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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20857

RE: Guidance for Industry - Qualifying for Pediatric Exclusivity
Under Section 505A of the Federal Food, Drug, and Cosmetic Act
Docket No. 98D-0265

Ladies and Gentlemen:

The undersigned respectfully submits the following comments on FDA's June 1998
*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal
Food, Drug, and Cosmetic Act.*

Section 505A, added by section 111 of the 1997 Food and Drug Administration
Modernization Act ("FDAMA"), is a legislative effort to address an issue that has been a public
health concern for a number of years, namely, the lack of reliable information on the use of many
drugs in children. Section 505A aims to increase the availability of such information, and in so
doing, enhance the safety and efficacy with which certain drugs are prescribed for the pediatric
population. The incentive for the development of this information is six months of additional

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protection from generic competition provided that pediatric studies are conducted and reported in accordance with specified procedures.

Clearly, the underlying goal of section 505A - to generate more useful information to guide physicians in prescribing drugs for children - is a worthy pursuit that serves the public interest. Offering a meaningful financial reward to companies to perform the work needed to accomplish this goal is sensible. Still, one must keep in mind the real risk that the pursuit of the financial reward may become the overriding objective, thus undermining the intent of the law.

In this light, the ethical imperative not to expose human beings, especially children, to clinical experimentation without a valid scientific rationale, must be given close attention. Proposed pediatric studies must be critically reviewed to ensure that the usefulness of the information that may be derived for the safe and effective prescribing of drugs in children overrides the inherent risks and discomforts of clinical testing. It is therefore essential that FDA exercise vigorous case-by-case oversight to prevent situations where sponsors' desires to obtain the financial rewards of pediatric exclusivity result in children being exposed to experimental protocols without a valid public health justification. For example, does the pediatric population really need the seventh "me too" drug in a therapeutic class if that drug offers no clinical advantage for that population over the six that preceded it? This would clearly be a case of needless exposure of children to clinical experimentation, and therefore the sponsor proposing such a study should not be allowed to perform the study for the sole purpose of obtaining the financial rewards of exclusivity. Additionally, it is well known that the treatment of some disease states in children does not differ substantively from treatment in adults. In these cases as

well, pediatric studies provide no additional value to the health care of children. Here again, a sponsor should not be awarded exclusivity. And in order to effectively carry out Congress's intent, decisions of this importance can only be made on a case-by-case basis with a clear understanding of the pertinent risks and benefits.

In addition to preventing needless clinical experimentation on children, strict FDA oversight would also help to avoid needless increased costs to the consuming public. Since the six months of pediatric exclusivity are additive to whatever patents and other exclusivities currently protect a branded product from generic competition, this is six more months during which the public will be deprived of access to lower-cost generic drugs. In many cases, this additional six months of protection can put millions of additional dollars into the pocket of the sponsor, and take corresponding millions of dollars out of the pockets of the public. It is thus important that the additional cost to the consuming public be justified by a meaningful benefit to children. Exclusivity must not be awarded frivolously.

Given these very real concerns, FDA's guidance document appears inadequate in that it fails to provide sufficient controls and oversight over the types of studies that qualify for the six-month exclusivity extension, and fails to require adequate justification for the need for the proposed study data. Toward correcting these inadequacies we offer the following suggestions for modification of the guidance:

- A. In order to maximize the likelihood that pediatric studies under Section 505A will be truly useful, proposed pediatric study requests submitted by the NDA holder or other interested parties should be required to include:

1. A description of the disease for which the product is indicated, focusing on the similarities and differences between adults and children and including a rationale for how additional studies on the drug's behavior in the pediatric population would benefit these patients and the health care community.
2. A review of the literature focusing on available therapies for the disease in question and for the treatment of children with the disease. This information should address the use of alternative therapies and include an assessment of the available pediatric literature on these alternatives, including safety and efficacy data. Again, the usefulness of the proposed additional studies should be outlined with emphasis on the clinical advantages that might be derived from these studies with respect to the drug under review.
3. A detailed justification for the need for additional study on the product proposed for exclusivity, including a description of the benefit such study will offer pediatric patients when viewed in the context of the potential risks. Among the issues this justification should address is the size of the pediatric population that would stand to benefit from the additional information provided by the study.^{1/}

^{1/} In this respect, FDA's criterion of at least 50,000 prescription mentions a year for considering a drug to be "widely used" in the pediatric population, if one takes into account a typical monthly refill schedule, could reflect as few as 4,000 or so pediatric patients - in reality, a minuscule number.

