Shifting the Pediatrics PARADIGM

BY AUTUMN KONOPKA

The FDA's push for pediatric studies since the late 1990s has nearly doubled the pediatrics market, which is expected to keep growing in the coming years. Nevertheless, children remain "therapeutic orphans," and some experts believe that the pediatrics market may never be able to sustain itself without governmental incentives.

Regulations and incentives in recent years have forced a paradigm shift in the way pharmaceutical companies approach pediatric drug development. For almost a decade, federal regulations and incentives have helped to build an infrastructure for conducting clinical research in children. Since then, developers, investigators, and regulators have learned much about how to study a drug's effect and the appropriate use of medication in children. Additionally, more than 100 labeling changes have been made to include these data.

The Incentives

In September 2005, the U.S. Food and Drug Administration (FDA) issued a draft guidance for compliance with the Pediatric Research Equity Act (PREA). PREA, which went into law in 2003 and is retroactive to

Dr. Cameron Durrant

There are a couple of gaps in the legislation. There may need to be even more incentives to be able to conduct studies in tricky pediatrics subcategories.

Dr. Albert Allen

People tend to focus on the six months of marketing exclusivity, but ultimately the real beneficiaries have been the kids.

April 1999, requires pediatric studies for all new drug applications (NDAs) and biologics licensing applications (BLAs), unless the applicant has obtained a waiver or deferral. The law also gives the FDA the authority to require such studies from the sponsors of already marketed products under certain circumstances.

PREA is the latest step in the FDA's ongoing efforts to increase the safety and efficacy of pharmaceuticals used to treat children. Beginning in the early 1990s, the FDA initiated voluntary measures to increase pediatric studies and, therefore, labeling information; but those measures were largely unsuccessful.

In 1997, the agency proposed the first pediatric rule, which mandated pediatric assessments of new drugs and biological products, as well as marketed products under compelling circumstances. The rule was formalized in 1998, and the first studies were required in December 2000. But in October 2002, the rule was overturned in a federal district court. With strong support from Congress and the Bush administration, a modified version of the rule, PREA, was introduced the following year and became law in December 2003.

PREA, the mandatory legislation, works hand in hand with the FDA's Best Pharmaceuticals for Children Act (BPCA), the agency's voluntary incentive program, as a "stick and carrot" model to induce pharmaceutical developers to increase pediatric testing. BPCA became law in 2002 and is the successor of the FDA Modernization Act (FDAMA) of 1997, which first introduced pediatric-testing incentives. It provides a six-month marketing exclusivity incentive to sponsors of marketed products that conduct pediatric studies in response to a written request from the FDA. Unlike FDAMA, BPCA includes a partnership between the FDA and the National Institutes of Health (NIH) to promote pediatric studies for off-patent products.

Because PREA works in tandem with the voluntary BPCA legislation, industry leaders have been anxiously waiting for the FDA guidance to provide clarity on what to comply with and how to comply.

"So far, the only comments that we've received have been positive," says Lisa Mathis, M.D., acting director of the Division of Pediatric Drug Development at the FDA's Center for Drug Evaluation and Research. "Companies are glad to have the guidance so they can figure out how to work through the legislation."

Christopher-Paul Milne, D.V.M., M.P.H., J.D., assistant director at the Tufts Center for the Study of Drug Development (CSDD), says there's still some confusion at pharma companies.

"It's not as if companies have a lot of choice; they're going to go to school on this guidance," he says. "And it certainly has to help because it focuses on PREA, on the mandatory part. Before, there was a mix of the voluntary and the mandatory, so companies that had no interest in pursuing BPCA or a voluntary program had to interpret what did and didn't apply to them. Now they can look at the guidance to figure out what they have to do and how they are going to deal with it."

Dr. Milne says the guidance is particularly useful considering the ever-expanding number of players in the drug-development field. Many smaller and newer companies do not have the well-honed regulatory offices that the major pharma and big biotech companies have, he says, so the guidance is certainly helpful.

