

# American Academy of Pediatrics



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June 5, 2000

Dockets Management Branch (HFA-305)  
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Dear Sir/Madam:

The American Academy of Pediatrics is pleased to provide comments on the pediatric studies program established by the Food and Drug Administration Modernization Act of 1997 (FDAMA). The AAP would like to begin comments by commending Congress and the Food and Drug Administration (FDA) for their continued commitment to children's health. The pediatric exclusivity program is the most successful program the FDA has developed to generate studies of medications in children, and the AAP will actively work with Congress to reauthorize this program prior to its expiration in 2002.

The Academy believes that the pediatric studies provision in FDAMA has advanced therapeutics for infants, children and adolescents in a way that has not been possible in several decades prior to passage of this law. Despite several efforts by the Food and Drug Administration over the past 30 years to secure more studies to support more complete usage information for children, the alarming lack of pediatric drug labeling and information available to pediatricians and other health professionals continued. Statistics as recent as 1998 highlight the need for pediatric drug studies. Of the 30 new drugs approved by the FDA that year, only six or 20 percent had been studied and labeled for pediatric use.

The need to study drugs in pediatric populations is most recently illustrated in a 1999 case in Knoxville, Tennessee. Seven cases of infantile hypertrophic pyloric stenosis (IHPS) in neonates occurred as a result of prescribing oral erythromycin to neonates who had been exposed to pertussis. Although oral erythromycin is commonly used in newborns to treat pertussis, it is not labeled for newborn use. As a result of this lack of study upon which to base pediatric prescribing information for neonates seven newborns, roughly five percent of the group treated with erythromycin in Knoxville, required surgical treatment for IHPS.

The AAP offers the following perspective related to the effectiveness, impact and modifications for the pediatric studies provision:

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## **The effectiveness of the program in improving information about important pediatric uses for approved drugs**

While the FDAMA legislation was signed into law on November 21, 1997, implementation of the pediatric studies provision could not begin until the FDA had, at the request of Congress, consulted with the AAP, the US Pharmacopeia and the Pediatric Pharmacology Research Unit Network to develop a priority list of drugs needing additional pediatric information. FDA moved expeditiously to compile the list, which was first issued in May 1998. In June 1998, FDA published guidance to the industry providing detailed information on how to participate in the process of securing market exclusivity in return for conducting pediatric drug studies. That same month the FDA issued the first written request for pediatric drug studies to a pharmaceutical company.

With the pediatric studies provision actively in place for only two full years, it is premature to assess its full impact. But it is abundantly clear that it is already providing important advances for pediatric therapeutics. To date, seven label changes have been completed as a result of the pediatric studies provision. As of May 2000, the FDA has issued 145 written requests to pharmaceutical companies asking for over 298 pediatric studies. This is an extraordinary success rate by most standards.

The AAP recognizes that it often takes 12-18 months after completion of a study to use the findings to change drug labels, so the Academy is pleased with this initial progress. The positive impact of this provision will continue to expand as more written requests are issued by the FDA, more studies are completed by the pharmaceutical industry, and the process of securing more and better labeling information is finalized.

In assessing the effectiveness of the pediatric studies provision, it is important to note that designing study protocols, enlisting investigators and enrolling subjects requires significant lead time, as well as staff resources. The Food and Drug Administration has made tremendous strides, with limited resources, to implement this provision fairly and in a timely manner. While we are anxious to increase the momentum that has been built over the last two years, the AAP believes the FDA has acted swiftly and judiciously in its efforts to improve the therapeutic status of children.

## **The adequacy of the pediatric exclusivity incentive**

It appears that the incentive is sufficient. In the seven years prior to the passage of this provision the FDA reported it was promised 70 pediatric studies but only 11 studies were completed. In the two years since the passage of FDAMA, the pharmaceutical industry has initiated 177 proposals for written requests to do pediatric studies and 145 written requests have been issued by FDA.

Over 50 pharmaceutical companies are currently participating in this program. The AAP believes that this is an indication that the six-month extension of market exclusivity provided for companies to conduct pediatric drug studies is an ample incentive.

## **The economic impact of the pediatric exclusivity program on taxpayers and consumers and the impact of the lack of lower cost generic drugs on patients, including on lower income patients**

While it is necessary to assess the economic impact of this pediatric exclusivity program on the taxpayer, without a doubt, the greatest impact of this program will be on non-taxpayers – the infants and children of this nation.

Dollars and cents arguments can not adequately provide the evidence of the effectiveness and importance of this program for children. Nor can these arguments take into consideration the untenable position which pediatricians and other health professionals are placed in to either prescribe a drug without sufficient information or withhold treatment that may provide the best treatment for a child who is more vulnerable than adult. While off-label use of medications is a legal and acceptable part of medical practice by physicians, it should not be the standard. Unfortunately for children, off-label use is the primary therapeutic option for care.

Data are difficult, if not impossible, to find that provides evidence of the cost to a state or the federal government if a child is temporarily or permanently injured because of an adverse effect of a medication used without benefit of proper study and labeling for their age. Equally as impossible to determine is the cost society has already assumed for less than optimal care for children because medicines were not available for them. In addition, the expense of lawsuits related to such occurrences are a financial consideration. In an attempt to assess the economic impact, the AAP offers the following observations:

Better labeling will reduce medical errors and adverse effects. Included in most medical and surgical treatment of pediatric patients in the hospital is the administration of medications that may be associated with undesirable effects as well as the therapeutic effects. Adverse reactions to medications include those that are usually unpredictable, such as idiosyncratic or allergic responses, and those that are predictable and thus potentially avoidable, such as side effects or toxic reactions that are related to the inherent pharmacologic properties of the drug.