B. Given the resources required to review Proposed Pediatric Study Requests and to generate and issue Written Requests for Pediatric Studies, it is unlikely that FDA will be able to devote the necessary time and level of scrutiny required by these documents in light of other competing activities. Therefore, it is proposed that these Proposed Pediatric Study Requests and Written Requests for Pediatric Studies be published for public review and comment prior to FDA's taking any action on them. Only in this way can the complex medical, ethical and practical issues be adequately posed to stakeholders, including clinicians, consumers, industry and all those concerned with children's health, thus ensuring a truly independent outside assessment rather than one motivated by financial incentives. The potential impact of these issues on public health, the potential risks to children involved in proposed studies, and the potential economic costs of a possible grant of exclusivity clearly justify providing an opportunity for public comment.

C. FDA has consistently recognized that unless information on pediatric use is included in a drug's labeling, medical practitioners have no reliable means of gaining access to such information, and the utility of the information in guiding the use of the drug in children is effectively lost. The American Academy of Pediatrics has also strongly supported this view in a letter to FDA earlier this year, stating that "[t]he intended goal of the [FDAMA] pediatric exclusivity provision is to get more drugs

labeled for pediatric use.”^{2/} For this reason the requirements regarding labeling revision on the basis of pediatric studies should be stricter and better defined. All new information, positive or negative, that is generated from these studies should be incorporated into labeling. The implementation date of this labeling should be established by FDA in the approval of the labeling supplement which includes the information obtained on pediatric use.

D. As noted above, there is a significant financial incentive to conduct unwarranted pediatric studies to obtain exclusivity. This incentive is even greater with respect to pharmacokinetic (PK) studies, which may generate data of questionable utility at minimal cost in exchange for a valuable six-month extension of exclusivity. The ethical ramifications of dosing drugs to healthy children are considerable. Issues of obtaining informed consent for tests not directly of benefit to the child, as well as obtaining adequate blood samples for analysis, require a substantial justification for the advisability of such studies. Thus, the data to be obtained from proposed PK studies should be required to have a clear impact on medical practice, and should be required to be disseminated through labeling changes. It was for precisely these reasons that FDA, in finalizing its 1994 rule on pediatric labeling, liberalized data requirements by allowing, in

^{2/} Letter from the American Academy of Pediatrics to Dr. Michael A. Friedman, Feb. 2, 1998, Docket No. 98D-0265, C4, at 3-4.

some cases, a pediatric labeling statement to be based on studies in adults if additional information exists to show that the course of the disease and the drug effects are sufficiently similar to permit extrapolation from adult data to children.^{3/} Ethically, all drugs proposed for exclusivity should first be reviewed for this potential extrapolation to ensure that PK as well as clinical studies will truly provide significant enough information to justify their risks and costs.

The history of FDA's attempts to grapple with the problem of inadequate pediatric labeling shows that the agency is keenly aware of the public importance of this problem, and of the need to carefully and thoughtfully weigh competing scientific, clinical and ethical issues in addressing it. It would be tragic if FDA, having finally been provided with a meaningful tool to motivate sponsors to take the necessary steps to acquire information in support of better pediatric labeling, abdicated its responsibility to ensure the responsible and effective use of that tool. We urge FDA to adopt the proposals put forth above, to modify its Guidance along these lines, and to reflect the above proposals in the implementing regulations it is developing.

Respectfully submitted,



DAJ/

^{3/} *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of the "Pediatric Use" Subsection in the Labeling*, 59 Fed. Reg. 64,240 (1994).

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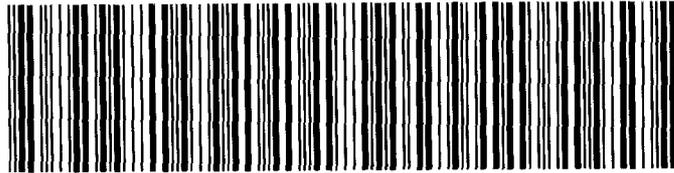
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