"In addition to easing the confusion among company officials, the guidance will help to make the FDA more comfortable with approving pediatric studies," says Philip D. Walson, M.D., professor of pediatrics and pharmacology at the University of Cincinnati, and director of the clinical pharmacology division and clinical trials office at Cincinnati Children's Hospital Medical Center. "The potential negative fallout has left some FDA line officers wary. They're afraid of reviewing pediatric studies because they're risky. Without a guidance that tells them what to do, they will err on the side of caution, making it very hard for a company to do a study."

Although PREA primarily focuses on NDAs and BLAs, one of the concerns with the legislation is the provision whereby the FDA could require studies for an already marketed product. Some in the industry worried that this might circumvent the voluntary mechanism of BPCA. What's more, the new guidance focuses exclusively on new drugs and does not provide guidance for how marketed products can best comply with the mandatory legislation.

"I think the question has been: Is the FDA going to shift the balance between using collaborative market-based approaches to encourage additional studies versus a mandated approach?" says Albert J. Allen, M.D., Ph.D., medical director for the Strattera product team at Eli Lilly & Co. "And to that extent, it's too soon to tell."

According to Dr. Mathis, at least for right now, PREA is only triggered by new products and already marketed products that submit applications for a new ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration.

"If an application comes in with any of those conditions, then we will apply PREA," she says.

Dr. Milne explains that PREA enables the agency to insist upon pediatric assessments for already marketed drugs and biologicals if the product represents a significant therapeutic benefit to the pediatric population, or if it's being

Robert Keith

Whether a product has a label is just the tip of the iceberg. There has to be a continuous commitment to innovation, and companies have to promote the product.

Dr. Philip Walson

There is a growing number of investigators who know how to do studies in children.

used in a significant pediatric population, and, most importantly, if the absence of label information represents a public-health threat. But he says the FDA rarely invokes such clauses.

"The real upshot of BPCA is for sponsors to be able to exhaust all of the voluntary avenues before they are compelled to do a pediatric study," Dr. Milne says.

Why Incentives Were Needed

Historically, drug developers have had little incentive to conduct pediatric clinical studies for products that originally were developed to treat adults. According to a 2004 Frost & Sullivan analysis of the world pediatrics market, the main challenge facing pharmaceutical companies has been economics. Because children represent a smaller portion of the population than adults, with less purchasing power and political voice, there wasn't enough of a return on investment for pharma companies to conduct pediatric studies.

Yet, because children required treatments for which there were no pediatric products, they often received off-label prescriptions for adult products that have no specific pediatric dosing or safety information.

In fact, according to Tufts CSDD, before the FDA initiated its original pediatric rule and pediatric incentives in the late 1990s, about 70% of the drugs used to treat children in the United States were dispensed without adequate pediatric dosing information.

"There's a disenfranchisement of children in this country," says Cameron Durrant, M.D., MBA, former president and CEO of PediaMed Pharmaceuticals. "Children are probably among the neediest group in the country, and there's a disproportionate share of children who are living in poverty as it's defined by various government statistics. Also, kids tend not to have a political voice, even though organizations such as the American Academy of Pediatrics (AAP) do a great job of advocating."

But industry thought leaders agree that the FDA initiatives over the last several years have had a profound impact. According to FDA officials, the agency has made more than 100 pediatric labeling changes under its voluntary and mandatory programs, and it has issued more than 300 written requests. These actions have meant that more than 44,000 pediatric patients have been included in clinical studies.

"The biggest thing that FDAMA did was to create the infrastructure for doing clinical studies," Dr. Walson says. "There is a growing number of investigators who know how to do studies in children. There are now companies that have had successful pediatric programs and CROs that know where to go to recruit patients for these studies. Many things are happening to bring pediatric studies up to the same caliber as adult studies."

The one thing that the industry has to do is to make pediatric assessment part of its routine drug development, Dr. Milne says.

"If companies don't have the people to do it, they need to get the people who can," he says. "As we move along, the FDA is going to be less willing to automatically defer the pediatric studies. Regulators expect companies to be taking these trials into account."

