United States General Accounting Office

GAO

Testimony

Before the Committee on Health, Education, Labor and Pensions, U.S. Senate

For Release on Delivery
Expected at 9:30 a.m.
Tuesday, May 8, 2001

PEDIATRIC DRUG RESEARCH

Substantial Increase in Studies of Drugs for Children, But Some Challenges Remain

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Chairman Jeffords, Ranking Member Kennedy, and Members of the Committee:

I am pleased to be here today to discuss the pediatric exclusivity provision of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Children are subject to many of the same diseases as adults and are often treated with the same drugs. However, only about 25 percent of drugs in use today have been studied and labeled for pediatric patients. Doses for children are often merely adjusted for their smaller weight, but there are many other differences in children that can affect how drugs act in the body. The lack of pediatric testing and labeling can place children at risk of under- or overdosing, and the lack of age-appropriate formulations, such as liquids or chewable tablets, can result in improper administration of drugs. To help address these concerns, FDAMA authorized 6 months of additional marketing exclusivity for drugs tested by manufacturers and other sponsors for use in children, and placed a sunset date of January 1, 2002, on the provision.[1]

To assist the Committee in evaluating the pediatric exclusivity provision, Chairman Jeffords, you, and Senator Dodd asked us to provide information on some of the initial results of this provision. Today, I would like to focus on (1) the number and types of drugs being studied, (2) whether these studies have resulted in useful new information for using drugs in children, and (3) two remaining challenges to achieve the objective of providing better information on drugs commonly used in children.

To address these issues, we met with representatives of the Food and Drug Administration (FDA), the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH), the Pharmaceutical Researchers and Manufacturers of America (PhRMA), the Generic Pharmaceutical Association (GPhA), the American Academy of Pediatrics (AAP), the National Organization of Rare Disorders (NORD), and Public Citizen, a consumer advocacy organization. We examined the statute, FDA's list of drugs for which pediatric information may be beneficial, and FDA's January 2001 report to Congress on the pediatric

[1]Drug manufacturers or other drug sponsors may obtain marketing exclusivity through patents or by compliance with the requirements of the Orphan Drug Act (P.L. 97-414) or Drug Price Competition and Patent Term Restoration Act (P.L. 98-417). In addition to drug manufacturers, sponsors can include government agencies, health care institutions, individual physician-investigators, and others.

exclusivity provision.[2] We also examined supporting documents provided by FDA, as well as those provided by the other groups we contacted. We conducted our work from March through April 2001 in accordance with generally accepted government auditing standards.

In brief, since enactment of the pediatric exclusivity provision, both the numbers of drugs studied in children and the therapeutic classes they represent have substantially increased. Hundreds of studies are being done on drugs that are important to pediatric patients. Some are tests on relatively small numbers of pediatric patients to determine the correct dose for a specified age group. Others are more complex and costly evaluations of a drug's safety and effectiveness in children of various ages. While there has been some concern that exclusivity may be sought and granted primarily for drugs that generate substantial revenue, most of the drugs studied are not top sellers, and less than 1 in 10 generates revenues of more than $1 billion a year. As of April 1, 2001, 28 drugs had been granted marketing exclusivity extensions, and research results have provided new and useful information about how drugs work in children, which have been incorporated into labels for 18 drugs. However, challenges remain to ensure that the results of pediatric research are expeditiously incorporated into drug labels, and that incentives are provided to encourage pediatric studies of off-patent drugs widely used in children.

Background

According to the American Academy of Pediatrics, only about a quarter of all approved drugs marketed in the United States have had clinical trials performed involving pediatric patients. FDA's January 2001 report to Congress on the pediatric exclusivity provision noted that evidence from several studies conducted since 1973 showed that between 71 and 81 percent of drugs were inadequately labeled for use in pediatric patients. According to the legislative history of FDAMA, several factors appear to have contributed to the lack of pediatric studies. Drug companies indicated that they had little incentive to perform pediatric studies on drugs they intended to market primarily to adults and that these drugs would provide little additional revenue from use in children. Companies also said they were concerned about liability and malpractice issues and

[2] *The Pediatric Exclusivity Provision, January 2001 Status Report to Congress*, Department of Health and Human Services, U.S. Food and Drug Administration.

the difficulty of attracting enough pediatric patients for studies because of the small number of children with a particular disease.

