

Pediatric Drug Testing Update, United States

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PROBLEMS OF DRUG TESTING IN CHILDREN

Children obviously need medicines, medical health professionals agree, but they are considered “therapeutic orphans” when it comes to drug development.¹ Most drugs are studied, approved, and labeled for use in adults. To use one of these approved drugs for the same disease in children, it is important to know which doses work best in children and which kinds of adverse reactions are likely to occur.¹ Other drugs are used for diseases specific to children, and adequate and well-controlled studies of their effectiveness and safety are needed. The physician labeling on the product normally includes a disclaimer that safety and effectiveness have not been established for use in children. That is the usual procedure with most of today’s drugs. Even morphine, which is a standard, necessary pain medication, has not included explicit labeling for use in children.

Pharmaceutical firms have had little incentive to study drugs for use in children because the population—and therefore the financial return—is likely to be small.² Moreover, drug testing in children is more complicated than testing in adults. Pediatric drug trials are often performed in children’s hospitals and can be more involved because great effort is made to ensure that parents and children understand the consequences of taking medications. Children are less likely than adults to be used as control subjects in clinical trials; most children in trials have the disease being studied. There is greater reluctance on the part of the medical community to use drugs in children for whom there would be no potential benefit.

It is naïve to believe that the solution to this problem is to simply give children lower doses of the required drugs. Young children sometimes metabolize or absorb drugs at different rates than adults do, and therefore it is difficult to estimate a suitable dose from a child’s size.³ The same holds true for older adults, when compared with younger adults. In recent years, the U.S. Food and Drug Administration (FDA) has paid more attention to establishing specific dosages for elderly patients, and the same kind of attention is needed for children.

At present, fewer than 25% of all FDA-approved drugs include an indication for use in children.⁴ Nevertheless, nearly all drugs currently on the market in the U.S. have been used in patients younger than 18 years of age.⁴ It is legal for physicians to prescribe a pediatric drug that is currently on the market but that has no labeling for children. Physicians may legally prescribe approved drugs for whatever uses they deem appropriate, according to their medical judgment.

The question is, how do pediatricians know the proper dose of a drug if it is not specifically labeled for children? The answer is, there is no standard source of information.

Textbooks on pediatrics usually mention drug dosages, but



the source of the information is seldom specified and the reliability is questionable. In addition, therapeutic regimens for children are often based on individual case reports, case series, and small or limited studies published in medical journals or based on past experiences of pediatric clinicians.

A HISTORY OF PROPOSED SOLUTIONS

1979

The FDA, working under the aegis of the Congress, began to persuade pharmaceutical companies to provide pediatric labeling information on drugs if such data were available. Initially, a 1979 FDA regulation required full clinical trials in pediatric populations as the basis for drug labeling for children,⁵ but progress in achieving this goal was made very slowly. The 1979 regulation permitted pediatric claims only if there had been adequate and well-controlled studies of the drug in children. This regulation, contrary to its purpose, stymied the hope that drug labels would provide adequate information for using drugs in children. For the words “Pediatric Use” to appear on the label, there needed to be “substantial evidence derived from adequate and well-controlled studies.”^{5,6}

Thus, most prescription drugs did not contain pediatric doses on labels because the required clinical trials of children were not available at the time. The 1979 regulation said that if a specific pediatric indication existed, it should be described in the “Indications and Usage” section of the labeling and the appropriate pediatric dosage should be listed in the “Dosage and Administration” section.

Even with this regulation, it was disappointing to the FDA and to pediatricians that only 20% to 25% of all drug labels included pediatric information; this reinforced the fact that very few drugs were being tested for safety and effectiveness in children.⁷ Although little testing was done and sparse information appeared on labels, health professionals could still prescribe a drug for children for “off-label” uses. Without pediatric drug data, however, physicians were sometimes reluctant to treat children.⁸

1994

Because of the continued slow progress in pediatric drug studies as well as in meaningful pediatric drug labeling, it took significant congressional pressure to achieve passage of a new legislative rule in 1994.⁷ The rule revised the “Pediatric Use” subsection of the prescription drug-labeling requirements.

The new regulation seemed to promise that drugs would be labeled with additional pediatric information that was crucial to the well-being of many of the nation’s children. The rule allowed companies, in some situations, to base pediatric labeling on data extrapolated from adequate and well-controlled adult studies along with other information on treating children. However, the rule specified that such pediatric-use statements could be made only if the course of the disease and the drug’s

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effects were sufficiently similar in children and adults. The manufacturers were required to take the necessary steps to modify existing labeling. Triggered by the need for additional information that might produce health benefits in children, the regulation included a six-month pediatric exclusivity that prolonged the patent life of the active moiety. Manufacturers were required to submit supplemental pediatric dosing information on their products to the FDA by December of 1996.

