Children, Drugs, and the Food and Drug Administration: Studies of Pediatric Drugs Are Beginning to Catch Up

Editor's Note: Although this topic applies to all drugs (not just dermatologic preparations), it is included in this issue because it is so important to the future of pediatric practice.

Studies of the effects of drugs on pediatric patients have proliferated since 1997. These studies have begun to correct a deficit (when compared with studies in adults) that developed after 1962. To appreciate the importance and magnitude of this recent change in attitude regarding drug studies in children, one needs to understand the history of such studies.

EARLY ATTEMPTS TO IMPROVE PEDIATRIC LABELING

The first legislation requiring that drugs be demonstrated effective was passed in 1962, as the Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act.[1] Six years later, Shirkey first described children as "therapeutic orphans" because they had been abandoned in studies of new drugs.[2] At that time, 80% of drug labels contained no information or incomplete information about pediatric dosing, indications, or effectiveness. Because the label reflects only the disorders and the patient population in which the drug was studied and approved by the Food and Drug Administration (FDA), pediatric patients were being left out.

Labeling of drugs for pediatric patients failed to improve, even after Shirkey identified the problem. For example, Wilson reviewed the 1973 *Physicians' Desk Reference* and found that 78% of drugs still included a disclaimer or lacked dosing information for children.[3] Similarly, in 1991 Gilman and Gal noted that 81% of the drugs in the *Physicians' Desk Reference* contained disclaimers or restricted use to certain pediatric age groups.[4] A review of new molecular entities, approved by the FDA each year from 1991 through 1997, showed that the percentage of new drugs with pediatric labeling actually decreased from 56% to 33%.[5,6] During this same interval, the American Academy of Pediatrics and the FDA both encouraged studies of new drugs in children "so they can enjoy equal access to existing as well as new therapeutic agents." However, this met with little or no success.[7]

In 1994, the FDA took a new step to facilitate the labeling of drugs for pediatric patients. In the 1994 Final Rule, the FDA asked pharmaceutical companies to evaluate (1) the extent of off-label use of their drugs for pediatric patients and (2) the available data regarding the use of the medications in the pediatric population. These could then be included in the "Pediatric Use" section of drug labels.[8] The FDA thus offered pharmaceutical companies the opportunity to label drugs for the "pediatric population" based on previously published, well-controlled investigations without requiring new studies. However, this applied only to a special situation. This shortened process could be used only if the course of the disease and the effects of the drug were sufficiently similar in adults and children to permit extrapolation of efficacy from adults to children, without conducting additional pediatric trials. If such extrapolation were possible, labeling to describe the use of the drug for pediatric patients would have to be supported

only with additional data for this population, such as dosing, pharmacokinetics, and safety information.

Unfortunately, the results from this Rule were disappointing.[5,6] From the thousands of drugs on the market, the FDA received 430 submissions for labeling changes, and only 65 of these provided for adequate labeling for all pediatric age groups. In fact, 330 (77%) of the changes were judged to provide no improvement in labeling.[6] Many of those changes simply added the disclaimer, "Safety and effectiveness of [this drug] has not been established in pediatric patients."

THE CARROT AND STICK APPROACH SEEMS TO BE WORKING

Real progress to increase the study of drugs in children began after the FDA Modernization Act of 1997 (FDAMA) was passed on November 21, 1997.[9] Section 111, the Pediatric Studies portion of this bipartisan legislation, provided a 6-month extension of market exclusivity in return for studies of drugs in children.[10] Implementation language for Section 111 of the FDAMA was published in June 1998, and interest in studying drugs in pediatric patients has continued to increase since then.[10]

Exclusivity prevents the submission or approval of an application and the marketing of an identical product for a period of time that varies.[11] Three types exist: Hatch–Waxman (5 years for a new molecular entity, 3 years for a new use), 7 years for an Orphan Drug, and 6 months for Pediatric Exclusivity. The exclusivity in the FDAMA for pediatric studies must be attached to a preexisting market exclusivity or patent, so it does not apply to generic drugs whose patents have expired. Under the FDAMA, the extension of market exclusivity applies not to the indication, but to the active drug moiety and all products containing it if they each still have exclusivity.

The process of qualifying for an extension through the FDAMA begins with a Written Request by the FDA for studies. This Written Request can originate solely from the FDA, or follow a proposal by the manufacturer to study a particular drug in pediatric patients. It outlines (1) what types of studies are needed to fill gaps in current knowledge about the drug in pediatric patients (eg, safety, kinetics, efficacy), (2) the number of subjects to be studied, and (3) the time for completion of the studies. To qualify for an extension of market protection, the studies must be completed before the drug loses its market exclusivity, and the studies must fully address the Written Request. Although the FDAMA stipulates that all candidates must also be on a list of drugs "for which additional information may produce health benefits in the pediatric population," the list is not closed. Manufacturers may request the addition of a drug to that list. If the FDA agrees that studies are likely to provide health benefits, the drug can be added.