Previous FDA efforts to address the problem of inadequate pediatric testing and drug labeling information had been unsuccessful. For example, in 1994 FDA tried to encourage sponsors to provide more pediatric information and conduct new studies. However, it did not require sponsors to conduct new pediatric studies, and pediatric use information did not substantially increase.

In 1997, the Congress recognized the importance of learning more about how drugs work in children by including in FDAMA a financial incentive for pharmaceutical manufacturers and drug sponsors to conduct pediatric studies and submit the results to FDA. The pediatric exclusivity provision offered 6 months of additional marketing exclusivity for drugs tested by manufacturers and other sponsors for use in children. This provision also required FDA to develop, prioritize, and publish an annual list of approved drugs for which new pediatric information may produce health benefits in the pediatric population. FDA's initial priority list, issued in May 1998, was developed based on recommendations from experts in pediatric research from the American Academy of Pediatrics, PhRMA, GPhA, the National Institutes of Health, the Pediatric Pharmacology Research Units Network,[3] the U.S. Pharmacopoeia, and several others. To be included on FDA's priority list, a drug had to meet one of the following criteria:

- The drug would be a significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of a disease in the relevant pediatric population.
- The drug is widely used in the pediatric population, with at least 50,000 projected uses per year.
- The drug is in a class or for an indication for which additional therapeutic or diagnostic options are needed for pediatric patients.

The process for obtaining the pediatric exclusivity extension usually begins when a sponsor submits a proposal to conduct pediatric studies to FDA.[4] If FDA officials believe the studies will provide useful information,

[3]In 1994, NICHD established a network of Pediatric Pharmacology Research Units (PPRUs) to facilitate and conduct pediatric drug trials that can improve pediatric labeling of new and existing drugs.

[4]Drugs do not have to be on FDA's priority list in order for FDA to consider a sponsor's proposal.

the agency issues a formal written request for sponsors to conduct the studies. FDA also issues written requests without sponsor proposals. The written request addresses, among other things, the type of studies to be performed, study design, appropriate study age groups, and clinical endpoints. The sponsor then decides whether to conduct studies requested by FDA. Once the sponsor submits the results of the studies to FDA, the agency generally has 90 days to determine whether the completed studies reported meet the terms of the written request and were conducted properly.[5] If FDA officials determine that the sponsor's efforts were sufficient, the 6-month marketing exclusivity extension is granted.

Substantial Increase in the Number of Drug Studies in Children

There has been a substantial increase in pediatric drug research compared to the very limited amount of such research before enactment of FDAMA. As of April 1, 2001, FDA had issued 188 written requests covering 155 drugs already on the market and 33 new drugs not yet approved. About 73 percent of the written requests were for drugs that treat anti-inflammatory, cardiovascular, anti-viral, oncology, neurology, or endocrine diseases or conditions.

A written request can ask for more than one study of a drug, and the 188 requests include 414 studies involving potentially more than 23,200 children as research subjects. Of the 414 studies requested, 33 percent were to examine drug safety and efficacy in pediatric patients, about 30 percent were to examine both a drug's safety and its pharmacokinetics, or how it is absorbed, distributed, and eliminated from the body. Another 20 percent of the studies were to examine only a drug's safety in pediatric patients, and about 9 percent were to study both pharmacokinetics and pharmacodynamics, or how different individuals, such as children at various stages of development, respond to a drug.