The 1994 regulation also clarified the FDA's "final rule" requesting specific pediatric-use information from the drug manufacturers.⁹ For example, the FDA might request pediatric-use data for a drug that was widely used, was a safety hazard, or was therapeutically important in children. The rule, however, did not limit the manner in which a practitioner prescribed an approved drug. Further, if there was not substantial evidence to support a pediatric indication or a pediatric-use statement for any children (or for a specific age group), the Pediatric Use subsection had to state that the "safety and effectiveness in pediatric patients [or the age group] have not been established."⁷

A special pediatric FDA subcommittee staff tracks the implementation of the regulations and takes steps to ensure that the various possibilities of pediatric testing and use are explored. Its Center for Drug Evaluation and Research made efforts to increase the number of pediatric studies included in submissions for new prescription medicines. The agency also works closely with the National Institute of Child Health and Human Development (NICHD) to conduct pediatric trials and with sponsors of new products to ensure that the necessary pediatric data are included. Manufacturers whose products were clearly not of benefit to children or whose pediatric dosage formulations were not feasible could apply for waivers exempting them from these requirements.⁴

The response to the 1994 rule did not adequately address the lack of pediatric-use information for marketed drugs and biological products. Manufacturers submitted pediatric labeling supplements for approximately 430 drugs and biologicals, a small fraction of the thousands of prescription drugs and biological products on the market.⁹ Of the supplements submitted, approximately 75% did *not* substantially improve pediatric-use information. More than 50% of the total supplements submitted simply requested the addition of the statement that the "safety and effectiveness in pediatric patients have not been established."⁹ Others requested minor wording changes or submitted unorganized, unanalyzed collections of potentially relevant data. Almost 15% (approximately 65) of the supplements provided adequate pediatric information for all relevant pediatric age groups, and another 8% (approximately 35) provided adequate pediatric information for some, but not all, relevant age groups.⁹ The rule did not work well.

1997

The FDA's Modernization Act (FDAMA) of 1997 required the FDA to specify which drugs needed to carry pediatric labeling.⁴ The intent of the list was to focus on those products that were widely used in children and for which the absence of labeling information might lead to serious misuse.

1998

In 1998, the FDA listed the drugs that it said needed to carry pediatric labeling. Some drugs that met the labeling criteria and that did not carry a pediatric indication included albuterol inhalation solution, ampicillin (e.g., Unasyn®, Pfizer) for intravenous use, fluoxetine (Prozac®, Eli Lilly), and methylphenidate (e.g., Ritalin®, Novartis) in children younger than six years of age.^{10,11} Although the FDA expects the six-month marketing exclusivity offered by the Modernization Act to provide a substantial incentive for sponsors to conduct some pediatric studies, the voluntary nature of the incentive provided by this Act is likely to leave many drugs, age groups, and indications unstudied.

The Modernization Act provides no incentive to conduct studies on certain categories of products, including most antibiotics, biologicals, and off-patent products. Under the Best Pharmaceuticals for Children Act (BPCA), off-patent drugs that are no longer the property of any single drug firm will undergo pediatric drug trials sponsored by the U.S. Department of Health and Human Services (DHHS). Under Section 1789, a fund would be created for off-patent pediatric research in instances when manufacturers of off-patent drugs decline to conduct pediatric research. The FDA and the manufacturers would negotiate the wording of pediatric labeling for off-patent drugs and approvable new drugs within a six-month period. The bill would reauthorize pediatric exclusivity incentives until October 1, 2007.

2002

Following is a summary of the legislation signed and approved by Congress on January 4, 2002. On January 1, 2002, Congress had passed the "Pediatric Rule" for the FDA to follow (see "Pediatric Exclusivity" later). As of January 31, 2003, the status of the FDA's Pediatric Rule was as follows:

- The pediatric incentive program, which provides six months of additional marketing exclusivity for approved drugs (not biological products), is in effect; the "sunset" law is to end on January 1, 2007.
- In effect are the other BCPA provisions, which authorize FDA to request pediatric studies of already marketed drugs with National Institutes of Health (NIH) and FDA involvement and studies by others if the manufacturer refuses.
- The FDA's 1997 Pediatric Rule, which had applied to both drugs and biological products, is not in effect.

The current Pediatric Rule (BCPA) requires pharmaceutical companies to study new and marketed drugs and biologicals in children to determine their safety, efficacy, and dosing. The FDA could apply the rule if an agent promised to bring a "meaningful therapeutic benefit" over current treatments or if more than 50,000 children were affected. Approximately 12,400 children are found to have cancer each year in the U.S., and the rule might have applied in pediatric oncology only if an agent represented a therapeutic advance. Another requirement of the rule is that the disease or an agent's indication or mechanism of action must be the same in children and adults.

