



The Pediatric Drug Development Challenge

FDA approval method can help increase the number of pediatric drugs

Today, the pharmaceutical industry finds itself mired in an ethical dilemma centered on pediatric drug development. Only about a quarter of all drugs available for prescription contain labeling information for children, and more than two-thirds of drugs prescribed to children have not been studied and labeled for pediatric use. As a result, off-label prescribing has become an accepted practice among physicians, leading to the prescription of extemporaneous formulations with untested bioavailability and stability in children.

BY **PETER R. JOINER**

Why aren't more drugs labeled for pediatric prescription? You can't blame Congress—in recognition of the need for pediatric labeling instructions, Congress included incentives for conducting needed pediatric studies in the Food and Drug Administration (FDA) Modernization Act of 1997. When this failed to have significant impact, Congress passed, in January 2002, the Best Pharmaceuticals for Children Act (BPCA), which provided the innovator a six-month extension to exclusivity if prescribed studies were performed. Later, in 2003, Congress passed the Pediatric Research Improvement Act (PRIA), which provided the FDA with the authority to use bridging data from adult studies for the approval of pediatric medicines. In September 2007, the FDA Amendments Act reauthorized both the BPCA and the PRIA until 2012.

Although the three acts are designed to encourage the development of pediatric drugs, to date they have failed to significantly increase the percentage of pharmaceuticals labeled for children. Why? The challenges facing pediatric drug development fall into four categories: ethics, economics, logistics, and technical considerations. In almost all cases, developing pediatric drugs is more complicated and less remunerative than developing drugs for adults, but that doesn't remove the moral obligation for drug companies and doctors to provide pharmaceuticals that are safe and effective for their smallest patients.

An important opportunity for pharmaceutical companies lies with an underutilized FDA approval method, 505(b)(2), which can play a significant role in quickly bringing to market pediatric drugs in appropriate dosage forms (see Figure 1, p. 30).

AN ETHICAL DILEMMA

Are pediatricians who prescribe an adult medication to a child by guessing at the appropriate dosage and method of administration performing a moral act?

On one hand, they are offering a treatment or analgesic to a patient who may have no other option. On the other hand, they may be subjecting patients to risk—based on inappropriate dosing—with inadequate consideration of the differences in childhood metabolism.

Children, like adults, deserve tested drugs, and they also deserve to benefit from scientific and pharmaceutical progress. Because issues of growth and development must be taken into account, because trials are more complex, and because the overall market is smaller, it has been easy for pharmaceutical companies to put pediatric drug development on the back burner.

Drug development, like many things, is driven by economics, and pediatric drug development lacks what is known as profit potential. The overall market is smaller, and patients are constantly growing out of it, so the chances of a blockbuster drug are greatly diminished.

Additionally, pediatric clinical trials are often more complicated and expensive, involving different endpoints than adult trials and, in many cases, requiring a greater number of participants. The logistics of conducting pediatric trials are further complicated by the lack of infrastructure and limited availability of baseline information on frequency of disease and treatment of choice.

A FASTER PATH TO MARKET

The 505(b)(2) regulatory process provides new pharmaceutical applications for drugs that are of proven clinical efficacy and safety, because they are already on the market. The process involves bioequivalence studies and patient efficacy trials that are usually relatively small. Because the drug is already known in adults, the clinical testing process is typically shorter and less costly than for a new drug compound, for which more extensive testing is required. The clinical testing process used at Madeira Therapeutics (Leawood, Kan.), for example, can be completed in as little as three years after the pre-investigational new drug

application meeting with the FDA.

Because the 505(b)(2) process is typically faster and less costly than traditional approval routes and can result in a branded product with market exclusivity, investors are willing to back what may be a smaller return overall because of the significantly reduced risk.

Applications that fall under 505(b)(2) are for new chemical entity/new molecular entities (NCE/NME) or changes to previously approved drugs, including:

- dosage form;
- strength;
- route of administration;
- formulation; and
- dosing regimen.

PRACTICAL APPLICATIONS OF 505(B)(2)

In children and adolescents, hyperlipidemia may be secondary to associated conditions like obesity, but heterozygous familial hypercholesterolemia (HeFH) is one of the most common and clearly documented conditions with important cardiovascular consequences that begin in childhood. The identification and management of HeFH in children is, therefore, of great consequence.