Precise data on study costs is not publicly available. The estimates we were provided vary considerably. Officials at NICHD, which has conducted many pediatric drug studies, said costs vary depending on the number of children participating and type of drug being studied. They estimated that a safety and efficacy study may cost between $1 million and

[5]When FDA and the sponsor have a written agreement on a study's protocol, FDA has 60 days to review the study results and decide whether they were conducted properly.

$7.5 million, while the cost of a pharmacokinetic study can range from $250,000 to $750,000 per age group. Limited data provided by PhRMA suggested higher study costs, ranging from under $5 million to more than $35 million. Another study indicated that, based on a survey of drug companies, the cost of pediatric studies averaged $3.87 million per written request.[6]

As of April 1, 2001, 28 drugs had been granted marketing extensions based on research conducted in accordance with FDA's written requests. The drugs granted extensions treat a variety of diseases or conditions that afflict children. Table 1 provides some overall population information on the prevalence of diseases in pediatric patients that may be treated by some of the drugs granted market extensions.

Table 1: Prevalence of Diseases That May Be Treated by Drugs Granted Marketing Extensions

Condition	Estimated pediatric prevalence	Drug
Generalized anxiety disorder	486,000	Buspirone
Epilepsy	354,000	Gabapentin
Obsessive-compulsive disorder	268,000	Fluoxetine Fluvoxamine
Insulin-dependent diabetes (Type 1)	137,000	Insulin glargine Metformin
Juvenile rheumatoid arthritis	30,000 to 50,000	Etodolac Oxaprozin
Hypertension	36,000	Bisoprolol Enalapril
HIV infection and AIDS	5,600	Abacavir Lamivudine

Note: Figures are for patients under age 18 except for diabetes, which includes patients under age 20, and HIV, which includes patients under age 13.

Source: GAO analysis of data from the Centers for Disease Control, NIH, the Surgeon General of the United States, the Arthritis Foundation, and the 2000 U.S. Census.

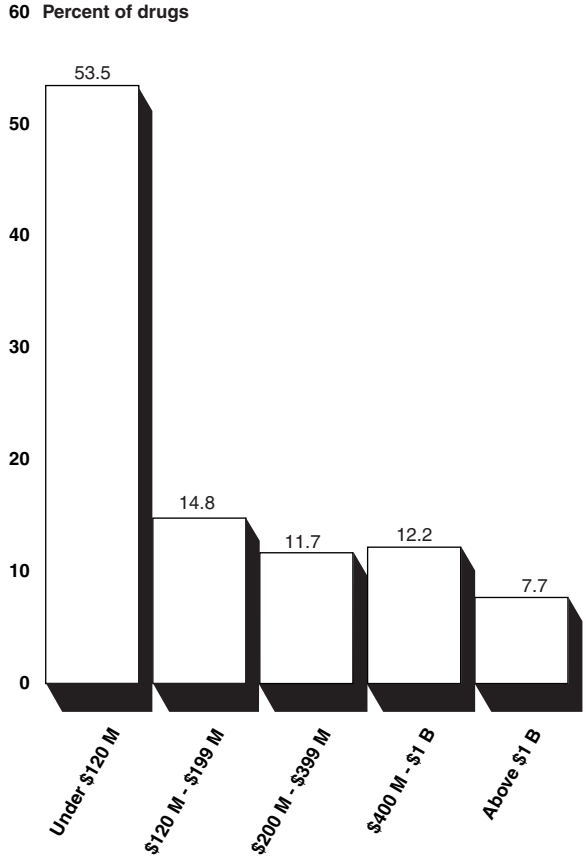
There has been some concern that exclusivity may be sought and granted primarily for drugs that generate substantial revenue. Our analysis found that sales revenue varied widely for the 155 approved drugs for which FDA has issued written requests.[7] As shown in figure 1, while 7.7 percent of the

[6] *The Pediatric Studies Incentive: Equal Medicines for All*, Christopher-Paul Milne, Tufts Center for the Study of Drug Development, April 2001.

