD MARKET FOR PRESCRIPTION PEDIATRIC DRUGS

$ in millions at manufacturers' level



Source: Kalorama Information, New York. For more information, visit marketresearch.com.

allowed for an additional six months of marketing exclusivity if, prior to approval of an application, it was determined that information about pediatric use might produce health benefits in that population. It was a voluntary program in which companies would submit pediatric testing and in which the FDA could request that pediatric data be submitted.

Then the FDA enacted the Pediatric Rule in 1998, which required manufacturers to provide labeling information for pediatric use. The rule required that every application (drug or biologic) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, contain a pediatric assessment or a deferral or waiver of the requirement for this assessment. The FDA also could require pediatric studies of marketed drugs and biological products used in a substantial number of pediatric patients for the claimed indications and where inadequate labeling could pose significant risks.

This rule, however, was repealed in October 2002 when the U.S. District Court for the District of Columbia held that the FDA lacked statutory authority to require such studies. This decision prevented the agency from enforcing the requirements that were mandated in the pediatric rule.

In December 2002, the Bush Administration decided not to appeal the ruling and instead called on Congress to work with the FDA to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials.

Before the repeal of the pediatric rule, authorities recognized the need to provide financial incentives to manufacturers. In January 2002, the

Protecting a Vulnerable Population

The AHRP proposes guidelines for all clinical research in which children are experimental subjects.

FROM AN ETHICAL STANDPOINT, SOME SAY THE RECENTLY PASSED SENATE BILL (PEDIATRIC RESEARCH EQUITY ACT OF 2003) DOESN'T PROVIDE THE NEEDED SAFEGUARDS TO PROTECT CHILDREN WHO WILL BE ENROLLED IN CLINICAL TRIALS TO TEST THE SAFETY AND EFFECTIVENESS OF NEW DRUGS AND BIOLOGICAL PRODUCTS.


VERA SHARAV

Many drugs are unlikely to be used by children, and testing them in pediatric populations puts the children at unnecessary risk, say those with the Alliance for Human Research Protection (AHRP). The law will expose thousands of child subjects to unjustifiable risk, according to the group. Under this law, only the Secretary of Health and Human Services can waive the required tests in children of all ages.

The AHRP recommends that drugs be tested in children only when they have been proven safe in adults and a role for the drug in the pediatric population is anticipated by the manufacturer, and only in children who have the condition for which this drug is a treatment may be used in clinical trials.

"AHRP opposes putting children in harm's way — unless it is to save a child's life," says Vera Sharav, president of AHRP. "We believe it is immoral to put the burden of risk, pain, and discomfort on children who are not competent volunteers. Clinical trials are not necessarily the best — and certainly not the only way — to obtain valuable dosing information for practicing physicians. Clinical trials are decidedly not a reliable method for gaining information about drug side effects; they are not designed to elicit serious, but infrequent side effects.

"Also, it is not ethical to expose children to risks of harm and discomfort for the benefit or convenience of others, including practicing physicians who can, and do, obtain needed information in other ways."

The AHRP proposes the following guidelines for all clinical research in which children are experimental subjects:

- Restrict the use of children in research to studies involving no greater than minimal risk unless the potential benefit to their condition justifies the risk. Establish a Children Protection Committee to monitor recruitment, to assess the reasonableness of their parent's permission, to assess the adequacy of disclosure in the informed consent documents, and to monitor a child's continued willingness to participate in the research, thereby ensuring that child subjects are not exploited.
- Prohibit conflicts of interests, such as paying a fee to physicians who recruit children.
- Establish a registry of all pediatric clinical trials and require mandatory reporting of serious adverse effects.
- Impose stiff penalties when foreseeable risks have not been disclosed or informed consent requirements have been violated.
- Assure every child who participates in clinical trials will be protected by no-fault insurance coverage against possible adverse effects that may arise from, or in the course of, participation in such research.
- Assure every child who participates in clinical trials is exposed to no greater risks than the child would incur if given the currently available best standard of medical treatment.
- Prohibit use of financial enticements to induce parents or guardians of children to enroll them in research.
- Mandate long-term monitoring for adverse effects.
- Require all researchers who conduct research on human subjects to be trained and certified as proficient in the knowledge of medical ethics and the best standards of medical care.
- Restrict children from being used as subjects in trials of therapies that are not intended for children.

Testing, unfortunately, does not always assure drug safety, AHRP executives say. Experimental subjects can be harmed, and patients who receive approved drugs also can be harmed. Rare, but severe adverse effects often will not emerge in premarketing studies, but only later, when the drug is in wide use. Because of this, companies have to be vigilant when studying the pediatric population.

Source: The Alliance for Human Research Protection, New York. For more information, visit ahrp.org.