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Table 1 Label Changes Affecting Drug Use in Children

Drug	Trade Name	Reason for Label Change
Midazolam	Versed® (Roche)	Higher risk of serious life-threatening situations in children with congenital heart disease and pulmonary hypertension who need lower doses than predicted to prevent respiratory compromise
Etodolac	Lodine® (Wyeth-Ayerst)	Recognition of a need for a dose two to three times (in mg/kg) the dose used in adults for effective treatment of childhood arthritis
Fluvoxamine maleate	Luvox® (Solvay)	Inadequate dosing of adolescents leading to ineffective therapy or no effect for obsessive-compulsive disorder while some girls, aged 8 to 11 years, were receiving potential over-doses with levels up to two times higher than expected
Gabapentin	Neurontin® (Pfizer)	A need to use higher doses in children younger than five years of age in order to control seizures and new adverse events, such as hostility and aggression, identified in children younger than 12 years of age
Propofol	Diprivan® (AstraZeneca)	Increased mortality when used for pediatric sedation in intensive-care units; potential of concomitant administration with fentanyl to result in serious slowing of heart rate
Sevoflurane	Ultane® (Abbott)	New precaution about potential of product to cause seizures in children without a previous history of them

RESULTS AND RECENT DEVELOPMENTS

After several years of clinical studies, important label changes have had an impact on the use of these drugs in children (Table 1).

2002 and 2003

In January 2003, the Secretary of DHHS revealed that 12 commonly prescribed drugs would now require clinical testing for use in children.¹² The governmental agencies (DHHS and FDA) have planned to support the testing of the drugs starting this year. Pediatric drug testing is required, according to the BPCA, as signed into law in 2002. The law provides for DHHS agencies or pharmaceutical companies to sponsor pediatric tests of certain drugs that have already been approved for marketing but have never been tested specifically for their effects in children. These drugs are the dozen highest-priority agents needing pediatric review.¹² DHHS contends that now is the time to understand fully the effects of these medications in children (younger than 21 years of age).

The list of drugs to be studied was developed by the NICHD, part of the NIH, in consultation with the FDA and experts in pediatric research. The list is to be updated each year.

After a drug has been approved for a particular use, physicians may prescribe it for other uses as deemed necessary. The 12 drugs on the list are currently prescribed for children, but their safety and effectiveness have been established only in adults. The drugs and their indications are summarized in Table 2.

Each drug is expected to undergo approximately two years of testing, followed by an evaluation of test results by the FDA. The NICHD will oversee the testing process and will consult closely with other NIH branches and the FDA. These drugs are no longer under patent and therefore are not the property of any single drug firm. For this reason, the BPCA provided for government sponsorship of these pediatric drug trials.

At the same time, DHHS is taking separate action to test new drugs in children.¹² The agency will seek new legislation from Congress to clearly establish the FDA's authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on new drugs and biologicals. Pursuing the legislative authority would be quicker and more decisive than legal appeals.

On October 17, 2002, a federal court struck down the FDA's effort to require drug manufacturers to conduct tests in children to determine whether new drugs would be safe and effective for pediatric use. In a challenge to the Pediatric Rule by the Association of American Physicians and Surgeons, Inc., the U.S. District Court for the District of Columbia said that Congress did not authorize the FDA to set a pediatric requirement when it passed the Food, Drug, and Cosmetic Act years ago.¹³ The court pointed out that many drugs are tested for safety and effectiveness in adults only, because of the difficulty in finding substantial pediatric populations to undergo tests, along with the ethical complications associated with testing new drugs on children.

Although the court ruling presented a problem for the FDA, the agency still actively encouraged manufacturers to conduct pediatric testing of new drug entities. Meanwhile, the FDA could take its case to appeals courts and possibly even to the Supreme Court, or Congress could amend the Food, Drug, and Cosmetic Act to give the FDA specific authority to require pediatric testing.

Currently, the incentive for voluntary pediatric testing by drug companies in return for market protection remains in place under the BPCA, Public Law (P.L.) 107-109, passed by Congress in 2002. DHHS will seek new legislation from Congress to clearly establish the FDA's authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on new drugs and biologicals.

In 2003, the Secretary of DHHS said that legislative authority would be pursued because it was quicker and more decisive than legal appeals. He did not want to go back to the

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Table 2 Drugs Requested by the U.S. DHHS for Clinical Evaluation in Pediatric Patients