[7] Since a drug sponsor is not required to conduct studies based on a written request, it is possible that some of the 155 drugs are not part of ongoing studies.

drugs covered by written requests had sales exceeding $1 billion in 1999, 53.5 percent had sales under $120 million in 1999. Another 14.8 percent of the drugs had sales that were more than $120 million but less than $200 million.

Figure 1: U.S. Sales of 155 Drugs Issued Written Requests Under the Pediatric Exclusivity Provision



Source: GAO analysis of FDA data and sales revenues of the top 200 selling prescription drugs in 1999 as compiled by IMS Health Inc.

Studies Have Led to Better Labeling and Infrastructure

Research conducted under the pediatric exclusivity provision is providing new and useful information about whether and how drugs work in children. As of April 1, 2001, labels for 18 of the 28 drugs granted marketing extensions had been changed to incorporate findings from research conducted to obtain the extensions. Some of these label changes

include new statements that the drug can be used for younger children or for a new use. Other label changes provide additional and more specific guidance regarding the effective dose or additional warnings about adverse events in children or information on related medications. In addition to making label changes, sponsors for three drugs developed new formulations that are easier to administer to children.

A few examples will help illustrate the new information derived from these studies.

- Ibuprofen: this commonly used drug to reduce fever had no dosing information for children under 2 years of age. Studies in thousands of infants established a safe and effective dose in infants and children from 6 months to 2 years.
- Ranitidine: studies in neonates provided accurate dosing information for safer and more effective use of this drug in the management of reflux of stomach contents—a life-threatening event in seriously ill neonates—and the label now says the drug can be prescribed to newborns and 1-month-olds.
- Fluvoxamine: studies with this drug, used to treat children with obsessive compulsive disorder, indicated that the dose in adolescents may need to be as high as in adults but may need to be lower for girls ages 8 to 11 years.
- Etodolac: study results allowed for indication on the label that the drug can be used to treat juvenile rheumatoid arthritis in children 6 to 16 years old.
- Midazolam: studies with this drug, used as a sedative, led to a new oral formulation for use in infants and children. In addition, the study results showed that this drug has a high risk for an adverse event in children with congenital heart disease and pulmonary hypertension.

Experts agree that, since FDAMA, there also has been significant growth in the infrastructure necessary to conduct pediatric studies. For example, NICHD has expanded the number of PPRUs from 7 to 13.[8] These units, located in children's hospitals and academic research centers specializing in pediatric research, have conducted an increasing number of pediatric drug studies. Prior to FDAMA, the PPRU Network had conducted 17 studies in collaboration with drug sponsors. By 2000, the PPRUs were

[8] NICHD provides full or partial funding for investigators and researchers, and pharmaceutical companies pay the clinical costs of individual pediatric studies.

conducting 73 pediatric drug studies in collaboration with drug sponsors. The pharmaceutical industry also has increased its capacity to conduct pediatric studies since enactment of FDAMA. According to a recent survey, contract research organizations, which conduct pediatric trials for drug sponsors, are working on over 100 pediatric studies involving 7,000 patients. [9] In addition, two of the largest contract research groups have established pediatric-specific research ventures, which collectively can call on the services of 500 doctors with pediatric training and nearly 2000 investigators.

While the new information generated by the increasing number of pediatric studies has resulted in a variety of benefits, the cost of granting additional market exclusivity can be very large. The cost to the public of providing the brand named drugs with an additional 6 months of market exclusivity presents a delay in consumer access to lower-cost generic drugs. Delaying access to lower cost generic drugs increases health care spending overall and may be particularly burdensome for those without prescription drug coverage that must pay for the drugs out-of-pocket. FDA estimates that the delay in availability of generic drugs could increase national drug spending by about one half of one percent, or on average about $695 million per year over a 20-year period.[10] The Agency did not attempt to develop a quantitative estimate of cost savings from improved health outcomes at this time.

