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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

PHARMACIA

RE: Docket No. 00D-1223
Draft Guidance: Clinical Investigation of Medicinal Products in the Pediatric Population

Dear Sir or Madam:

Pharmacia appreciates the opportunity to review the *draft* guidance, "Clinical Investigation of Medicinal Products in the Pediatric Population."

The following are the points we wish to raise to your attention:

General Point

In numerous instances throughout the guidance, there are references: 1) to the need to minimize the volume of blood drawn from children for pharmacokinetic purposes, 2) to minimize the number of blood samples taken, and 3) to use as few subjects as possible in emphasizing benefit relative to risk to this population. However, all of these factors are relevant in evaluating the specific goal of pediatric pharmacokinetic trials. That is, is the objective of the trial to provide descriptive pharmacokinetic characteristics in the pediatric population that can be qualitatively related to the reference adult database or is the goal to compare these databases using highly powered and sensitive statistical criteria? The guidance provides no useful information regarding how many subjects would be sufficient in these trials; to do this, it is necessary to define the statistical intent. We recommend that language be included in the guidance to aid in determining the number of subjects sufficient to support pediatric drug development goals.

General Point

The broad nature of the guidance makes it difficult to assess what pediatric data may be necessary for drugs having certain drug disposition characteristics. As an example, we cite the case of a drug principally metabolized by CYP2D6. For such a drug, we would characterize the pharmacokinetics and pharmacodynamics in both extensive and poor metabolizers in the adult population and among various ethnic groups. Given the goals of getting sufficient information in pediatrics, would it be necessary to include children characterized as poor metabolizers in pediatric assessments? We think there is value in having some basic guidance language that addresses fairly common drug development issues such as this.

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Section 1.4

We recommend the guidance acknowledge that products are often administered to children without sufficient data for their appropriate use, both in terms of safety and efficacy. This section, or perhaps section 1.1, may be the most appropriate place to make such a statement.

Section 2.1

Paragraph 2

Consider adding a bullet for "Route of administration."

Section 2.3.2

It should be emphasized that planning for pediatric studies should begin before phase I clinical trials are initiated in adults. This will ensure a rapid transition into pediatric studies as soon as preliminary data is available in adults. One must balance the risk of exposure to a few children in a phase I/II trial with the potential risk of lack of treatment of many children should an effective chemical entity be delayed in its pediatric development. This is of course less of an issue for diseases where there are well established and effective therapies, but becomes critical for diseases where there are no therapies or existing therapies of marginal efficacy or unacceptable toxicity.

Section 2.4; Types of Studies

The guidance states, "When a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors that could impact the extrapolation of data to other regions should be considered." No further elaboration of this statement is provided; consequently, it suggests that the bridging of populations having different ethnic backgrounds, currently targeted at comparing adult populations, may need to be duplicated in pediatric populations. This must be clarified.

The comparison of ethnic factors, which is specifically intended to address potential "pharmacogenetic" differences, is an issue that is reasonably and completely addressable in adult populations. There is no added value in repeating these trials in pediatric populations, if sufficient pediatric data are collected in a population primarily comprised of subjects representing one ethnic group. Further, repeating unnecessary studies in a group of pediatric subjects is contrary to one of the overall goals of the guidance, which is to limit drug testing in children to only those studies minimally required. We recommend that, except for the case where a drug is developed exclusively for treating pediatric populations, the language cited above be clarified such that bridging studies in pediatric populations not be required

Section 2.5

With regard to the age classifications, it may be more appropriate from a physiological and development standpoint to separate infants from toddlers. There is perhaps more difference physiologically and developmentally between a 2-month-old and an

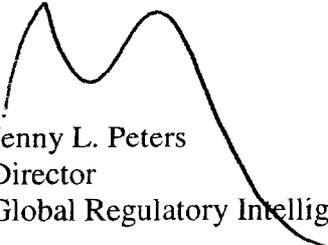
18-month-old compared to the difference between a 18-month-old and a 5 year old. Renal and hepatic physiology generally stabilize by 3 months of age and most infants stop breast-feeding by 1 year of age. We suggest the following age break:

Preterm neonates (breakdown by gestational age and/or birth weight)
Term neonate (0 - 27 days)
Infants (28 days - 12 months)
Toddlers and Children (1 year - 11 years)
Adolescents (12 to 16 to 18 years (dependent on the region))

Again, thank you for the opportunity to comment. Should any clarification of our input be required, please don't hesitate to contact Jenny Peters at (616)-833-8141.

Sincerely,

Pharmacia Corporation



Jenny L. Peters
Director
Global Regulatory Intelligence

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