Developing pediatric drugs is more complicated and less remunerative, but that doesn't remove the moral obligation for drug companies and doctors to provide pharmaceuticals that are safe and effective for their smallest patients.

Five statins have been approved by the FDA for the treatment of children with HeFH who are at markedly elevated risk of premature coronary artery disease. Several recent randomized, controlled clinical trials established both the efficacy and the safety of statin therapy in children ages 8 to 18 with HeFH.

The American Heart Association currently recommends initial statin treatment in childhood at 10 years in males and after the onset of menses in females. In patients with extremely high low-density lipoprotein levels, associated lipid abnormalities or other risk factors, or the presence of a particularly worrisome family history, statin therapy may be initiated at a younger age.

Madeira Therapeutics is seeking to gain approval under 505(b)(2) for a statin formulation in liquid form for oral dosing. This route of administration provides the flexibility to customize dosage, allowing individualized therapy based on the child's age, weight, and specific recommended goal.

PAIN RELIEF IN CHILDREN

When examining the argument that children deserve to benefit

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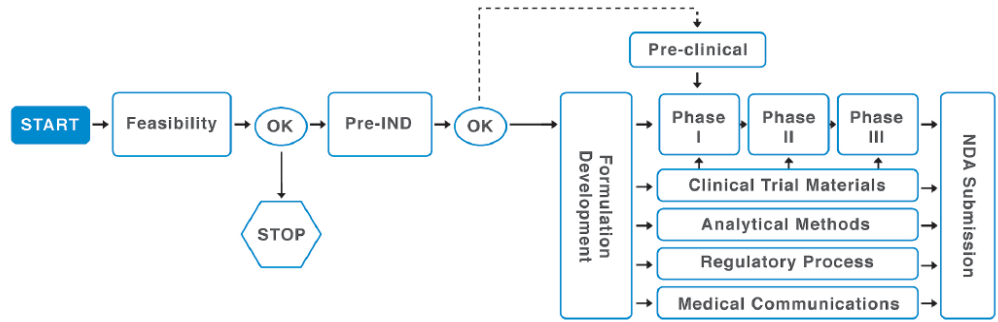
as much as adults from the advances made in medicine and pharmaceuticals, consider the fact that few potent analgesic medications are labeled for pediatric use, and many children are not receiving therapeutic doses of pain medication.

The analgesics currently used to treat acute pain in children include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. The analgesic efficacy of acetaminophen

and NSAIDs is often inadequate to treat pediatric postoperative pain in cases such as dental extractions, tonsillectomy, and adenotonsillectomy. The use of opioid analgesics for postoperative analgesia in children, however, has been shown to significantly increase the time to, and reduce the amount of, rescue analgesia.

Ideally, an analgesic for acute pain in children should be available in an oral formulation with high potency, should not cause respiratory depression, and should have a favorable adverse event profile. Under the provisions of 505(b)(2), Madeira Therapeutics is moving forward with an analgesic oral solution

Figure 1. 505(b)(2) Pathway



The 505(b)(2) pathway process uses bioequivalence studies and patient efficacy trials for clinical testing that can be completed in as little as three years.

that has a potency that is intermediate between that of NSAIDs and opioids. The company is confident this will provide an effective and well-tolerable analgesic suitable for use in children for the treatment of acute pain.

With both of these formulations, issues of taste and palatability must be considered. Studies show that pills and capsules are often difficult to administer to young patients, so we are pursuing liquids for oral formulations. Of course, all pharmaceuticals must be approached with the final consumer in mind, but this is especially true for children. A medicine that's difficult or unpleasant to take will affect adherence, so formulations are only deemed successful if they can be effectively flavored.

Possibly the biggest challenge in developing a more reasonable percentage of drugs studied and labeled for children lies with pediatric physicians themselves. There is no question that the medical community as a whole has adapted to the lack of pediatric labeling with pill splitting, dose guessing, and pharmacy-compounded ad hoc formulations that may or may not be safe.

Getting information to physicians so they can make the best choices in prescribing medications for individual pediatric patients is very important. Given a choice, physicians prefer to write an on-label prescription, because not only does it help to protect them from a malpractice scenario, but the insurance company is more likely to reimburse an on-label script. Additionally, a liquid formulation helps physicians to prescribe the right dose.

Children deserve drugs that are proven safe and efficacious, that come in appropriate dosage forms, and that are labeled specifically for their use. ■

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