The Pediatric Market

In addition to building regulatory infrastructure, the FDA's legislation has stimulated substantial growth in the pediatrics market. According to Frost & Sullivan's 2004 analysis, the worldwide market for pediatric pharmaceuticals generated revenue of $8.73 billion in 2002; revenue is estimated to increase to $14.48 billion by 2010.

According to others in the field, the pediatric market could be substantially larger. Dr. Milne says the U.S. market alone was about $7 billion to $8 billion in 1997, when Tufts CSDD began following it. He adds that those figures have nearly doubled since then, to about $13 billion to $18 billion in a recent estimate for 2002.

Dr. Milne attributes the variability in the market figures to a variety of fluctuating factors and unknowns.

"There are estimates based on pediatricians' use, and that may be only two-thirds of what is being prescribed," he explains. "There are estimates that don't include off-label use. Some of the estimates include vaccines, some don't. This is, no doubt, why there is such a wide range of estimates."

According to Dr. Durrant, the pediatric drug market is growing faster than other segments, including the senior market.

"Growth is being driven by a number of factors, including increased visits to doctors' offices, greater awareness and diagnosis of certain conditions, increased patient and caregiver empowerment, and better treatments for conditions," he says. "Many of these factors are present worldwide, so I would predict strong growth to occur on a global basis."

This breakthrough medical product will make it to market in record time. It was tested in 30 countries with thousands of subjects with no paper case report forms. Investigators and coordinators entered data quickly using a secure, simple user interface and robust edit checks were performed instantaneously. Monitors and data managers leveraged real-time access to listings, metrics and aggregate reports, and ultimately cleaner study data led to faster and better decision-making at a lower cost. **Hope it's not your competitor's…**

medidata®
Medidata Solutions Worldwide

Medidata Solutions. Technology for a healthy world.™ +1.212.918.1847 www.mdsol.com

Lance Lira

Additional pediatric testing can provide some protection for drug companies, giving them ammunition for defense against overzealous lawyers.

Dr. Christopher-Paul Milne

There is a growing recognition of the need to treat some of the so-called adult diseases in kids, and therefore we need to have labeled products to be able to do so.

Nevertheless, it's been estimated that pediatric products account for only about 5% of the worldwide pharmaceuticals market.

"There will be a need for continuing pediatric incentives because it may never be a market on its own," Dr. Milne says.

According to Frost & Sullivan, the key challenge facing the pediatric market is economics. Children form a relatively small segment of the population, at about 20% to 25% of the total adult market in any region. Because of the high cost of developing drugs — estimated at more than $800 million from discovery to commercialization — pharmaceutical manufacturers are compelled to address the larger markets first, which has often meant postponing or omitting drug testing for children.

Pediatric study costs can vary by 20-fold depending on when and for how long they are conducted, regulatory requirements, testing protocols, therapeutic area, geographic region, and whether a new formulation is needed.

What's more, industry experts say pediatric clinical-trial costs are on the rise. According to Tufts CSDD, average pediatric study costs are expected to rise four-fold through the late 2000s as requirements expand, patients and investigators become more difficult to recruit, and site availability becomes more variable.

"Drug companies must do everything they can to ensure the safety of the patient population; but studies are very expensive and can sometimes yield results that might remove some of the population as potential drug recipients," says Lance Lira, industry manager, pharmaceuticals and biotechnology group, at Frost & Sullivan.

"I think whether a product has a pediatric label is just the tip of the iceberg," says Robert W. Keith, president and chief operating officer of Verus Pharmaceuticals Inc. "Assuming the product does have a pediatric label, the second, and to some extent more significant, dilemma for the pediatric patient is the fact that the product may not be in a pediatric-friendly formulation."

Legislative Gaps

Of particular concern to some in the pediatrics area was the drop in pediatric studies conducted in the early 2000s, despite the FDA incentives. During that period, there were 27% fewer studies than in the years following the introduction of FDAMA in 1997.

Tufts attributes the decline in studies to: a drop in the number of FDA requests for studies; greater emphasis generally on R&D for drugs without pediatric use; and failure to include additional incentives in the BPCA for pediatric R&D challenges such as antibiotics, neonates, and formulation development.

