

American Academy of Pediatrics



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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr.
Room 1-23
Rockville, MD 20857

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DOCKET NUMBER 98N-0222

Dear Sir or Madam:

The American Academy of Pediatrics is pleased to provide comments to the proposed rule for Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices (Docket Number 98N-0222). This is an issue of tremendous importance and potentially far-reaching negative impact to infants, children, and adolescents. The rule promulgated for this provision must avoid providing a disincentive to manufacturers to submit the results of pediatric studies for labeling.

The American Academy of Pediatrics believes that the proposed rule to disseminate information of unapproved/new uses for drugs will not improve, and may harm, the status of children as it relates to availability of information concerning drugs for the pediatric population.

Recently, the Food and Drug Administration has made significant strides in addressing long-ignored issues related to the pediatric population. It is imperative that the final rule issued for Dissemination of Information on Unapproved/New Uses of Marketed Drugs, Biologics and Devices not reverse or impede the strides made by FDA as they relate to the therapeutic needs of infants, children and adolescents. Three examples of recent pediatric-specific rules are of note:

1. The release of proposed rules "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," (Docket No. 97N-0165);
2. The release of the List of Approved Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population (Docket No. 98N-0056), as part of Section 111, Pediatric Studies of Drugs, of The Food and Drug Administration Modernization Act of 1997 (FDAMA) law (Pub. L. 105-115); and
3. The release of "Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act." (Docket No. 98D-0265).

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AAP OPPOSITION TO DISSEMINATION OF PEDIATRIC INFORMATION:

The AAP is on record as opposing efforts to directly disseminate to physicians information on pediatric unapproved uses of drugs. This opposition is based on the following factors:

- Children are at an extreme disadvantage in not having pediatric clinical studies performed on drugs. With only 20 percent of drugs currently having pediatric labels, children do not have the advantage of safety and efficacy studies on the vast majority of drugs.

The adult population has safety and efficacy established in a drug labeled for an indication for which an unapproved use is being disseminated. Expanding the use of the drug from its approved purpose (e.g., anti-convulsants) to use for another condition (e.g., heart arrhythmia) still affords adult baseline safety and efficacy information about the drug.

- Should the pediatric population be included in the proposed dissemination of information rule, the vast majority of unapproved uses for an infant, child or adolescent will not likely be based on the type of rigorous comprehensive clinical studies required by FDA for labeling purposes. Rather, the information provided to health professionals would likely be based on smaller studies that form the basis for articles that appear in peer-reviewed journals or reference publications.
- Pediatricians who work with infants, children or adolescents on a regular basis, are forced to rely on limited information in prescribing medications to the pediatric population. It may be argued that the risk to children is increased when a physician not specializing in the care of children prescribes drugs to those populations. Given continuing efforts to expand the medication prescribing authority to health professionals outside physicians, the risk to the pediatric population may become even greater.,
- A manufacturer who can disseminate (some argue 'promote') drug use information without doing studies in the pediatric population is significantly less likely to spend the time and resources to undertake rigorous comprehensive studies to file for labeling of that drug for children.

RECOMMENDATIONS:

Current regulations allow for industry to provide physicians with information about an unapproved drug use if the physician specifically requests such information. The Academy recommends that new rules related to efforts to expand dissemination of information of unapproved uses of drugs beyond current regulations include the following provisions:

- . For those drugs without labeling for pediatric populations, drug manufacturers may not disseminate off-label use information about pediatric populations, unless such information is specifically requested by the physician.

- . For those drugs with pediatric age specific labeling, drug manufacturers may not disseminate off-label use information about age populations not specified in the label, unless such information is specifically requested by the physician.

RATIONALE:

The Food and Drug Administration Modernization Act (FDAMA) includes Section 111 – Pediatric Studies, which provides incentives to manufacturers to conduct pediatric studies. Inclusion of the pediatric population in the proposed rule for dissemination of information may have a significant negative impact on the intended outcome of Section 111. The intended goal of this provision is to get more drugs labeled for pediatric use. As Representative John Dingell, ranking minority member on the House Commerce Committee noted in remarks on the House floor during consideration of the conference report on S. 830 (FDAMA), “Market incentives are included in the bill to encourage pediatric studies, so that labeling of these products will be useful to pediatricians.”

Section 401 – Dissemination of New Uses of FDAMA is silent on the specific populations for which information may be disseminated. Thus, FDA has the authority and responsibility to determine if a particular population maybe disadvantaged by a proposed rule (e.g., infants, children and adolescents), and should thereby be excluded.

