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The FDA Modernization Act of 1997: Impact on Pediatric Medicine

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Fewer than one quarter of all drugs approved by the Food and Drug Administration (FDA) are given an indication for use in children. Despite this, nearly all drugs currently marketed in the United States have been used in patients less than 18 years of age. In the past, the limited marketability and small size of the pediatric patient population have resulted in minimal support for research in pediatric pharmacology. Therapeutic regimens were often based on individual case reports, case series, and small-scale studies found in medical journals or, more frequently, the past experiences of an individual clinician. This is now beginning to change, in large part because of the recent attention given to pediatric patients by the FDA.¹⁻³

The FDA has long recognized the limitations of its current approval system for new drugs. The 1938 Food, Drug, and Cosmetic Act that provided for the development of the FDA stipulated that drugs be proven safe for the use intended by the manufacturer. The 1962 Harris-Kefauver Amendment required the additional proof of effectiveness and initiated the sequence of pre-marketing clinical trials for new drugs that is still in place today. Special populations like pregnant women, children, and the elderly typically were excluded from participation in the clinical trials that made up the supporting evidence submitted to the FDA, and as a result were not included in the approved uses for most drugs. Pediatric health care providers were forced to use most drugs off-label, which although legal, meant that no pediatric-specific dosing, administration, or adverse effect information was available on the label packaging, or in any product information available from the manufacturer.^{4,5}

In October 1992, the FDA took the first steps toward improving the amount of pediatric information available on drug labeling as part of their ruling entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Revision of 'Pediatric use' Subsection in the Labeling." These new regulations were designed to promote the inclusion of both information gained from new clinical trials as well as previously published studies and case reports in children in an effort to provide basic dosing and monitoring information. Pharmacokinetic and pharmacodynamic studies were highlighted as being particularly valuable.

As a result of these regulations and support from the National Institutes of Health, a network of pediatric pharmacology research units (PPRUs) were developed in 1993 to conduct studies in children and serve as a resource and model for other investigators. Many of the PPRUs are based in university teaching hospitals with well established research programs. To date, the PPRUs have provided research data on more than two dozen drugs commonly used in pediatrics.⁶

Further progress was made in December 1994 when the FDA announced plans to mandate labeling information on pediatric use for all pertinent new drug applications. This ruling also required manufacturers to submit supplemental pediatric dosing information on their products to the FDA by December 1996. Manufacturers were required to examine both their new and existing products to determine if there was adequate cause to modify their pediatric sections; in other words, to determine whether their products might be of use in the pediatric population. If applicable, the manufacturers were to provide labeling information on dosing, administration, and adverse effects in children.

The 1994 ruling also established a pediatric subcommittee of FDA staff to oversee implementation of the regulations and provide guidance on compliance. Manufacturers whose products were clearly not of benefit to children or where pediatric dosage formulations were not feasible could apply for waivers exempting them from the requirements.

As anticipated, this ruling generated considerable concern on the part of manufacturers who saw this as a potential roadblock to drug approval for adults patients and an additional expense. The FDA took a stronger stance with the enactment of the Modernization Act on November 21, 1997. The Modernization Act was the first major amendment of the Food, Drug, and Cosmetic Act and was designed to incorporate changes for the 21st century, including advances in technology and trade practices, as well as changing public health concerns. The Act covers many different aspects of the drug approval process, such as fast track policies, industry guidance, and post-marketing studies, but one of the most significant changes has been the tightening of regulations relating to pediatrics.^{7,8}

In an effort to prompt manufacturers to comply with earlier regulations, the Modernization Act required the FDA to specify which drugs should be required to carry pediatric labeling. The list was meant to focus on those products widely used in the pediatric population and where absence of labeling information might lead to serious misuse. In March 1998, a threshold of 50,000 pediatric prescriptions per year was set for identifying which drugs would be required to have pediatric labeling. Using this threshold, over 300 prescription drugs were identified for labeling changes. An initial list of drugs was published by the FDA on May 20, 1998. Some examples of drugs which met this threshold that did not previously carry a pediatric indication include albuterol inhalation solution, ampicillin for intravenous use, fluoxetine, and methylphenidate in children under 6 years of age.^{1,9,10}

The list of drugs for which the FDA is requesting pediatric-specific dosing information, often referred to as the Pediatric Priority List, has been updated annually to incorporate new drug entities and remove drugs which now carry pediatric labeling. The last update was published on May 19, 2000 and is available on the Internet.¹¹ Members of the public may request that other

drugs of value in the treatment of children be considered for addition to the list. Petitions may be made to the FDA at any time.

In addition to publication of the Pediatric Priority List, the FDA may issue written requests to individual manufacturers for pediatric labeling information, requesting voluntary participation. For information considered to be highly valuable, the 1997 and 1998 pediatric rulings also allow the FDA to mandate industry participation if needed. The FDA is currently considering issuing written requests and/or mandates for manufacturers producing drugs used to manage conduct disorder, panic disorder, and schizophrenia in children and adolescents, as well as attention deficit/hyperactivity disorder in children under 6 years of age. Pediatric information has already been received from manufacturers of drugs used to treat post-traumatic stress disorder, mania, social anxiety, and adolescent premenstrual dysphoric disorder.¹²

In return for their compliance with the new pediatric labeling requirements, the Modernization Act permits the FDA to award an additional 6 month period of exclusivity rights to manufacturers. This prolongation of the patent provides the manufacturer with a longer period as sole supplier, before any generic products can be produced. The exclusivity rights pertain only to the product given the pediatric labeling. Some manufacturers have supported a revision to allow "wild card" exclusivity, in which the manufacturer successfully submitting pediatric data for one product could choose among any of its patents to apply the additional 6 months exclusivity. This revision was suggested as a means of encouraging manufacturers to comply with the regulations, but has not been adopted by the FDA.¹³