A 6-month extension of market exclusivity may not seem significant to those not familiar with the magnitude of drug sales. For a drug that leads in sales, such as omeprazole, 6 months of sales amounts to more than $2 billion.[12] Sales will be more than $500 million during 6 months for each of the 18 best-selling drugs in the United States. Manufacturers' shift of resources to study drugs in pediatric patients attests to the effectiveness of this reward. This allows drugs for children to compete more effectively with those for adults for research funding within individual companies. As of December 1, 2000, 26 active moieties had been granted this exclusivity (Table 1).[13] More active moieties should qualify from the 170 Written Requests issued by the FDA by December 1, 2000 (Table 2).

This opportunity for financial reward is not open ended, at least at this time. The Pediatric Studies section of the FDAMA expires on January 1, 2002, unless renewed by Congress during 2001 when a formal review of its effects is required. Design and completion of studies frequently takes a minimum of 1½ to 2 years, so some companies are rushing to complete studies to qualify for this financial reward.

Part of our responsibility as caregivers for pediatric patients involves ensuring that these studies are appropriately designed, safe, and likely to answer their primary aims. The FDAMA is providing a strong impetus for developing the evidence needed to provide more rational drug therapy for the pediatric population (Table 2). The start is strong, but many more investigations

must be completed to overcome the deficit of pharmacologic studies in pediatrics.

This FDAMA reward or "carrot" approach has been complemented recently by "the stick," a requirement enacted in December 1998 as the 1998 Final Rule.[5] It differs from the FDAMA in several important features (Table 3). Under this regulation, studies of new drugs may be required if (1) they provide a significant therapeutic benefit over existing labeled therapies for the pediatric population, (2) the absence of labeling could pose a risk to pediatric patients, or (3) they are indicated in a condition for which few other products are labeled for pediatric use. As with the 1994 Final Rule, if a disease in children is similar to a disease in adults and the effectiveness of the medication has been demonstrated in adults, the effectiveness may not have to be restudied in the pediatric population. If the medication is needed for the treatment of children, the FDA may require a *new* formulation by the 1998 Final Rule. This is potentially a significant gain for children because it could reduce "customized" liquid formula-

TABLE 1

Active Moieties That Had Been Granted Exclusivity as of December 1, 2000[13]

Abacavir*	Insulin glargine*
Ammonium lactate*	Lamivudine
Azelastine*	Loratidine
Bisoprolol	Metformin
Buspirone	Midazolam*
Cromolyn*	Oxaprozin
Enalapril	Pemirolast*
Etodolac*	Propofol
Famotidine	Ranitidine*
Fluoxetine	Remifentanil
Fluvoxamine	Sevoflurane
Gabapentin	Sotalol
Ibuprofen*	Tramadol

**Labeling changes as of September 1, 2000.*

TABLE 2

Pediatric Exclusivity Statistics as of December 1, 2000[14]

Review Division	Proposed Pediatric Study Requests Received	Written Requests Issued
Cardio-renal drug products	28	24
Neuropharmacologic drug products	28	18
Oncology drug products	10	10
Medical imaging and radiopharmaceutical drug products	0	0
Anesthetic, critical care, and addiction drug products	15	10
Gastrointestinal and coagulation products	15	6
Metabolic and endocrine drug products	27	16
Anti-infective drug products	3	2
Anti-viral drug products	20	20
Dermatologic and dental drug products	14	8
Anti-inflammatory, analgesic, and ophthalmologic drug products	22	36
Over-the-counter drug products	5	3
Pulmonary drug products	13	10
Reproductive and endocrine drug products	1	1
Special pathogen and immunologic drug products	10	6
Total	211	170

TABLE 3

Comparison of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the 1998 Final Rule to Require Manufacturers to Study Drugs in the Pediatric Population

Features	FDAMA	1998 Final Rule
Participation	Voluntary	Mandatory
Studies needed if	Additional information may produce health benefits in the pediatric population	Medication is likely to provide a meaningful therapeutic benefit over existing treatments and is likely to be used in a substantial number of pediatric patients
Extent of studies	Studies requested for age ranges with gaps in knowledge, even about off-label uses	Studies required for children of all ages likely to use the medication, but only for the requested indication
Reward	6-month extension of market exclusivity if studies respond to the Written Request	None
Duration	Scheduled to end 1/1/02	Indefinite

Data from references 5 and 10.

tions whose stability and bioavailability may not have been studied. Studies will not be required, however, if waivers have been granted on the grounds that the drug will not be used in children, it is not an improvement over current therapy for children, a formulation cannot be developed after good faith efforts, or there are too few children afflicted with the disorder to permit a practical study.

