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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 03D-0001; Draft Guidance, *Draft Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products, 68 Federal Register 5301 (February 3, 2003)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discovering and developing best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline is comprised of approximately 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products. We commend the FDA for providing this draft guidance on the role and timing of nonclinical studies in the safety evaluation of pharmaceuticals intended for the treatment of pediatric patients. We begin with general comments followed by more specific concerns with the proposal.

Summary of BMS Comments on Proposal

This guidance proposes new nonclinical pediatric studies in young animals (most often rodents), in which exposures occur from as early as possible through sexual maturity (defined in the guidance as postnatal day 4 through 100). This guidance requires this type of study for drugs intended for use in pediatric populations, even when data exist in adult humans. The guidance justifies the need for this type of study by providing examples of drugs used in pediatric patients that have different safety profiles when used in adults. We believe that the majority of the examples provided do not clearly support a need for preclinical pediatric studies. An important question to consider is: "What is the true predictive value of studies in juvenile animals when estimating risk in human pediatric populations?" The guidance implies that all drugs are *de facto* assumed to have different and potentially adverse effects in juveniles because immature systems are expected to react differently to drug treatment than mature systems.

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The guidance further suggests that pediatric testing would be of benefit in off-label use scenarios in pediatric populations. The document further suggests that nonclinical pediatric studies are warranted because nonclinical developmental toxicity studies have traditionally focused on prenatal development with only limited assessment of postnatal effects. Since perinatal/postnatal studies (e.g., Segment III studies) focus entirely on postnatal endpoints from birth through sexual maturity and reproduction, we disagree with the assertion that these studies have only limited relevance when assessing risk in pediatric populations. A more accurate statement regarding any limitation of the Segment III study in this context is that exposure of the offspring to the drug may be considered limited because the offspring are not directly administered the drug. Nevertheless, most drugs cross the placenta and are found in maternal milk, providing drug exposures during multiple sensitive periods of development for various organ systems. Thus, it would be imprudent to dismiss the results of these studies as irrelevant to pediatric safety. Therefore, we would encourage a paradigm that utilizes Segment III study outcomes as a trigger for the conduct of a pediatric/juvenile toxicity study.

The guidance further states that standard toxicology studies using adult animals or safety information from adult humans cannot adequately predict drug effects in immature systems, even though these data are considered predictive enough to serve as the basis for dose selection for nonclinical pediatric studies. Although the guidance states that in some circumstances studies in juvenile animals would not be informative and are not necessary, this scenario seems likely to be a rare exception, given the expectation of this guidance that most drugs react differently in immature versus mature systems. To say that data from existing toxicology and reproductive toxicology studies could be deemed adequate to predict safety for juvenile populations seems to contradict the premise of the guidance. Although exceptions may be granted when potential safety concerns for pediatric populations are determined to be negligible (e.g., drugs intended for geriatric populations or erectile dysfunction), these scenarios would seem to represent a minority of cases. Therefore, a nonclinical pediatric study will be required for nearly all new drugs.

The specifics of the recommended study design call for an administration period relevant to the intended clinical use of the drug. However, it seems likely that in practice, the dosing period of the study will need to be long-term in many cases, since drugs may not be administered to pediatric patients according to the patient's exact age (or age range), even when prescribed for the same clinical use. Juvenile patients will not be exactly the same age when they contract a disease or sustain an injury requiring a given drug. The FDA's past concerns in these situations has not been limited to the adverse effects at the time of treatment but extend to the longer-term consequences of early childhood exposures.

To summarize, this guidance requires additional expensive and resource-intensive nonclinical developmental toxicity studies for drugs that are intended for use in pediatric populations as well as those that are likely to be used off-label. The benefits of these additional studies in evaluating overall risk/benefit of a specific therapy in the pediatric population will be speculative in many cases. Although the document alludes to the possibility of modifying one or more existing toxicology study designs by adjusting the age of the test animals, the guidance needs to provide greater clarity on this subject. Furthermore, the necessary modifications mentioned in this guidance are significant and could require numerous additional endpoints. We would encourage the Agency to use the findings from the Segment III study as the pivotal basis for requiring a pediatric/juvenile toxicity study, rather than requesting additional resource intensive pediatric animal studies for virtually all drugs.