"There are a couple of gaps in the legislation," Dr. Durrant says. "There are pediatric challenges — particularly in neonatology, preterm infants, adolescents, and in some cases formulation development. It may be that there needs to be even more meaningful incentives to be able to do these types of tricky studies in challenging subcategories."

Additionally, he says another concern is the gap created by big pharma's burgeoning R&D focus on products that have limited pediatric applications.

"If there aren't additional incentives to make sure that pediatrics are well looked after in certain areas — particularly where there's a strong unmet need — then that might mean that things slow down further," Dr. Durrant suggests.

But Dr. Milne thinks the recently issued guidance might help to refocus the industry's efforts on pediatric drug development.

"We may see an upswing again," he says. "Certainly the guidance that came out in 1998 for FDAMA was very helpful; in fact, I don't think things really got going until after that."

Despite the challenges to pediatric drug development, there is revenue to be made, particularly in light of the FDA's exclusivity incentives under the BPCA. Tufts researchers estimate that a hypothetical company issuing three written requests and gaining two pediatric exclusivities in 2004 would have earned an estimated $35 million in

- **Between 1998 and 2005**, almost 100 medicines were newly labeled for pediatric use.
- **Drug developers initiated pediatric studies for 95%** of all FDA requests in 1998-2001, exceeding the projected 80% response rate.
- **Fewer FDA requests for pediatric studies** and declining interest in incentives led to a drop in pediatric studies in 2000-2004.
- **Fewer than one-half the medicines** awarded pediatric exclusivity are in the 200 top-selling drugs.
- **Pediatric study costs can vary by 20-fold** due to length, methodology, regulatory requirements, testing protocols, geographic region, and therapeutic area studied.
- **Pediatric study costs are expected to rise** through this decade as requirements expand and patients and investigators become more difficult to recruit.

Source: Tufts Center for the Study of Drug Development, Boston.
For more information, visit csdd.tufts.edu.

undiscounted profits per drug, based on median 2004 sales for all pediatric exclusivity drugs after accounting for costs and market protection extensions.

"Obviously a fair number of drugs are going to fall below the level where it's worth a company pursuing, and there are going to be some drugs that will fall in the $100 million to $200 million range," Dr. Milne says. "But $35 million is $35 million. Considering the alternative was that the companies would have to do it anyway, just by regulation, it seems to be a fair bargain."

Some specialty pharma companies, like PediaMed and Verus, focus exclusively on pediatrics and offer big pharma outsourcing and outlicensing capabilities to reduce the burden of conducting required pediatric studies.

"If you think about the traditional economic argument, if a drug is not a $500 million or $1 billion drug, a company is probably not going to go after it," Mr. Keith says. "Now they have the regulatory requirements hanging over their heads, but there is also an opportunity for them to partner with pediatric specialty pharma companies such as Verus to reduce that regulatory burden. And by allowing us to develop the products, develop the formulations, and commercialize the products, they benefit economically as well."

What's more, Mr. Lira suggests the studies could offer companies more than financial benefits.

"While it has certainly added to the cost of

Sound Bites from the Field

PHARMAVOICE ASKED EXPERTS AT CONTRACT RESEARCH ORGANIZATIONS TO DISCUSS THE MAJOR CHALLENGES TO CONDUCTING PEDIATRIC CLINICAL TRIALS AND HOW DRUG DEVELOPERS CAN OVERCOME THOSE CHALLENGES.

ALAN DAVIES, M.D., MRCP, is European Medical Director for Kendle, Cincinnati, a global CRO delivering innovative and robust clinical-development solutions — from first-in-human studies through market launch and surveillance — to help the world's biopharmaceutical companies maximize product life cycles and grow market share. For more information, visit kendle.com.

"The major challenges to pediatric clinical trials are writing protocols that are achievable, finding knowledgeable and experienced pediatric investigators, and recruiting and retaining patients. Biopharmaceutical companies typically require complex studies, comprised of a single study protocol, run across two, three, or more continents. Such studies require clarity of leadership, using an experienced project leader who can pull together disparate medical cultures, recruitment projections, and regulatory submission timelines quickly and efficiently. Consent and assent are always quoted as the major challenge but are manageable with the right approach and the right protocol.

