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

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

Dear Sir or Madam:

The FDA Modernization Act of 1997 (FDAMA), signed into law by President Clinton on November 21, 1997, created section 505A of the Federal Food, Drug and Cosmetic (FD&C) Act (21 U.S.C. 355a). Novartis Pharmaceuticals Corporation (Novartis) believes that by providing product sponsors with the incentives described in §505A, both Congress and the President clearly intended to achieve important and meaningful labeling information regarding the use of pharmaceutical products in children. Novartis applauds this effort, and the efforts of FDA to implement this section expeditiously. However, we are concerned that several sections of the Guidance may serve to hinder, rather than facilitate, this important goal.

II. HOW DOES A NEW DRUG APPLICATION QUALIFY FOR PEDIATRIC EXCLUSIVITY?

This section describes a series and sequence of events that must occur before a drug will qualify for pediatric exclusivity, including the stipulation that pediatric study reports should be submitted only *after* FDA makes a request. Section IIIC of the guidance reiterates this point, stating that "studies submitted before FDA issued a Written Request should *not* (sic) be used to request pediatric exclusivity." This requirement will cause needless delays in the submission of these data, as sponsors wait for FDA to issue a formal request, and may be in conflict with NDA regulations and the final pediatric rule of December 1994. Such delays are also clearly contrary to Congressional and Presidential intent.

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III. WHAT ARE PEDIATRIC STUDIES?

FDAMA defines pediatric studies as “at least one clinical investigation (that, at the Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups in which the drug is anticipated to be used.” The Guidance contains no indication of instances when a pharmacokinetic study may suffice, however, the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* written for Section 403 of FDAMA provides such language and specific examples. Novartis believes the Agency should adopt a similar approach, or continue to utilize the policies developed under the 1994 Pediatric Use rule, and accept pediatric pharmacokinetic data and other safety data (e.g., adverse reaction data) to establish pediatric safety and effectiveness. We also recommend that the Agency consider extrapolation of clinical efficacy of older pediatric patients to the younger age ranges. We believe such a policy would further encourage manufacturers to seek labeling of their products in younger pediatric patients, thereby expanding the therapeutic options available to pediatric healthcare providers for their youngest patients.

Section C states that literature reviews are not pediatric studies that will qualify for pediatric exclusivity. This section also states that “the party seeking exclusivity need not have conducted the studies it submits in response to a Written Request.” It should therefore be clarified whether a meta-analysis of published clinical trials conducted in pediatric patient populations would be acceptable. The exclusion of meta-analyses of literature supporting pediatric usage would be inconsistent with the intent of this provision as well as with Section 403 of FDAMA and the corresponding guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. The provisions set forth in Section 403 are not limited to adult claims and should therefore, apply equally to the pediatric population for pediatric effectiveness claims supported by study reports in published literature.

Section C also states that “Studies submitted before FDA issued a Written Request should *not* be used to request pediatric exclusivity.” However, the exclusivity provision became effective November 21, 1997, seven months before FDA issued its guidance. This situation would preclude those sponsors who submitted pediatric data after the enactment of FDAMA, but prior to the issuance of the guidance from receiving the 6-month exclusivity incentive. Clearly, the Congressional intent of this provision was that the incentive would be available November 21, 1997, not June 29, 1998. Otherwise, the legislation would have provided an effective date 90, 120 or even 180 days after enactment. How will the Agency address this discrepancy?

V. B. FDA Prioritization and Processing of Proposed Pediatric Study Requests

The timeline and prioritization scheme proposed in the Guidance is unrealistic. An inordinate number of products fall within priority category 2, including all unapproved products. Sponsors who file timely Proposed Pediatric Study Requests for “non-priority” products, which patents expire before March 31, 1999, will be forced to wait for FDA review until all previously unapproved products are reviewed, regardless of when the Proposed Pediatric Study Request was submitted or whether the unapproved product would be considered a “priority” drug or not. Novartis believes that it was the intent of Congress to provide a fair and reasonable incentive for product sponsors to conduct the pediatric studies necessary to result in meaningful pediatric labeling. Because of the need to allow sufficient time to complete the proposed studies requested by FDA, due consideration should be given to patent and

exclusivity expiration dates. Therefore, following review of priority products with patent expiration dates prior to March 31, 1999, FDA should next process submitted pediatric requests for all other products with expiry dates prior to March 31, 1999. The third priority should be those products whose patents expire prior to the end of 1999.