Challenges for Label Changes and Off-Patent Research Remain

While the pediatric exclusivity provision is working better than previous efforts to stimulate pediatric drug research, two important challenges remain. First, the law does not ensure that research results are incorporated into labels in a timely manner for drugs that are already on the market once marketing extensions have been granted. Second, the law provides no incentive to conduct pediatric research on drugs for which patents and marketing exclusivity have expired.

The statute requires that FDA decide whether to grant the 6-month marketing exclusivity within 90 days of receiving research results. The decision must be based solely on whether the research meets the terms of

[9] *The Pediatric Studies Incentive: Equal Medicines for All*, Christopher-Paul Milne, Tufts Center for the Study of Drug Development, April 2001.

[10] *The Pediatric Exclusivity Provision, January 2001 Status Report to Congress*, Department of Health and Human Services U.S. Food and Drug Administration, pages 15 through 17.

the written request. The sponsor is required to submit proposed label changes with the study results, but the decision to grant the extension is not contingent on reaching agreement with FDA on label changes.

Because it usually takes much longer than 90 days — often a year— to evaluate study results and negotiate label changes with manufacturers, drugs may be granted an additional 6 months of marketing exclusivity before appropriate label changes have been determined. We found that it took on average more than 9 months for FDA and sponsors to agree on label changes for the 18 drugs granted exclusivity that have had label changes. This is slightly faster than FDA's goal of reviewing other, similar changes to approved drug labels within 10 to 12 months. FDA officials told us that five drugs have gone for more than a year without label changes after the sponsor was granted exclusivity extension. In some cases, FDA officials said they have had substantial difficulty in getting drug manufacturers to incorporate unfavorable pediatric research results into drug labels.

We found a difference of opinion on whether a marketing extension should be contingent on label changes. Some officials we interviewed suggested that drug manufacturers should be required to incorporate results into label changes within 1 year. Others have suggested that the 6-month marketing extension be contingent on agreement on label changes based on the pediatric study results. PhRMA officials told us that the current requirement provides their members with a degree of certainty that they will receive an additional 6-months exclusivity when they successfully complete the pediatric studies requested by FDA. They have suggested some policy changes to ensure that label changes are agreed to more quickly after pediatric studies are completed.

Another remaining challenge is obtaining research and label changes for drugs on which the patent or marketing exclusivity has expired. The pediatric exclusivity provision was not designed for off-patent drugs and provides no incentive for drug sponsors to conduct research on these products. According to FDA, patents have expired for many drugs that are widely used in children but lack pediatric information in their labeling. FDA's analysis of 1994 data found that 6 of the 10 drugs most commonly prescribed for children were off-patent. In addition, only 9 of the 180 off-patent drugs on FDA's May 2000 list of priority drugs for pediatric research have been issued written requests. Although NICHD has conducted some pediatric research on off-patent drugs, there is no mechanism to ensure that the findings are incorporated into drug labels. Currently, only a drug sponsor can apply for a label change. NIH officials told us they believe that

academic and NIH researchers should be allowed to assume the drug sponsor role to negotiate with FDA to incorporate research findings into labels for off-patent drugs.

Concluding Observations

The pediatric exclusivity provision has been successful in encouraging drug sponsors to generate needed information about how drugs work in children. A wide range of drugs are being studied in many therapeutic areas. The infrastructure for conducting pediatric trials also has been greatly strengthened, which should help to support continued progress. While a number of drug labels have been changed to incorporate findings from research conducted under the pediatric exclusivity provision, label changes typically occur long after FDA has granted the extension of market exclusivity. In addition, there continues to be little incentive to conduct pediatric research on off-patent drugs.

This concludes my prepared statement. I will be happy to answer any questions that you may have.

GAO Contact and Acknowledgements

For future contacts regarding this testimony, please call Janet Heinrich, Director, Health Care—Public Health Issues, at (202) 512-7119. Other individuals who made contributions to this statement include Paul Cotton, John Hansen, Claude Hayeck, Julian Klazkin, and Gloria Taylor.

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