The complete Modernization Act became effective on April 1, 1999.¹⁴⁻¹⁷ The final ruling was published in the Federal Register and is available on the Internet.^{14,15} There is still work to be done to identify and minimize barriers to conducting research in pediatric patients who might benefit from new drug therapies. A document to provide pharmaceutical manufacturers with guidance on these regulations was published in 1998 and revised in 1999.¹⁸ In addition, the Pediatric Advisory Subcommittee of the FDA is continuing to address the specifics of how the requirements mandated by the final ruling are to be applied and monitored.¹⁹

While this regulatory process has followed a rather tortuous course over the past decade, the final result promises to be very beneficial to pediatric patients as well as health care providers. One recent example of the benefit of this process has been the changes in the labeling of lamotrigine. Initially approved by the FDA only for use in adults, lamotrigine was soon recognized to be of significant benefit as an adjunctive therapy in children with complex seizure disorders such as Lennox-Gastaut syndrome. While clinical trials in adults documented only rare reports of serious dermatologic reactions to lamotrigine, post-marketing surveillance soon revealed a much higher incidence of these adverse reactions in children.

While lamotrigine may cause Stevens-Johnson syndrome or toxic epidermal necrolysis in only one in every thousand adults, these reactions may occur in as many as one in every 50 to 100 children exposed to the drug. Despite the approval of lamotrigine only for adults, there was a need to provide information about the risks involved in treating children. The FDA responded by requiring a "black box" warning on the labeling for lamotrigine describing the serious dermatologic reactions that may occur with its use and highlighting the higher incidence of these reactions in children and the recommendation for slow dose titration.²⁰ This labeling change was possible because the restriction on mentioning off-label indications in product labeling was removed under the Modernization Act.²¹

The ability to call attention to an off-label use, previously not allowed in product labeling, is just one example of how pediatric information can be made more readily available to health care providers as a result of these regulatory changes.

The recognition of the rights of children to have access to safe and effective drugs and the needs of health care providers to have access to age-appropriate drug information is likely to have a major effect on pediatric biomedical research. The support of the FDA in mandating pediatric labeling will play an important role in providing the motivation to manufacturers to work with the PPRUs, as well as clinicians and researchers in other academic settings, 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 United States.

A report on the success of the new pediatric labeling mandates is due to Congress on January 1, 2001.⁸ It is hoped that these changes will usher in a new age in pediatric health care, where access to information on drug dosing and adverse effects will be as readily accessible for children as it has traditionally been for adults.

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Government Agency Updates

Pregnancy/Lactation Labeling Changes

The FDA is currently evaluating a plan to change requirements for drug labeling concerning pregnancy and lactation. Health care providers have lobbied for more information on product labeling, reflecting the data available in the medical literature. It is anticipated that an expedited review process will be used for this information, making it likely that changes will start to appear on drug labeling within the next year.

Oseltamivir Approved for Children

Oseltamivir (Tamiflu[®]) has recently been approved by the FDA for use in children 1 year of age and older. This agent, a neuraminidase inhibitor, is indicated for the treatment of influenza in patients who have been symptomatic for less than 48 hours. An oral liquid dosage formulation is expected to be released next month.

Rotavirus Compensation Proposed

By 2001, it is expected that the Vaccine Injury Compensation Program will be extended to include costs incurred in the management of children with intussusception associated with rotavirus vaccine use. A bill to amend the law governing the compensation program has passed both the House and Senate. The rotavirus vaccine was withdrawn from the market in 1999.

Pharmacology Literature Review

Developmental changes in warfarin kinetics

In this study, the effects of growth and developmental changes on warfarin pharmacokinetics and pharmacodynamics were evaluated. Drug concentrations, vitamin K-dependent proteins, and INR values were measured in 38 prepubertal children, 15 pubertal children (up to 18 years of age), and 81 adults. Clearance of the more potent S-warfarin enantiomer was significantly greater in the youngest patient group. The prepubertal group was also found to have lower plasma concentrations of protein C and prothrombin fragments, as well as an increased INR compared to the other groups. The pubertal patients

responded similarly to the adults. The authors suggest that, despite the more rapid clearance, standard doses of warfarin may produce an augmented response in children 1-11 years of age. Takahashi H, Ishikawa S, Nomoto S, et al. Developmental changes in pharmacokinetics and pharmacodynamics of warfarin enantiomers in Japanese children. Clin Pharmacol Ther 2000;68:541-55.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their combined November/December meeting on 12/15/00:

1. Rabbit anti-thymocyte globulin (Thymoglobulin[®]) was added to the Formulary.
2. The following actions were taken upon recommendation of the Antimicrobial Utilization Committee:
 - a. The fluoroquinolones were reviewed. Gatifloxacin (Tequin[®]) was added to the Formulary and levofloxacin (Levaquin[®]) was removed.
 - b. The combination lopinavir/ritonavir (Kaletra[®]) was added to the Formulary for the management of patients with HIV infection.
 - c. The combination atovaquone/proguanil (Malarone[®]) was added to the Formulary for the prevention or treatment of malaria in children and adults.
 - d. The neuraminidase inhibitors, zanamivir and oseltamivir, will be retained on the Formulary through the current flu season. This class will be reviewed again during the next year.

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