

# American Academy of Pediatrics



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June 5, 1998

Michael A. Friedman, MD  
Lead Deputy Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Room 14-71  
Rockville, MD 20857

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Dear Lead Deputy Commissioner Friedman:

The American Academy of Pediatrics (AAP) was pleased to assist the Food and Drug Administration in its efforts to develop a list of drugs for which additional pediatric information may produce health benefits in the pediatric population.

The AAP applauds several components of the list released on May 20. In issuing the final list, FDA formally embraced a critical concept long-sought by the AAP -- that any drug approved in adults for an indication that occurs in the pediatric population may have the potential for offering a health benefit to the pediatric population and therefore is considered to be on the list.

In addition, the FDA states that studies in support of an application for approval of a use that is currently not approved in adults may be eligible for exclusivity under the pediatric studies provision of the Food and Drug Modernization and Accountability Act of 1997 (FDAMA). This is seen as a critical component of written requests that the Secretary makes to pharmaceutical companies.

It is important to acknowledge, however, that the criteria for inclusion of drugs on the priority list remains troubling. A measure of 50,000 prescription mentions per year may exclude children with serious but infrequent diseases such as cystic fibrosis and metabolic diseases such as cystinosis or hypothyroidism.

In general, the list released on May 20 is an important step in the advancement of therapeutics for children. The FDAMA law required the rapid production of a list of drugs to qualify for potential market exclusivity under section 111 of the law. Ideally, the list of drugs should have been released in conjunction with industry guidance on the use of the list. However, the AAP believes that a brief delay in issuing guidance is acceptable in order to ensure that the document provides a thorough and detailed approach to outlining the scope and nature of pediatric studies of drugs under this section.

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As FDA develops the guidance, AAP recommends the following:

**The Nature and Scope of Pediatric Studies:** The intent of the new law is to improve pediatric practice for the ultimate health benefit of children and adolescents. To that end, any study that is adequate to support pediatric labeling for the relevant pediatric indications and pediatric populations should qualify for extension of patent exclusivity. The 1994 rule that was intended to stimulate labeling illustrated that pediatric studies may be conducted, yet not be adequate to qualify for labeling. Any study that is adequate for labeling should certainly receive the reward of extended market exclusivity.

The AAP recommends the following information be included in any written request for studies qualifying for market exclusivity made by the Secretary. The AAP urges that the Secretary develop written requests with the following attributes and obtain input from outside pediatric experts:

- scope of studies requested will be indication and drug specific;
- studies requested may include approved and not approved indications;
- age groups or stages of childhood maturation that need to be studied;
- type of published and unpublished prior data that would be acceptable to the FDA to support the application;
- number of children with analyzable data for each study;
- type of studies (e.g., duration, PK, safety and efficacy where appropriate, etc.);
- the size and number of independent trials should be stipulated;
- time frame for completing studies;
- scope/content of report that will be submitted to the Secretary;
- the issue of development of new formulations, if needed for the study of a particular portion/s of the pediatric population, should be considered.

**Formulations:** Depending on the drug and the age population/s that need pediatric studies, there may be a need for developing a formulation as part of the study (such as development of a liquid preparation where one was not available before). Formulation should be part of study requirements when necessary for the target population. Historically, the lack of age-appropriate formulations has been a significant block to getting drugs studied and labeled for children. The FDA should consider, on a case-by-case basis, whether development and testing of a new formulation that is more than a change in concentration should qualify for market exclusivity extension.

**Completion of studies:** The standard for "completion of the study" should include not only the submission of data but a requirement that the data be analyzed, assessed, interpreted by the manufacturer, and then be judged and accepted by FDA. The mere completion of a study in children should not necessarily qualify for extension of market exclusivity. Studies must adhere to principles of scientific investigation that utilize adequate and generally accepted study design and population size needed to accurately describe a drug product (age-specific kinetics,

dynamics, efficacy, and safety) and meet the need for information that will improve the health for a particular pediatric population.

Further, although current regulations require the reporting of adverse affects of medications during investigation for the protection of the patient and the company, ineffective treatment must be reported as well. This ensures that pediatric patients will not receive medications demonstrated to be ineffective and thus be deprived of a more effective treatment while receiving one that has been demonstrated not to be effective. In other words, labeling should also reflect when a drug is not effective for a pediatric indication or age group when that information is based on well controlled studies. Significant consideration must be given to what becomes of the data, particularly if the data have a negative impact on drug use. Avenues of disseminating this information must be explored.

Commonly accepted scientific principles and protocols: AAP would urge the FDA to set criteria, as part of the written request for pediatric studies, consistent with its long term commitment to high standards for investigation of drugs and meeting all existing GLP, GCP standards and the AAP Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. Criteria should also meet all current regulatory standards for studies intended to support an NDA or SNDA submission. An IRB's approach for studies should receive careful review to ensure that parents do not receive coercive rewards for volunteering their child to participate in drug studies.

Specific considerations should include, but not be limited to inclusion of an adequate number of pediatric patients to determine the outcome, how to handle a study when data are uninterpretable because of a problem with technical analysis, and how to deal with failure of the sponsor to complete studies in all the pediatric age groups identified in the written request.

Thus, pharmaceutical companies should not be able to completely control the process and extend market exclusivity for studies in children that may be inadequate in power to accurately reflect kinetics, establish optimal dose, or assess the outcome variables.

We thank you for the opportunity to offer these recommendations and would welcome an opportunity to further discuss this issue with you and your staff in the future.

Sincerely,



Joseph R. Zanga, MD, FAAP  
President

RJZ:eh

cc: Murray Lumpkin, MD  
Ann Witt  
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