Best Pharmaceuticals for Children's Act was enacted to provide additional incentives to develop the information needed to properly use medications in children.

The FDA plans to hire new staff to continue to define, develop, issue, and track written requests for pediatric studies; review submitted results from these pediatric studies within six months; and oversee ethical issues related to studies.

In addition, the FDA and the NIH will develop, prioritize, and publish an annual list of drugs for which there is an approved or pending new drug application, as well as those with no patent or market exclusivity protection for which pediatric safety and effectiveness studies are needed. (For more information, see box on page 46.)

Jeff Trewhitt, a spokesperson for the Pharmaceutical Research and Manufacturers of America (PhRMA), says, "The provision of the regulatory reform act was an honorable quid pro quo provision in this new FDA reform so that quite a bit of pediatric testing gets done in close cooperation with the FDA. We had always said the mandatory rule should be pursued in very close coordination with the voluntary provision of the reform law. If the pediatric rule was used as a last resort, then that was appropriate."

But without the regulatory mandate, some say incentives, especially the six-month exclusivity granted under FDAMA, are not enough to entice pharmaceutical companies to conduct the necessary trials to gather data on adequate dosing information in children.

It is unfair to our children to expect them to benefit from trickle down scientific research done for adults.

DR. JOHN YEE

"There are a couple of problems with the six-month exclusivity provision," Dr. Hildebrand says. "From my perspective, the incentive is not enough, and it only applies to drugs, not to biologics. And, biologics are definitely a growing force to be dealt with. Second, from a purely business perspective, the market for pediatrics just isn't very large. So there isn't a big incentive for manufacturers to do studies and develop drugs for children."

Dr. Hildebrand says a regulatory mandate that requires pharmaceutical companies to conduct studies of pediatric populations is critical. Legislative efforts over the past few years have tried to give the agency the authority to mandate clinical trials that involve children.

ADVANTAGES OF A RULE

Before the pediatric rule was in place, 80% of medications had not been tested on children, forcing pediatricians to guess at the correct dosage for children.

"Just look at what has happened with pediatric research before and after the pediatric rule," Dr. Hildebrand says. "Over the six-year period before the pediatric rule was enacted, 11 pediatric studies were submitted to the FDA. Over the ensuing two to three years, about 600 clinical studies were proposed either by the FDA directly or from the companies themselves. There are 40 plus

products that resulted in labeling changes. The pediatric rule is what changed things."

The new legislation complements the Best Pharmaceuticals for Children Act, says Mark Schreiner, M.D., executive medical director at Children's Clinical Research Institute, which is affiliated with The Children's Hospital of Philadelphia.

"The combination is what's powerful," he says. "Either incentives or mandates for pediatric trials alone will not be enough. The benefit from patent extension comes at the end of a product's patented life. Companies are often short sighted, and so they're going to look closer to the end of the drug's life span to see whether they should do the studies. Who knows if a better drug is going to come along and market share will disappear? Maybe there will be some adverse event and they will have to pull the drug altogether."

Wayne Matthew Dankner, M.D., senior medical director at Parexel International Corp., concurs. Dr. Dankner's concern is that without the rule and because the incentive is being tacked on to the end, companies will wait to submit the pediatric data closer to the product's patent expiration instead of when the application is made.

"The argument made by the groups that brought the lawsuit against the FDA was that regulators might hold up the approval of a product if a company didn't develop a pediatric plan," Dr. Dankner says. "I don't recall whether the FDA ever did that. But it needs that legal and regulatory recourse to be able to move things along. Would regulators ever hold up an application? The likelihood is no, because they wouldn't want the population that would benefit from the drug not to have access to it."

It wasn't until the pediatric rule and the incentives were put into place simultaneously that there was a true increase in the number of studies in pediatrics that led to labeling changes to address a drug's use in pediatrics, Dr. Dankner says. "We don't know if, with the incentive alone, there will continue to be the success that was demonstrated with the combination of the rule and the incentive."

Dr. Schreiner and others point out that the drugs on the market are being used in children even without proper labeling on appropriate dosing.

"Pharmaceutical companies have to be led kicking and screaming," he says. "Most of the legislation related to drugs — for example, the 1938 Food, Drug and Cosmetic Act and Kefauver-Harris Amendments of 1962 — were the direct result of tragedies that affected children. And the Food, Drug and Cosmetic Act was in committee for five years. The Kefauver-Harris Amendments were being debated for a prolonged period. It didn't look like anything was going to happen and then pictures

The Dilemma of Off-Patent Products

HHS officials named 12 commonly prescribed drugs that will be tested for use in children.