Some physicians have opposed this stick requiring that drugs be studied in children as unnecessary regulation of industry. Miller, who previously worked at the FDA, argued that physicians routinely and effectively extrapolate dosages from adults to children and they can continue doing this.[15] Rather than requiring studies, he recommended publishing a list of drugs without adequate pediatric prescribing information and appealing to drug companies, through moral and economic pressures, to obtain these data. This author believes that most pediatricians recognize the errors in such suggestions. Dosage extrapolations without pharmacokinetic studies, especially for rapidly developing newborns and young children, are simply inaccurate and often lead to overdosage or underdosage. Because efforts by the FDA to obtain voluntary labeling by companies through the 1994 Final Rule failed, it remains unlikely that companies will respond to new moral inducements to study drugs in children. It is possible that we, as pediatricians, will reach a point where we can choose to prescribe mostly labeled drugs for our patients and avoid drugs without a label. If supported by parents and pediatricians, such prescribing practices might provide both positive and negative financial incentives to manufacturers. This would stimulate pediatric investigations and additional labeling of medicines more effectively than would moral inducements.

What is the big deal about labeling drugs for children? Pediatricians have lived without this for most drugs since labeling of efficacy began in 1962.[1] Most physicians understand that off-label drug therapy for pediatric patients is neither unethical nor illegal, and that they, not the FDA, determine how to use a drug in treating a specific patient.[1,16] In fact, providing the most current treatment may require off-label use of a drug because label changes generally follow, rather than precede, innovations in therapy.

Without labeling, however, we may have to treat pediatric patients based on studies that are smaller than those required for labeling and less well controlled. In some situations, studies do not exist for the population being managed, especially when treating newborns. In such instances, physicians may have to rely on their own experience or that of their peers in using medications. Studies required by the FDA for labeling are careful, well-powered investigations that thoroughly evaluate dosage, effec-

tiveness, and adverse effects. Large, randomized, controlled studies have guided the treatment of many disorders in adults, but have seldom been available to guide the treatment of children.

Once a drug is labeled for the pediatric population, that information is available through the package insert and the *Physicians' Desk Reference* to all physicians who care for children. Labeling implies that the scientific basis for use of that drug in children is substantial. Recent labeling changes under the FDAMA have yielded examples of previous dosing guidelines leading to excessive and inadequate dosing in specific pediatric populations. Pediatric patients deserve better. Ideally, the first pediatric patient treated with each newly approved drug will receive that treatment guided by prospective, controlled trials in a similar pediatric population.

PROTECTING CHILDREN IN MEDICATION STUDIES

It is important for all pediatricians to participate in the study of drugs in pediatric patients. This participation, however, should be guided by sound, clinical judgment about the study design. The most effective protection of our pediatric patients occurs with clinical judgment and review by a conscientious institutional review board that balances the need to know more about the effects and effectiveness of drugs in children against the risks to those children from their participation. Academic institutions that receive federal funding must have special reviews of their institutional review boards through the Office of Human Research Protection at the National Institutes of Health. Freestanding, independent, contract institutional review boards do not have the same requirements at this time. The Health and Human Subjects regulations protecting vulnerable subjects in clinical trials, such as pediatric populations,[17] are more extensive than those of the FDA. However, the FDA is following the recommendations of its Pediatric Advisory Subcommittee from 1999 to include comparable safeguards for children in its regulations.[18]

CONCLUSION

Since the enactment of the FDAMA, more pediatric studies of drugs have been initiated than in the previous several decades. The dramatic response by drug manufacturers to the incentive of extended market exclusivity illustrates the power of the economic system in the United States. Although some observers suggest that such a reward should not be needed for studying drugs in pediatric patients, history does not support them. The 1998 Final Rule should continue to provide knowledge of new drugs in pediatric patients, but this encompasses a small proportion of pediatric therapeutics. Although it is too early to know how effective the 1998 Final Rule will be, the most successful opportunity for continuing the study of drugs in pediatric patients will likely rest with an incentive system that operates through renewal of exclusivity.

