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Laurie Smaldone, M.D.
Senior Vice President
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August 23, 2000

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

Re: Docket No. 00D-1335; Draft Guidance, Allergic Rhinitis: Clinical Development Programs for Drug Products 65 Federal Register 38563 (June 21, 2000)

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders; we have new chemical entities in development for allergic and immunologic diseases.

The BMS 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. Currently, the PRI pipeline comprises more than 50 compounds under active development including compounds used in respiratory diseases. In 1999, pharmaceutical research and development spending within BMS totaled \$1.4 billion. For these reasons, we are very interested in and well qualified to comment on this FDA draft guidance.

We commend the U.S. FDA for drafting a guidance document for clinical development in allergic rhinitis. However, there are several aspects of the proposed guidance that need to be reconsidered before a final guidance is completed. Below please find descriptions of our most significant issues and a listing of specific items FDA should consider in revising this draft.

General

Section III.A.1. specifies the need for at least two adequate and well-controlled phase 3 clinical trials for approval of allergic rhinitis indications. In subsequent subsections (2. Dose and 3.

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Safety Monitoring) reference is made to development of dose response data and safety data in “these” trials. “These” apparently refers to the phase 3 clinical trials discussed in the preceding subsection 1. It is inappropriate to develop dose-response relationships and safety data solely from phase 3 trials. This information should be developed earlier and throughout the drug development program, hence a clarification is required.

Throughout the document very specific guidance is provided on issues that are of general application to drug development. In order to avoid confusion and inconsistency, the guidance on the development of drugs in allergic rhinitis should only address development issues that are unique to this condition. For example, lines 81 through 104 address assessment of QTc interval prolongation, a major and contemporary drug development concern that should be addressed in a targeted guidance on this topic.

Effects of corticosteroids on adrenal function or growth or other toxicities of corticosteroids are addressed throughout the guidance. Since these issues are not specific to allergic rhinitis concerns, they would be better addressed in a separate guidance. Likewise, the document speaks to specific effects of antihistamines. We feel strongly that the guidance should give direction to the clinical development of drugs in allergic rhinitis without regard to existing compounds or their pharmacologic class. The guidance should be written in such a way as to support development of drugs with diverse and perhaps novel mechanisms.

There is need to be consistent with, and to cross reference particular sections of this draft with existing guidances. For example, text on lines 112 and 113 should be identical to that included in the referenced ICH safety database requirement guidance. In section III.B.1., brief reference is made to the requirements for establishing bioequivalence between oral formulations without referring to the existing detailed bioequivalence guidance document. Likewise, in section III.B.2. dealing with formulation changes for topical nasal preparations, cross reference should be made to the specific guidance being evolved for this issue. In section IV.A.2. dealing with pediatric development of drugs studied in adults, cross reference to the Pediatric Rule and associated guidances would be appropriate.

Under section III.B.2., it is very difficult to distinguish the “comparability approach” from the “stand-alone” approach for demonstration of comparability for a nasal product that has undergone a change in formulation. The difference could be clarified if the guidance provided the specific research objectives for each approach. As an example, the “stand-alone” approach might indicate the specific primary endpoint that should be designed into the recommended efficacy/safety trial. Also the guidance should state that the sponsor should select an approach in consultation with the Division.

We believe that the focus of the guidance should be a discussion of the elements contained in section V., Protocol Issues and Elements, as its greatest value to drug development is in this section. However, the rating system proposed in section V.F.3 (simultaneous use of both instantaneous and reflective scoring) is too rigid. The required use of both instantaneous and reflective symptom scoring will lead to multiple data points and inconsistencies in reported trial data. Employment of both measures requires patients to offer too many judgements. Patients become confused when offering both reflective and instantaneous measurements, leading to conflicting scores. The guidance also should state that the sponsor and Division should agree on

a rating system that is most appropriate for a particular development program.

Specific

- III.B.4. The guidance provided is not only relevant to corticosteroids, hence it should be moved to the appropriate section.
- IV.A. Rather than relate to drugs with known utility in allergic rhinitis and age groups in which pediatric studies should be accomplished for these products, the guidance should state what indications and dosage forms should be studied in specific age groups.
- IV.A.1. The guidance should describe what studies are required to avoid class precautionary labeling on pediatric growth.
- IV.A.3. The safety data requirement is ambiguous. Is it the intention to require 3 months or 1 month additional data for drugs already studied in adults?
- V.B. Inclusion criteria need to specify the duration of the symptomatic period required before enrollment, e.g., patients need to be symptomatic for 3 to 6 days.
- V.C. Reference to “super-potent” corticosteroids is open to interpretation.
- For oral drugs, rather than list specific drugs and suggested washout periods, a general reference to half-life e.g., 6 half-lives is adequate.
- VI.A. Baseline symptom scores to be used for change from baseline analysis should be clarified, e.g., average of last 3 measures.
- Additional secondary efficacy endpoint measures should include quality of life (“generic” and/or disease-specific) and physician global assessment. Physician-rated symptoms should be eliminated.
- VI. A new efficacy assessment category could be added as “E”, “Symptom-free Days”.
- There is also the need to assess the effect of pollen exposure in SAR trials and discussion of this should be included in section VI. Pollen exposure needs to be identified as a covariate.
- VII. This section should relate to the difficulty in capturing both the peak and the start of the allergy season.

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

Sincerely,

A handwritten signature in black ink that reads "Laurie Smaldone". The signature is written in a cursive style with a long horizontal flourish at the end.

Laurie Smaldone, MD
Senior Vice President
Regulatory Science and
Outcomes Research