SIX OF 10 OF THE DRUGS MOST COMMONLY PRESCRIBED ON THE MARKET IN CHILDREN ARE "OFF- PATENT," BASED ON LIMITED, IF ANY, PEDIATRIC STUDIES AND/OR ON THE PERSONAL EXPERIENCES OF HEALTH PROFESSIONALS, ACCORDING TO DATA FROM THE FOOD AND DRUG ADMINISTRATION.

Recognizing that there are few incentives for manufacturers to study products that are now off-patent, the Department of Health and Human Services has launched an initiative to research and gather data on pediatric response to certain approved products, according to the Food and Drug Administration. The testing is called for in the Best Pharmaceuticals for Children Act (BPCA), which was signed into law by President George W. Bush last year. The law provides for the National Institutes of Health (NIH) to sponsor pediatric tests of certain drugs already approved for marketing but that either were never tested or not fully tested specifically for their effects in children.

In January 2003, HHS officials named 12 commonly prescribed drugs that will be tested for use in children. Up to $25 million is available to launch the tests in fiscal year 2003 and up to $50 million is to be included in the fiscal 2004 budget proposal for such testing.

FDA officials say they plan to strengthen coordination with the NIH on the safety and efficiency of pediatric drugs. The regulatory agency also plans to hire new staff for the Center for Drug Evaluation and Research (CDER) to continue to define, develop, issue, and track written requests for pediatric studies; publish the final study reports on the docket; review submitted results from these pediatric studies within six months; oversee ethical issues related to studies; and disseminate appropriate information to the public.

The list of drugs released was developed by the National Institute of Child Health and Human Development (NICHD), part of the NIH, in consultation with the FDA and experts in pediatric research. The list, to be updated each year, includes:

Azithromycin, an antibiotic used to treat many different types of infections

Baclofen, a muscle relaxant used to treat the spasms/tightness of muscles in patients with cerebral palsy

Bumetanide, a diuretic that causes the kidneys to get rid of excess water and salt from the body

Dobutamine, a drug that stimulates the heart and is used in critically ill patients

Dopamine, a drug that is used to treat shock in critically ill patients

Furosemide, a diuretic that causes the kidneys to get rid of excess water and salt from the body

Heparin, a drug used for the prevention and treatment of harmful clots in the blood vessels

Lithium, a drug used for the treatment for bipolar disorder — extreme mood changes from depression to mania

Lorazepam, a drug used for the treatment for acute seizures and long-term sedation in the intensive care unit

Rifampin, a drug used in combination with other medications to treat tuberculosis, and to treat carriers of certain meningitis-causing bacteria

Sodium nitroprusside, a drug used to reduce blood pressure in critically ill patients

Spironolactone, a drug used as part of a regimen to prevent loss of potassium

Source: Department of Health and Human Services, Washington, D.C., and the Food and Drug Administration, Rockville, Md. For more information, visit hhs.gov and fda.gov.

There are a couple of problems with the six-month exclusivity. First, it is not a big enough incentive. And second, the incentive applies to drugs, but not to biologics.

DR. JAMES HILDEBRAND

of thalidomide babies appeared on the front page of *The Washington Post*. If the purpose of the drug rules is to prevent tragedies in children, then we have to study the drug in children to know."

In 1962, thalidomide, a sleeping pill, was found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, led to public support for stronger drug regulation. Kefauver-Harris Drug Amendments were passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them. In addition, the FDA was given closer control over investigational drug studies. FDA inspectors were granted access to additional company records, and manufacturers had to demonstrate the efficacy of products approved before 1962.

Opposition to a rule mandating pediatric trials, Dr. Schreiner says, is purely financial.

"Companies don't want to spend money," he says. "Regulations set the minimum of what should be done. Companies only want to do the minimum, but the minimum is not always the optimum."

Dr. Schreiner acknowledges that conducting trials in which children are subjects can take more time and can be more expensive. But, he says this is the trade off companies make for the right to do research.

"There is an ethical principal that is part of the basis for clinical research," Dr. Schreiner says. "That is the principal of justice, that the benefits and burdens of research should be distributed equally. Despite the vast increase in knowledge that we've accumulated over the past 50 years, children have not benefited nearly to the extent that adults have. Society does not give drug companies the right to do research because of the profit motive. The right to do research is because of the social good and value from new drugs, and companies must follow certain rules."

THE DOWNSIDE TO LEGISLATION

Nevertheless, the pediatric rule and the Senate bill both are controversial and have been criticized on many fronts.

From a business and medical perspective, a new law would be harmful because it would put additional regulatory burdens on manufacturers, says Sam Kazman, general counsel for the Competitive Enterprise Institute (CEI). CEI was one of the organizations involved in the successful court challenge to the FDA's pediatric testing rule last fall.

"It's great to have more data," Mr. Kazman says. "The problem is that in the regulatory sphere, there is a trade off. The more data the agency demands, the fewer drugs that result and the longer it takes to get them on the market."