Drug	Indication
Azithromycin (Zithromax®, Pfizer)	Antibiotic; treats many types of bacterial infections
Baclofen (Watson)	Muscle relaxant; relieves spasms, cramping, and tightness of muscles caused by medical problems (e.g., multiple sclerosis, spinal injuries)
Bumetanide (Baxter Anesthesia)	Diuretic; reduces swelling and fluid retention caused by various medical problems (e.g., heart or liver disease); antihypertensive agent; aids kidneys in eliminating unneeded water and salt from the body
Dobutamine (e.g., Dobutrex®, Eli Lilly)	Heart stimulant
Dopamine	Parkinson's disease, schizophrenia
Furosemide (Lasix®, Aventis)	Diuretic; reduces swelling and water retention
Heparin	Antithrombotic agent; decreases clotting ability of blood; helps prevent harmful clots from forming in blood vessels
Lithium (e.g., Eskalith®, GlaxoSmithKline; Lithobid®, Solvay)	Bipolar disorder (extreme mood changes from depression or anger to elation)
Rifampin (Rifadin®, Rifamate®, Rifater®, Aventis)	Tuberculosis; also treats carriers of meningitis-causing bacteria (in combination with other medications)
Sodium nitroprusside (Baxter Anesthesia)	Hypertension
Spironolactone (Geneva, Mylan)	Hypertension
Lorazepam (Ativan®, Wyeth-Ayerst)	Anxiety

needed and for which the DHHS Secretary must award contracts for the conduct of pediatric clinical trials. The FDA Commissioner is also required to consult with the NIH Director to issue written requests for studies to holders of approved applications for drugs lacking marketing exclusivity. To carry out these studies when drug companies refuse to do so, the law authorized \$200 million in fiscal year 2000, and such sums as are necessary for each of the five succeeding fiscal years.

2. *Foundation for the NIH.* This provision allows the DHHS Secretary to refer a drug to the Foundation for the NIH when he or she determines that there is a need for information relating to the use of the drug and the drug manufacturer does not agree to conduct a study.

3. *Institute of Medicine Study.* The DHHS Secretary is required to contract with the Institute of Medicine to conduct a study on best practices that relates to research involving children.

4. *National Cancer Institute Directives.* At least two pediatric oncology specialists from the National Cancer Institute (NCI) are required to participate on the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee to review and evaluate data concerning the safety and effectiveness of drugs for use in the treatment of pediatric cancers.

In addition to requiring the NICHHD and FDA to compile the list of drugs, the BPCA reauthorized an existing economic incentive (extended protection from market competition) for pharmaceutical companies that conduct pediatric studies requested by the FDA.¹²

P.L. 107-109¹⁴ also amends the Food, Drug, and Cosmetic Act to:

- eliminate the user fee waiver for pediatric supplements to a human drug application.
- provide priority status for pediatric supplements.
- include neonates within age groups for pediatric studies.
- provide for the dissemination of pediatric supplement information.
- set forth requirements for the additional six-month exclusivity period for new pediatric drugs or those already marketed.

In return for doing pediatric testing, the drug companies were allowed to ask for pediatric exclusivity—an extra six months of patent protection and freedom from generic competition for all formulations of the drug, not just the one being tested.

CONCLUSION

The recognition of the rights of children to have access to safe and effective drugs—and of the needs of health care providers to have access to age-appropriate drug information—is increasingly influencing biomedical research. Numerous drugs have

U.S. District Court for the District of Columbia for an appeal of its negative decision of the Pediatric Rule.

Pediatric Exclusivity

P.L. 107-109 of the BPCA reauthorizes the pediatric studies provision of the 1997 Modernization Act to improve the safety and efficacy of pharmaceuticals for children.¹⁴ It continues to encourage pharmaceutical companies to conduct studies of on-patent drugs that are used in pediatric populations (but that are not labeled for such use) by extending their market exclusivity. In addition, P.L. 107-109 authorizes studies for off-patent drugs by the federal government or other entities with the expertise to conduct pediatric clinical trials.

P.L. 107-109 contains some provisions pertaining to NIH:¹⁴

1. *Pediatric Drug List and Research Fund.* The Director of NIH, in consultation with the Commissioner of the FDA and experts in pediatric research, are required to develop, prioritize, and publish a list of drugs for which pediatric studies are

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now been studied for pediatric doses. The support of the FDA in mandating pediatric labeling will play an important role in motivating manufacturers to work with NIH pharmacology pediatric research units and with other academic clinicians and researchers to study both new and established drug therapies in children.

The result is likely to be an increase in both the quantity and quality of pediatric drug research conducted in the U.S. As a final example, the FDA has classified these drugs as important new pediatric therapies:

- Colfosceril palmitate/cetyl alcohol/tyloxapol (Exosurf®, GlaxoSmithKline) and beractant (Survanta®, Ross) are pulmonary surfactants for respiratory distress syndrome in newborn babies.
- Pegademase bovine (Adagen® Injection, Enzon) is an enzyme, adenosine deaminase, that is used to replace an enzyme missing in children with severe immunodeficiency disease.
- Succimer (Chemet®, Sanofi-Synthelabo) is an oral drug for the treatment of lead poisoning in children.

Pediatric drug testing, as authorized by Congress and the FDA, has turned the corner and seems to be heading in the direction of obtaining clinically acceptable efficacy and safety data for use in children.

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