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Regulatory Science & Outcomes Research

February 23, 2001

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

Re: Docket No. 00D-1595, Draft Guidance for Industry on Recommendations for Complying with the Pediatric Rule (21CFR 314.55(a) and 601.27(a)) [*65 Federal Register 75720, (December 4, 2000)]*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide healthcare company with principal businesses in pharmaceuticals, consumer medicines, and nutritionals. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need in adults and children. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 2000, pharmaceutical research and development spending totaled $1.5 billion.

For these reasons, we are very interested in commenting on this FDA proposed draft guidance. In the following we identify our single major concern and we also offer other suggestions for otherwise improving the text.

Major Concern

Section III. Part E. ends with the following sentence:

> *"To encourage use of properly labeled drugs in pediatric patients, the Agency may require that products carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled."*

We recognize that there are numerous examples of current labeling where reference to preferred use of alternative drugs is made. Typically this reference is made to either classes of compounds or broad categories of drugs to describe *when* and *how* use of the subject drug is recommended.

For example, certain antibiotics may be indicated only in patients who are allergic to penicillin or in settings where microbial resistance is high to stated compounds; a particular antiarrhymic drug could be restricted in labeling to conditions failing treatment with a first-line compound or compounds; cancer drugs may be labeled with warnings as to their not being used until a first-line therapy has failed. These are examples of circumstances that are markedly different than the circumstance provided for in the draft guidance.

The draft guidance would enable a recommendation for an alternative product based on the Agency's judgement of the relative utility of drugs in pediatric therapeutics. In the absence of adequate and well controlled studies comparing the relative safety and efficacy of the drugs in pediatric populations, reference to the drug for which studies had been completed would be inappropriate. Such referrals may reflect no more than the timing of the approvals of pediatric labeling and not the relative efficacy or safety of the drugs in questions.

Furthermore, how would the Agency apply this labeling practice? Would it maintain labeling by making timely judgements on pediatric therapies of choice to ensure that referrals remained accurate reflections of current scientific and medical information? Would the FDA limit application of the guidance to circumstances in which a drug failed to demonstrate safety and efficacy, or for situations in which the Agency decided there were no or insufficient data to support the use of the drug? How would a sponsor with a mention of an alternative drug update its label if the alternative drug is supplanted as the treatment of choice or is restricted in use or removed from the market? Would a sponsor be held liable for adverse occurrences that result from use of the alternative drug product even though it would have no control over its inclusion in its own drug label?

In summary, we believe the proposal to make references to alternative drug therapies would be unworkable and lead to unsubstantiated comparisons of drug safety and effectiveness. Therapeutic recommendations of this type are best left to professionals who can be guided in their selection of compounds by their peers, literatures, and associations. While we recognize that the Pediatric Rule enables the Agency to require statements in labeling recommending preferential use of drugs labeled for pediatric use, we respectfully recommend that the corresponding single sentence be stricken from the draft guidance. Based on the concerns identified, additional efforts should be made to finding more appropriate mechanisms to facilitate the use of drugs of choice in pediatric patients.

Other Comments

The guidance refers to "minutes from FDA meetings" to serve as documentation for development, deferral or waiver decisions. Other types of communications could document these decisions and these should be provided for in the guidance.

The questions and answer format of the guidance is prepared in the first person in places and in the third person in others. It should be revised to be in the third person throughout.

The expression "likely to be" should be deleted from IV.A.2. (first bullet, second paragraph).

The guidance does not give any emphasis to the need for flexibility in the crafting and negotiation of pediatric development programs in concert with Agency staff. For pediatric development to be

maximally successful there needs to be the recognition that programs are required to be tailored to a given situation based on project issues and complexities.

Bristol-Myers Squibb appreciates the opportunity to provide these comments and requests that FDA give consideration to our recommendation. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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