American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN

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Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

Docket Number 00D-1595

Dear Sir/Madam:

The American Academy of Pediatrics (AAP) is pleased to provide comments to the Food and Drug Administration on the Draft Guidance for Industry on Recommendations for Complying with the Pediatric Rule. The Pediatric Rule represents a momentous step in advancing the health of our nation's infants, children and adolescents. For the first time in decades, pediatric populations will have appropriate use information available to them for the indications for which the drug is labeled at the time the drug is approved, or shortly thereafter.

To ensure the best therapeutic outcomes for children, the language in the Guidance for Industry must be clear, concise and unequivocal. While the Draft Guidance for the Industry represents a helpful outline of the responsibility of the Industry in accomplishing pediatric studies and labeling of medicines -- the goal of the Pediatric Rule -- there are several areas that may be open to varied interpretation by the industry and therefore limit the effectiveness of this Rule.

The AAP provides the following recommendations for inclusion in the Guidance:

IV. THE PEDIATRIC PLAN

2. Other Products

This section states that the background package for end-of-phase 2 meetings should include plans for pediatric studies, including a time line for protocol finalization, enrollment, completion and data analysis. It further states that the review division will provide its best judgment of the pediatric assessment that will be required for the drug product, and whether its submission can be deferred.

AAP is concerned that if a review division does not have sufficient pediatric expertise, then a greater number of waivers and deferrals may be granted. There

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needs to be a mechanism to assess and, if appropriate, reverse a decision to grant a waiver or deferral by a review division. Currently, the review body that exists is the Pediatric Advisory Subcommittee. However there must be another step in the waiver and deferral granting process.

AAP Recommendation: Every child – beginning with the very first child receiving a newly approved drug – should have treatment guided by the information provided through pediatric studies. Waivers and deferrals have the potential to derail that goal if they are granted too widely or without proper oversight. Therefore, the AAP urges that the Guidance include specific language that states:

- The Pediatric Advisory Subcommittee will review reports of the waivers and deferral granted at each meeting of the subcommittee, or on an ad hoc basis, if necessary. Reports should include the specific reason for the waiver, without violating confidentiality agreements with manufacturers.
- After review of the report, if the Subcommittee has concerns about the appropriateness of the waivers or deferrals, the Subcommittee will advise the FDA Pediatric Committee (PEDICOMM) to make a thorough review of the waivers and deferrals in question and report back to the Pediatric Advisory Subcommittee at the next meeting. NOTE: the PEDICOMM should be encouraged to engage outside pediatric experts to review waiver and deferral requests. These experts should be screened for conflict of interest and be obliged to maintain confidentiality.
- Upon review of the PEDICOMM report, the Pediatric Advisory Subcommittee may request that the FDA Commissioner reverse the decision to grant a waiver or deferral for pediatric studies.

V. WAIVERS and DEFERRALS:

Partial Waivers:

In the November 13, 1997 AAP comments to the Food and Drug Administration (FDA) on the proposed Pediatric Rule, the AAP stated: "There will be instances where a waiver is appropriate. On the other hand, it is essential that this provision not become a loophole for avoiding pediatric studies." This concern remains for the AAP and is heightened by the language in the draft Guidance related to partial waivers.

Granting of partial waivers has the potential to unravel the entire intent of the Pediatric Rule. Under Section V (B), the sponsor can request either a full waiver of all pediatric studies or a partial waiver excusing the sponsor from carrying out studies in particular age groups if one or more of the grounds for waiver apply to one or more pediatric age group.

The draft guidance for both full and partial waivers requires the sponsor to provide one of several pieces of evidence. The first is that: "The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients (in that age group), **and** (emphasis added) is not likely to be used in a substantial number of patients[1] in that age group."

[1] FDA considers the term *substantial number of patients* to mean 50,000 pediatric patients in the U.S. with the disease or condition for which the drug or biological product is indicated.

AAP is concerned that a company would realize that they could not qualify for a full waiver but that they could be granted several partial waivers in specific age ranges.

To illustrate the concern: A company has a drug 'X' that meets the criteria for representing a meaningful therapeutic benefit and is used in a substantial number of patients. However, if that company wants to avoid the requirement for pediatric studies, the company could request partial waivers of drug 'X' by pediatric age groups. While drug 'X' would still meet the meaningful therapeutic benefit criteria, it may identify one or more pediatric age groups that do not meet the "substantial number" criteria and therefore could be granted a waiver or deferral. If the company does that on several pediatric populations, the result could be very limited pediatric use/label information.

AAP Recommendation: FDA should drop references to "substantial number of patients" in the criteria for a partial waiver. If a disease or condition occurs in a population of children, then it must be studied in all age groups in which the condition manifests itself. To allow a company to waive studies in a specific pediatric population on the grounds that there are insufficient number of children in that age group, even though the total number of children suffering from the condition is substantial, is unethical and potentially undermines the intent of the regulation.

III. THE PEDIATRIC PLAN
(Section B – Age Groups)

The Pediatric Rule requires the assessment of safety in each age group in which the drug of biological product will be provide a meaningful therapeutic benefit **or** (emphasis added) will be used in a substantial number (50,000) of pediatric patients for indications claimed. Age groups should be defined flexibly, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy.

AAP Recommendation: While the AAP supports flexibility of defining pediatric age groups, there must be an emphasis that studies need to be conducted in children at critical states of developmental change in drug metabolism and elimination and at periods when the sites of action of the drug within the body may change in responsiveness.

(Section C – Pediatric Formulation).

This section states: "FDA can waive the requirement for pediatric studies in age groups requiring a formulation if the manufacturer provides sufficient evidence that reasonable attempts to produce a pediatric formulation have failed."

To qualify for a waiver to this requirement, the sponsor should provide data showing that experts in pharmaceutical formulation chemistry have been unable to develop a liquid or chewable formulation because of insurmountable solubility, stability, compatibility and/or palatability problems using accepted formulation methods.

Assertions that the problems are insurmountable should be corroborated by the Formulations Working Group of the FDA CDER Pediatric Drug Development Organization. Cost to the industry should be only a limited a consideration in awarding a waiver if the drug is anticipated to be used in children.

AAP Recommendation: The AAP strongly urges FDA to include language in the Guidance that specifically states that the Pediatric Advisory Subcommittee will consult with the Advisory Committee for Pharmaceutical Sciences related to questions about whether "reasonable attempts" have been made to produce pediatric formulations in particular cases.

VIII. Role of the Pediatric Advisory Subcommittee

This section outlines the role of the Pediatric Advisory Subcommittee.

AAP Recommendation: FDA should add two more specific roles for the Pediatric Advisory Subcommittee:

- Review the Agency's record of granting waivers of formulation (for AAP rationale of this recommendation see comments in IV).
- Review a report of the list of pediatric studies that are expected to be conducted by a company after the FDA approval of an NDA and the status of those studies. The report should include a timeline in which the company expects to conduct and complete the pediatric studies.

The American Academy of Pediatrics appreciates the opportunity to comment on this important Guidance for the Industry on Complying with the Pediatric Rule.

Sincerely,

Steve Berman, MD, FAAP

Steve Berman, MD, FAAP
President

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These comments were also endorsed by the following pediatric organizations:

Ambulatory Pediatric Association
Association of Medical School Pediatric Department Chairs
Society for Pediatric Research
American Pediatric Society