Specific Comments

1) Under Section IIA, *Differences in Drug Safety Profiles between Mature and Immature Systems*: The guidance provides several examples of drugs used in pediatric patients that have different safety profiles in adults. We believe that the majority of the examples provided do not significantly strengthen the document. Although the primary emphasis of the document is focused on the increased susceptibility of pediatric patients to adverse effects of pharmaceuticals, the initial example of acetaminophen toxicity points to a decreased susceptibility to toxicity in children as compared to adults. Another example ascribes toxicity residing in differences in drug half-life between pediatric and adult patients. However, we suggest that compound half-life profiles should be safely obtainable in an initial, low dose pediatric study. A third example involves the development of Reye's syndrome, a complication that occurs in children and not adults. It is worth noting that no truly appropriate experimental model reflective of the clinical syndrome exists in juvenile animals. We encourage the agency to share examples of actual adverse effects that could have been predicted or prevented if these nonclinical pediatric studies had been conducted.

2) Under Section IIIB, *Timing of Juvenile Animal Studies in Relation to Clinical Testing*: Greater clarity is required for "short-term" vs. "long-term" exposure in the pediatric population. Specifically, what are the implications for duration, types, and timing of studies needed to support long- versus short-term exposures?

3) Under Section IIIB.2: *Shorter Exposure in Pediatric Subjects*: The guidance states that it is not necessary to complete juvenile animal studies prior to the initiation of pediatric clinical trials of short-term exposure, yet later recommends that it may be more efficient to complete juvenile animal studies early. This Section seems somewhat contradictory and would benefit from more specific guidance.

4) Under Section IIIB.3: *Insufficient Clinical Data to Support Initiation of Pediatric Studies*: This section appears to contradict the timing allowance in IIIB.2

5) Under Section IIIC, *General Design Considerations for Juvenile Animals Toxicology Studies*: The guidance suggests that sponsors perform a long-term evaluation in juvenile animals with the study design incorporating numerous endpoints applicable to a wide range (in age) of pediatric populations. Although the document alludes to the possibility of modifying one or more existing toxicology study designs by adjusting the age of the animals tested, the adjustments are significant and would require so many additional endpoints as to make the effort prohibitive. Among the endpoints to be considered: serial measurements of crown-rump length, tibia length, growth velocity per unit time, assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, and learning and memory.

6) Under Section IIID.2, *Issues to Consider Regarding Juvenile Animal Studies, Use of Available Data*: The first paragraph is confusing in the light of other Sections in regard to the defined need to conduct juvenile animal studies.

7) Under Section IVA, *Types of Studies*: The guidance implies that any findings in adult-animal in-life testing be evaluated in juvenile animals. We believe that such a broad requirement is

unnecessary and the evaluation should be scientifically driven.

8) Under Section IVB.1, *Species*. This guidance indicates that, unless there are specific scientific reasons to do so, an evaluation of juvenile toxicity in a nonrodent species may not be necessary when adequate studies in juvenile rodents are available and toxicity endpoints have been well characterized in both adult humans and animals. It may be beneficial to further clarify the circumstances under which the agency would expect to see juvenile toxicity studies in nonrodents.

9) Under Section IVC.3, *Dose Selection*. Further clarification of the dose selection needs to be provided when maximum feasible doses or absorption/pharmacokinetic factors are dose limiting in the absence of frank toxicity. Additional clarification of testing the "formulation" is needed. We believe that the evaluation of API exposure in juvenile animals versus pediatric populations is best accomplished by optimally dosing API without regard to "formulation".

10) Under Section VA, *Use in Clinical Trials*. It is recommended that the first sentence be reworded to reflect that the safety of pediatric populations in clinical trials is of importance, not the safety of the clinical trials.

11) Under Section VI, *Tables: Comparisons of Human to Animal Developmental Stages by Organ Systems*. We would encourage the agency to expand and update these comparisons of human to animal developmental stages by organ systems on a regular basis. In Table C, Skeletal System, there appears to be an error in that the rat epiphyseal plate is open throughout life.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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Drug Safety Evaluation

Laurie Smaldone, MD
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