The Pediatric Research Equity Act of 2003 mandates would impose yet more regulatory hurdles for new drugs. These might be trivial for some candidate drugs, but they could delay, or cancel altogether, the approval of others, Mr. Kazman says.

"If a company gets through all the hurdles involving the indication and the population that it plans to market to, it may still get hit with testing demands if certain off-label uses are found to be significant," he says. "It is going to add to the risks that a company considers when it decides whether to take the gamble of taking a drug through development."

A mandate to require pediatric studies of new drugs could be too restrictive if it doesn't take into account that some products are not likely to be used in children, says John Yee, M.D., M.P.H., of BBK Healthcare Inc.

"The pediatric rule should be carefully defined such that the requirement can only be put into effect when it is clear that those drugs will be used, or are commonly used, in a pediatric population," Dr. Yee says. "There are some drugs that would be very unlikely to ever be used in a pediatric population, at least for the approved indication. For example, it would be unlikely that most drugs being developed for the treatment of Alzheimer's disease would have an indication, even an off-label indication, in a population of children."

He says pediatric studies tend to be more difficult than adult studies for a number of reasons, including the fact that children are unable to volunteer themselves.

"Children have to provide their assent along with their parent's or guardian's consent," Dr. Yee says. "There are legal and ethical issues about enrolling in a study. But there are also practical issues that make pediatric studies difficult. There are often fewer children with a given condition than there are adults with the same condition. So the challenge of identifying, recruiting, and enrolling children in a study is often greater."

But, Dr. Yee says, if it is found that the drug could be used in children, it would be reasonable to expect the company to conduct the necessary studies of safety and effectiveness in a pediatric population.

"I do not believe a mandate is necessary as regulatory officials do an excellent job of guiding companies as to what studies are appropriate for pediatric studies," says Christy Shaffer, Ph.D., CEO of Inspire Pharmaceuticals Inc. "Each clinical trial program is unique. For example, a cystic fibrosis program is quite different and has different aspects than an asthma program. I believe the FDA has appropriate concerns regarding studies involving children and provides very good guidance for specific programs."

Mr. Kazman says there will likely be a political push to mandate additional testing in other special populations.

"And then we may finally get to the point where someone is going to say: let's forget about special populations altogether and consider mandated testing of any significant off-label use, period," he says. "In effect, the very concept of off-label use will be threatened."

Mr. Kazman points out that pediatric testing is already being carried out under

Required pediatric testing will mean a whole new set of testing demands. This is going to add to the risks a company has to look at when it decides whether to take the gamble of developing a product.

SAM KAZMAN

both federal funding and under the additional six months of patent protection granted to companies that do approved pediatric studies. "Mandated testing is an extreme approach, the need for which hasn't been established," he says.

Companies already are studying medicines for use by children. A survey released in May 2002 by PhRMA reported 194 medicines in clinical trials for children, 11 of which are for psychiatric disorders. Nine of the 11 are old drugs that manufacturers are seeking approval for new indications, including attention-deficit/hyperactivity disorder (ADHD), depression, post-traumatic stress disorder, schizophrenia, and acute bipolar disorder.

According to the PhRMA report, the other medicines include 32 for cancer, 10 for AIDS, 10 for asthma, 16 for cystic fibrosis, as well as medicines that target diabetes, epilepsy, eye disorders, rheumatoid arthritis, hypertension, familial high cholesterol, congenital heart disease, Crohn's disease, mucopolysaccharidosis, Fabry's disease, sickle cell disease, Duchenne's muscular dystrophy, Pompe disease, ear infections, pneumonia, cerebral palsy, autism, bronchitis, and other diseases.

Dr. Dankner also points out that the incentive provided to companies depends on the market for the drug.

Millions of children are receiving drugs for which there is no information. To me, not only is this unethical, it's immoral.

DR. MARK SCHREINER

"Six months of continued exclusivity is a pretty significant incentive," Dr. Dankner notes. "While the costs to conduct a pediatric development program will vary, those costs may likely be only a fraction of what some of these companies will receive in revenue from the additional six months of exclusivity."

Efforts already are under way to test marketed products for their effects in children. In January 2003, the Department of Health and Human Services named 12 commonly prescribed drugs that will be tested for use in children.

The government-supported tests of these drugs will begin this year, with up to $25 million available to launch the tests in fiscal year 2003 and up to $50 million to be included in the fiscal 2004 budget proposal for such testing. (For more information, see box on page 46.)

The testing is called for in the Best Pharmaceuticals for Children Act, which was signed into law by President Bush last year. The law provides for the National Institutes of Health to sponsor pediatric tests of certain drugs already approved for marketing but either never tested or not fully tested specifically for their effects in children. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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