Don't assume that an adult protocol or approach will work. Second, be aware that pediatric centers are typically smaller and the diseases are quantifiably and qualitatively different from adult diseases. And third, recognize pediatric-specific presentations and recruitment strategies."

CYNTHIA R. JACKSON, D.O., is VP of the Medical and Scientific Services Group at Quintiles Transnational, Research Triangle Park, N.C., which provides a broad range of professional services, information, and partnering solutions to the pharmaceutical, biotechnology, and healthcare industries. For more information, visit quintiles.com.

"The major challenge for most pediatric clinical trials is finding the appropriate patient population and successfully recruiting patients for participation. This is compounded by the fact that the pool of motivated, experienced pediatric investigators is small and the competition for enrollment, especially in certain therapeutic areas, is large.

In my opinion, there are two issues that need to be addressed to overcome the challenges to pediatric trials: protocol development and the therapeutic area to be investigated. I have seen many protocols that were originally developed for the adult population with only minor modifications, such as changing the age groups to be studied. Thoughtful protocol preparation is key. Also, a clear understanding of the FDA's requirements and communication with the agency are necessary.

Second, certain therapeutic areas are of particular interest at present, so there is significant competition for the investigative sites. The option to complete a portion of the trials outside the United States is a good strategy. I believe global pediatric trials are the wave of the future and will be the only method of effectively studying certain pediatric patient populations and indications."

MAXINE STOLTZ, PH.D., is VP, Early Development Services, at PRA International, Reston, Va., a clinical development organization with offices in North America, Europe, South America, Africa, Australia, and Asia. For more information, visit prainternational.com.

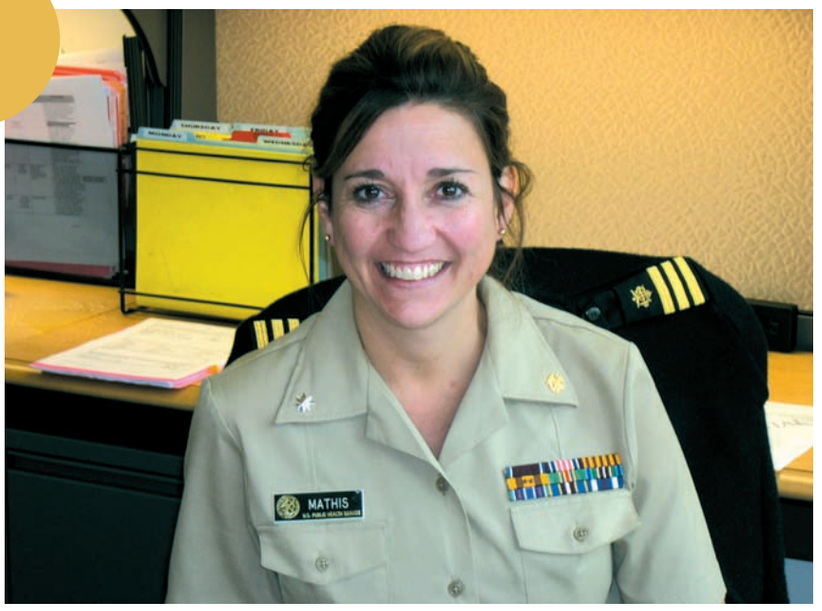
"Unique challenges in the conduct of pediatric studies include: recruitment of children for participation in clinical trials using unproven therapies; potential for participating in a trial to come across as involving a form of coercion, therefore, patient payments must be carefully reviewed by institutional review boards (IRBs); studies must be designed to minimize risk and distress (e.g., blood sampling, interventional procedures) while maximizing benefit; ethical implications of the use of placebo; and informed-consent issues, whereby the study must be signed by a guardian but the child must also give assent.