V. C. Changes to the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population

Inclusion on the pediatric list required meeting one of three criteria:

- The drug product, if approved for use in the pediatric population, would be a significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of disease in the relevant pediatric population; or
- The drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year (IMS database, we assume); or
- The drug is in a class or for an indication for which additional therapeutic options for the pediatric population are needed.

In general, Novartis believes that any inclusion criteria should be based on prevalence of disease and the resulting therapeutic need, not an arbitrary measure based on clinical practice. The first criterion used by the Agency considers products that will provide a significant improvement over existing therapies. The Agency has not defined "significant improvement," leaving this criterion open to arbitrary interpretation. Without clear definition, the Agency will have difficulty administering this provision consistently, particularly as the list is expanded. Novartis believes that the criteria previously proposed for marketed products are superior:

- The product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric patients; or
- The product was indicated for a very significant or life threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Novartis considers the second criterion of 50,000 prescriptions mentions to be an arbitrary and artificial measure of "widely used" in the pediatric population. Prescription mentions are an estimate of annual use and do not reflect actual use. In fact, a "mention" covers a range of possibilities, including prescriptions written, literature distributed, or a verbal recommendation of a product as a possible course of treatment but not necessarily resulting in a prescription. A mention also does not reflect noncompliance with prescriptions dispensed, nor does it account for the fact that most treatment regimens consist of multiple refills on any one prescription dispensed. Using the number of prescriptions will dilute the actual number of patients affected by the disease and thus available for clinical study. Novartis believes any changes to a product's prescribing information should be based on sound scientific evidence and not the number of times a physician prescribes a product to a pediatric patient. The question of producing a health benefit for pediatric patients should be based on prevalence of disease. For it is this very circumstance of disease state that motivates any patient or healthcare provider to seek therapeutic intervention, either for prophylaxis or treatment.

Novartis further believes that the list of marketed products should be based on therapeutic class, and not individual drug products. The third criterion, "The drug is in a class or for an indication for which additional therapeutic options for the pediatric population are needed," addresses therapeutic need based on drug class and disease. A broader application of this criterion could effectively capture those products that may best produce a health benefit for the pediatric population. We believe the Congressional intent of this section was to allow for a broad range of products to be eligible for the exclusivity incentive. The use of therapeutic class would ensure that all approved products within a class would be eligible for this incentive and therefore result in multiple therapeutic options for the pediatric population.

We suggest that FDA consider the following criteria: number of patients with the targeted disease; disease severity; disease and current treatment morbidity; pediatric safety issues including potential risk due to use of extemporaneous formulations, inappropriate dosing and administration; and societal costs due to absence of pediatric information.

VII. WHAT ARE COMMONLY ACCEPTED SCIENTIFIC PRINCIPLES AND PROTOCOLS?

An additional issue not addressed in the guidance, but specific to the conduct of pediatric studies, is the outcome of those studies. Novartis believes the intent of the Pediatric Studies provision under FDAMA is to serve as an incentive measure for the conduct of pediatric studies. If those studies, as agreed to by FDA and conducted under good clinical practice within the agreed time frame, do not result in positive findings, but rather show that a drug is either ineffective, unsafe or are equivocal, the drug product should still receive the 6-month exclusivity extension. The goal of any clinical study is to produce positive therapeutic findings. However, it is impossible to predict the outcome of any study and therefore, a positive outcome should not be required as a condition by which a study is eligible for the 6-month incentive.

Finally, Novartis would like to commend FDA for acknowledging that a *request* to conduct pediatric studies is not a *requirement*. This is appropriate, fair and consistent with the intent of Congress and the President to provide an incentive for product sponsors to conduct these trials. Likewise, by allowing an additional six-month period of exclusivity for conducting a second pediatric study (*e.g.* in a different pediatric group), the Agency has proposed a fair and reasonable solution to a potentially confusing question.

Thank you for the opportunity to comment on this important guidance document. Novartis looks forward to working with FDA to ensure the continued availability of safe and effective products for all patients.

Sincerely,



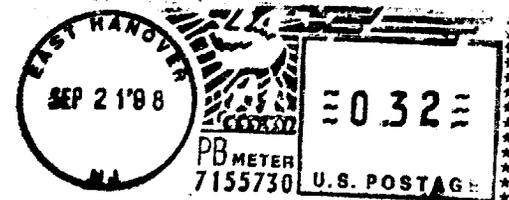
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cc: Marjorie Powell, PhRMA



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