REFERENCES

1. Drug Amendments of 1962. Part A-Amendments to assure safety, effectiveness, and reliability. Pub L No. 87-781: sections 101-308.
2. Shirkey H. Therapeutic orphans. *J Pediatr.* 1968;72:119-120.
3. Wilson JT. Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women. In: Morselli PL, Garattini S, Sereni F, eds. *Basic and Therapeutic Aspects of Perinatal Pharmacology.* New York: Raven Press; 1975:411-421.
4. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates: a quiet frontier. *Clin Pharmacokinet.* 1992;23:1-9.
5. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients: final rule. *Fed Regist.* 1998;63:66631-66672.
6. Murphy D. 1999 pediatric initiatives. Presented at the 35th Annual Meeting of the Drug Information Association; July 1999; Baltimore, MD.
7. American Academy of Pediatrics Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics.* 1995;95:286-294.
8. 21 CFR §201.57. Specific requirements on content and format of labeling for human prescription drugs: revision of "Pediatric Use" subsection in the labeling: final rule. *Fed Regist.* 1994;59:64240-64250.
9. Food and Drug Administration Modernization Act of 1997. Pub L No. 105-115 (1997 Nov 21); 111 Stat 2296. Available at: www.fda.gov/cder/guidance/105-115.htm.
10. Pediatric Studies of Drugs. Food and Drug Administration Modernization Act of 1997. Pub L No. 105-115 (1997 Nov 21); 111 Stat 2296. Available at: www.fda.gov/cder/guidance/105-115.htm#sec.111.
11. Cusumano L. Exclusivity: pediatrics and 505(b)(2)s. Presented at the Food & Drug Law Institute Annual Education Conference; December 16-17, 1999; Washington, DC.
12. Latner AW. The top 200 drugs of 1999: the more things change, the more they stay the same. *Pharmacy Times.* April 2000;66(4):16-32. Available at: www.pharmacytimes.com/top200a.html.

13. Approved active moieties to which FDA has granted exclusivity for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act. Available at: www.fda.gov/cder/pediatric/exgrant.htm.
14. Pediatric exclusivity statistics as of December 1, 2000. Available at: www.fda.gov/cder/pediatric/wrstats.htm.
15. Miller HI. Kids and FDA drug trials? Not a good idea. *Baltimore Sun.* December 21, 1998:17A.
16. American Academy of Pediatrics Committee on Drugs. Behavioral and cognitive effects of anticonvulsant therapy. *Pediatrics.* 1985;76:644-647.
17. Federal Policy for the Protection of Human Subjects. Subpart D–Additional DHHS protections for children involved as subjects in research. 45 CFR 46.401-46.409 (1999).
18. FDA Ethics Working Group consensus statement on the Pediatric Advisory Subcommittee's November 15, 1999 meeting. Available at: www.fda.gov/cder/pediatric/ethics-statement.htm.

Robert M. Ward, MD, FAAP, FCP
Professor of Pediatrics
Department of Pediatrics
University of Utah Hospital
Salt Lake City, Utah

CALENDAR

April 25, 2001: Clinical Implications for Breastfeeding Practice: Current Thinking in Nutrition and Distressed Infant Behavior. To be held in Long Island, New York. For more information, contact Carol Kolar, 1400 North Meacham Road, Schaumburg, IL 60173; telephone: (847) 519-7730, ext. 223; e-mail: ckolar@llli.org; website: www.lalecheleague.org.

April 28, 2001: Sports Medicine for the Active and Athletic Child. To be held at Weill Medical College and the Hospital for Special Surgery, New York, New York. For more information, contact Christina Chan, Program Coordinator; telephone: (212) 606-1057; fax: (212) 734-3833; e-mail: education@hss.edu.

July 5-7, 2001: Breastfeeding for Health: Looking to the Future, Mindful of the Past. To be held at the Hilton Chicago, Chicago, Illinois. For more information, contact Carol Kolar, 1400 North Meacham Road, Schaumburg, IL 60173; telephone: (847) 519-7730, ext. 223; e-mail: ckolar@llli.org; website: www.lalecheleague.org.

July 23-25, 2001: Advances in Perinatal and Pediatric Nutrition. To be held at Stanford University Medical Center, Stanford, California. For more information, contact Symposia Medicus, 399 Taylor Blvd., Suite 201, Pleasant Hill, CA 94523-2200; telephone: (800) 327-3161; fax: (925) 969-1795; website: www.symposiamedicus.org.

August 6-10, 2001: Adolescent Health Care. To be held in Jackson Hole, Wyoming. For more information, contact Contemporary Forums, Dept. 703, 11900 Silvergate Drive, Dublin, CA 94568; telephone: (925) 828-7100, ext. 0; fax: (925) 828-2121; e-mail: info@cforums.com; website: www.cforums.com.

September 6-7, 2001: Utah Chapter of the National Association of Pediatric Nurse Associates and Practitioners Fifth Annual Pediatric Pharmacology Conference. To be held at the Yarrow Hotel, Park City, Utah. For more information, contact Paula McGibbon; telephone: (801) 265-2002; e-mail: paulamcgibbon@msn.com.

September 26-29, 2001: Clinical Issues in Pediatrics. To be held in San Antonio, Texas. For more information, contact Contemporary Forums, Dept. 972, 11900 Silvergate Drive, Dublin, CA 94568; telephone: (925) 828-7100, ext. 0; fax: (925) 828-2121; e-mail: info@cforums.com; website: www.cforums.com.