Of all the factors driving the urgency of conducting trials in pediatrics, it is clear that in cases of serious and life-threatening diseases, studies should be conducted very early in development. Many excellent collaborative groups — comprised of public, private, and academic sectors — have played significant roles in improving outcomes for childhood cancers.

These collaborative models apply to other serious diseases as well because they drive: increased funding of research in developing better pediatric dose formulations; data- and knowledge-sharing on recruitment and retention of pediatric patients in studies; technology improvements in super-micro bioanalytical methodologies that allow very low-volume blood sampling for use in pharmacokinetic/pharmacodynamic studies; and the creation of high-profile forums that enable researchers to learn from experiences with unique study design issues."

Dr. Lisa Mathis

The industry has learned a lot about how to conduct these trials, and there are a lot of pharmacology centers and medical research centers that now focus on children.



drug development, the additional testing can also provide some protection for drug companies in an increasingly litigious society, giving them additional ammunition for defense from overzealous lawyers," he says.

The Marketing Challenges

Another challenge facing the industry is how to commercialize, or at least raise awareness about, products that have new pediatric labels. While the FDA's incentive program has spurred significant clinical activity in the pediatric space, some in the industry suggest that the ROI is not enough for companies to put marketing efforts behind these products.

According to Tufts, more than 60 sponsors spent about $350 million per year during the period between 1999 and 2003 to conduct pediatric studies, but only a quarter of them have used the pediatric exclusivity protection to date, valued at an estimate of $700 million.

"We know the labels have changed," Dr. Walson explains. "But we don't know that anybody else knows that. Where should they get that information? We're putting this information into continuing education programs for pediatricians. But most of the information physicians get is from a company's detail salesforce, and there's not a lot of incentive for reps to inform physicians about labeling changes."

"It seems that some companies might benefit from the financial upside without committing to what I think is an ethical obligation to let people know that the product is available in those categories," Dr. Durrant says.

Without adequate promotion, some experts say newly labeled products will not experience much variation in terms of prescribing activity. This could present a danger to public health, considering that a significant number of the studies conducted thus far have illustrated underdosing, overdosing, ineffectiveness, and safety problems. ✦

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

Experts on this topic

ALBERT J. ALLEN, M.D., PH.D. Medical Director, Strattera Product Team, Eli Lilly & Co., Indianapolis; Lilly is committed to developing a growing portfolio of best-in-class and first-in-class pharmaceutical products that help people live longer, healthier, and more active lives. For more information, visit lilly.com.

CAMERON DURRANT, M.D., MBA. Formerly, President and CEO, PediaMed – The Pediatrics Company, Florence, Ky.; PediaMed is a specialty pharmaceutical company focused on pediatric patients, parents, and the healthcare professionals that serve them. For more information, visit pediamedpharma.com.

ROBERT W. KEITH. President and Chief Operating Officer, Verus Pharmaceuticals Inc., San Diego; Verus is building a portfolio of products for the unmet medical needs of children with an initial focus on the treatment of asthma, allergies, and related diseases. For more information, visit veruspharm.com.

LANCE LIRA. Industry Manager, Pharmaceuticals and Biotechnology Group, Frost & Sullivan, San Antonio; Frost & Sullivan is a global consulting company. For more information, visit frost.com.

LISA MATHIS, M.D. Acting Director, Division of Pediatric Drug Development, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Rockville, Md.; The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biologicals, devices, and products that emit radiation. For more information, visit fda.gov/cder.

CHRISTOPHER-PAUL MILNE, D.V.M., M.P.H., J.D., Assistant Director, Tufts Center for the Study of Drug Development (CSDD), Boston; Tufts CSDD, an independent research group affiliated with Tufts University, provides information for drug developers, regulators, and policy makers on improving the quality and efficiency of pharmaceutical development, research, and utilization. For more information, visit csdd.tufts.edu.

PHILIP WALSON, M.D. Professor, Pediatrics and Pharmacology University of Cincinnati, and Director, Clinical Pharmacology Division and Clinical Trials Office, Cincinnati Children's Hospital Medical Center, Cincinnati; U of C is a public university founded in 1819. For more information, visit uc.edu.