It must be noted that, the Secretary of Health and Human Services is required to arrange for the conduct of a study to determine “the impact of such subchapter on research in the area of new uses, indications, or dosages, particularly the impact on pediatric indications and rare diseases.” It is appropriate and important that this study should focus on whether the exclusion of pediatric populations from dissemination of information has had any impact on new uses, indications or dosages.

Should FDA choose to move ahead with inclusion of pediatric populations in the dissemination of information of unapproved uses, the following critical points must be addressed:

The AAP strongly disagrees with the inclusion of a new age group as a criterion for a “new use” in the dissemination of information. The definition of “new uses” as described in the proposed rule states: “a use that is not included in the approved labeling of an approved drug or device or a use that is not included in the statement of intended use for a cleared device.” The proposed rule provides a list of “new uses” that would require approval of a supplemental application. The list includes a “new age group.”

As described in the proposed rule, if a drug does not include a specific age group on the label, then a manufacturer could disseminate information about that age group, so long as a supplemental application was filed/intended to be filed. Even with the requirement of filing a supplemental application for the new use, children are placed in a tenuous situation. A supplemental could take 3 ½ years or longer for completion and the new labeling information to be made available. During the time the supplemental application is being developed and

reviewed, information about the new pediatric use will be widely disseminated, based on information more limited than that for adults.

While it is appropriate to include a new age group when seeking labeling changes within a supplemental application, it is inappropriate to disseminate information about an age group while a supplemental application is pending. The outcome of such a measure is a disincentive for manufacturers to undertake studies that lead to labeling.

Supplemental Applications: In the List of Approved Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population (Docket No. 98N-0056), FDA concluded that information on 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. Therefore, if a drug seeking a supplemental application for a new use appears on the FDA “List,” then the supplement should include studies in all pediatric populations in which the drug may be used.

Within the proposed rule, there are two circumstances identified in which it would be appropriate to exempt a manufacturer from the requirement to submit a supplement for a new use: (1) it would be economically prohibitive, and (2) it would be unethical to conduct studies.

AAP recommends very limited use of exemptions for manufacturers from having to submit supplemental applications for study of the new use being promoted. If the data are adequate to support dissemination for treatment of the pediatric population, it should be adequate justification to conduct proper study of this treatment.

Regarding a request for an exemption for economic reasons: Estimates of costs for studies to support the supplemental application must consider that dissemination of information may increase sales. AAP agrees with FDA that those costs should substantially exceed revenues to qualify for an exemption. The AAP further agrees with FDA that the cost estimates be based on the Statement of Standards for Attestation by AICPA.

Regarding a request for an exemption for ethical reasons: It is almost inconceivable that the study of a new use of a drug in the pediatric population could be viewed as unethical. The proposed rule notes: “Evidence suggesting that the drug or device is the standard of care for the intended use can add weight to the argument that conduct of a needed study or studies would be unethical.” It should be noted that rarely are the diverse opinions of the medical community in agreement about what treatment is considered “the standard of care” throughout the United States.

In addition, the proposed rule discusses the use of evidence that a new use represents standard medical therapy as one element of an argument that studies cannot ethically be conducted and includes as a consideration whether the new use is “consistent with sound medical practice.” “Consistent with sound medical practice” is not the same as “standard of care”. Though an unapproved treatment may be consistent with “sound medical practice,” it will often be

appropriate for study to support labeling to provide for wide dissemination of information about that treatment.

Record keeping: AAP recommends that the FDA require manufacturers to keep records of health care professionals by name, health plans and pharmacies that receive information, in case of a recall of the approval.

Prominently displayed statement: AAP recommends that the lack of availability of pediatric studies on a particular use should be clearly and prominently stated within the appropriate section of the information being disseminated to health professionals.

The AAP appreciates the opportunity to comment on the proposed rule. We strongly urge that dissemination of information of unapproved/new uses of marketed drugs, biologics, and devices exclude pediatric populations. We would be pleased to discuss these recommendations further.

Sincerely,

A handwritten signature in black ink that reads "Joseph R. Zanga, MD". The signature is written in a cursive, flowing style.

Joseph R. Zanga, MD, FAAP
President

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The following national organizations endorse these recommendations and comments:

American Pediatric Society
Association of Medical School Pediatric Department Chairmen
National Association of Children's Hospitals
Society for Pediatric Research