In contrast to adverse drug reactions are medication errors, which are defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use.” *United States Pharmacopeia. The Standard. November/December 1995:10*

Lack of proper information for pediatric patients related to dosing, toxicity, adverse effects, drug interactions, etc. can lead to medical errors and potential injury. Medication errors produce a variety of problems, ranging from minor discomfort to substantial morbidity that may prolong hospitalization or lead to death.<sup>i ii iii</sup> Drug errors associated with morbidity and mortality increase health care costs by an estimated \$1900 per patient.<sup>iv</sup> The emotional, physical, and

financial costs to the child, family, and public and private health and social programs can be astronomical.

Better labeling will provide millions of children access to better therapeutics. While the prescribing frequency for all the 24 drugs which the FDA has granted exclusivity to under the pediatric studies provision of FDAMA is not available, it can be assumed that millions of children will benefit from properly studied and labeled drugs.

Several examples of drugs receiving market exclusivity under FDAMA are provided below\*:

<u>Product</u>	<u>Label Statement</u>	<u>Off-Label Prescribing Frequency</u>
Beclomethasone Dipropionate	Safety and Efficacy (S&E) in children below the age of 6 have not been established	174,000 to children <6
Cromolyn Sodium	For inhalation solution, S&E Below age 2 have not been Established. For inhalation Aerosol solution, S&E have Not been established below Age 5	109,000 to to infants <2 399,000 to children <5
Fluvoxatine	S&E in children have not Been established	349,000 to children <16
Sertraline	S&E have not been Established in children	248,000 to children <16

\* The Pike, January 17, 1997 (Data published with permission, IMS America, Ltd., 1994)

Economic incentives provided to industry raises the amount of R&D budgets and translates to better information for all populations (specifically, children) It is estimated that the average cost of developing one new drug is \$300 million to \$600 million (Mathieu MP, ed. Parexel's pharmaceutical R&D statistical sourcebook 1998. Waltham, Mass.: Parexel International Corporation, 1999). Providing incentives can be expected to increase the amount of funds a pharmaceutical company would dedicate to research and development.

### **Suggestions for modification**

The AAP clearly and strongly believes that the pediatric studies provision should be retained and reauthorized by Congress in the coming years. The success seen at this early stage of implementation are merely the beginning of a momentum that is building and will continue to advance therapeutics for children.

- The AAP urges Congress to provide appropriate funding for additional FDA staff that will be required to review and approve the increasing number of pediatric studies which will be generated as a result of FDAMA to maintain the progress that has been made in these first 2 years.
- Congress might consider instating prescription drug user fees for companies seeking pediatric exclusivity. The AAP believes this may increase the number of pediatric studies requested, shorten the review time of such studies and reduce the time needed to secure pediatric information on drug labels.
- The AAP urges FDA and Congress to seek avenues for getting off-patent drugs tested and labeled for infants, children and adolescents. This is a large and very important group of drugs with extremely limited pediatric labeling. FDAMA's pediatric studies provision does not address drugs whose market exclusivity has expired (the so-called "off-patent" drugs.) Currently, there is little incentive for companies to conduct pediatric studies. AAP would like to explore avenues for getting these off-patent drugs studied in pediatric populations.
- Congress should explore connecting the market exclusivity incentive to actual label changes. Labeling information is a critical component toward ensuring that children have the same access, safety and effectiveness to therapeutic drugs as do adults. Currently, a company is granted market exclusivity then the process of changing the label to reflect new information begins. As stated earlier, this process can take as long as 12-18 months. Meanwhile, important information achieved from the pediatric studies that can assist pediatricians in providing therapies to children is unavailable.
- FDA should explore ways to disseminate information generated by pediatric studies. Pediatric studies conducted under the pediatric studies program are likely to provide much useful information that may not result in label changes. For example, information about lack of effectiveness for treatment of children is important for providing optimal healthcare. A possibility is for FDA to expand the label to include important information that is broader than the categories of information currently on the label (e.g., dosing, adverse effects, etc.)
- Congress should explore a varied level incentive program based on need for information to improve prescribing safety and effectiveness for physicians. Financial incentives clearly work to generate studies of drugs in children. Currently, the strongest incentives are for drugs with greatest profits. However, drugs with the greatest profit are not necessarily those of greatest need for study as judged by pediatricians and other health care professionals who care for children.
- Antibiotics should be included as part of the pediatric studies program.

Thank you for your consideration of these suggestions.

Sincerely,



Donald E. Cook, MD, FAAP  
President

\*These comments are also endorsed by the American Pediatric Society, the Society for Pediatric Research and the Association of Medical School Pediatric Department Chairs.

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<sup>i</sup> Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA*. 1995;274:29-34

<sup>ii</sup> McKenzie MW, Stewart RF, Weiss CF, Cluff LE. A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. *Am J Hosp Pharm*. 1973;30:898-903

<sup>iii</sup> Evans, RD, Classen DC, Stevens LE, et al. Using a hospital information system to assess the effects of adverse drug events. *Proc Annu Symp Comput Appl Med Care*. 1993;17:161-165

<sup>iv</sup> Physicians Insurers Association of America. *Medication Error Study*. Washington, DC: Physician Insurers Association of America; 1993