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November 15, 2001

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

**[Docket No. 01D-0269] - Draft Guidance for Industry on the Clinical Studies Section of Labeling for Prescription Drugs and Biologics - Content and Format; Availability (65 Federal Register No. 131 page 35797; July 9, 2001)**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified global 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, infectious diseases, neurological disorders and oncology. In 2000 alone, Bristol-Myers Squibb dedicated more than \$1.8 billion for pharmaceutical research and development activities. The company's more than 4,300 scientists are committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on the **Draft Guidance for Industry on the Clinical Studies Section of Labeling for Prescription Drugs and Biologics - Content and Format**

## Summary of BMS Comments

We believe that the proposed Draft Guidance for the Clinical Studies Section for product labeling represents a significant contribution to understanding the FDA's current thinking on (1) what studies should be included in the CLINICAL STUDIES section, (2) how to describe individual studies, and (3) how to present study data, including presentation of data in graphs and tables. We therefore, support the proposed Guidance Document subject to the following provisos and considerations under the following headings as presented in the Guidance:

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## II. IDENTIFYING STUDIES FOR INCLUSION IN THE CLINICAL STUDIES

### A. Studies That Should Usually Be Included in the Clinical Studies Section (Guidance page 2):

We believe that studies addressing safety as a significant endpoint may provide important clinical information. We suggest the following bullet be added:

- *“Other clinical studies that contribute critical safety data where the study was designed to evaluate specific safety endpoints”*

In addition the term “safety” should be added to footnote 4 as part of the concept of “other data”.

We request further clarification for the statement:

- *Clinical studies that provide important information about the limitations of effectiveness.*

Examples of such studies would be helpful to understand what type of studies the FDA would like included in this section. If observations concerning limitations of effectiveness are associated with subgroups they should be undertaken with caution since they were not planned in advance and thus constitute post-hoc analyses.

## III. DESCRIBING STUDIES IN THE CLINICAL STUDIES SECTION

### A. General Principles (Guidance page 3 - 5):

#### 2. Amount of Detail

*Ordinarily, less detail is needed in the following situations:*

*The clinical endpoints measured in the study are not readily measurable or applicable in clinical practice (e.g., exercise testing in a study of heart failure can demonstrate effectiveness but does not translate to a measurable clinical outcome).*

- We would like to assure that all endpoints that have been previously agreed to with the FDA can be incorporated into the Clinical Studies section regardless of subsequent determinations that they may not “be applicable in clinical practice”.

#### 3. Endpoints

We appreciate the flexibility in trying to deal with multiple endpoints. However we request clarification for the statements:

- *“Composite Endpoints: In general, effects on all components of a composite endpoint should be presented.....”* Please note that implicit in the concept of a “composite endpoint” is the understanding that the study is statistically powered for only the composite and not the individual components of the composite endpoint. Addressing a single component of the composite endpoint can be misleading unless qualified. Therefore some reference to this concern should be addressed in the guidance.
- *“Primary and Secondary Endpoints: The terms primary endpoint and secondary endpoint should only be used when they would be helpful to understanding a drug’s effect.”* Both terms are commonly understood and have widespread use. Their use in the package insert reflects agreements reached with the FDA to address the study design for endpoints and outcome data. Primary endpoints are the critical endpoints that must be met for regulatory approval, and “secondary” endpoints are adjunctive, providing important supportive data. In addition, there is an established credibility built into these

terms therefore, making this distinction in the package insert beneficial for prescribers. We request that you provide further insight into the rationale for removing or replacing these well accepted clinical and statistical terms.

- “Closely Related Endpoints: If two or more endpoints are closely related and convey essentially the same information, only one should be presented”. We feel this may be inconsistent with the statement for the “Composite Endpoints”. Please note we would like to retain the option to include data from closely related endpoints when appropriate.

#### 4. Comparative Data

Clarification is requested with reference to the first paragraph vs. the second paragraph as per the identification of the “comparator”.

- The first paragraph indicates that a comparator can be identified if “comparator contributes information that is essential to a clinician’s understanding of the drug’s effects” (*with the use of an explanatory statement regarding limitation of comparative data*). The second paragraph indicates that the name of the “comparator should be omitted if the data are not adequate to support a comparative claim”. Please provide clarification for this possible discrepancy.

### C. Summarizing Study Findings (Guidance page 6 - 8):

#### 1. Disposition of Patients:

We express concern for what appears to be a significant amount of new information regarding the disposition of patients:

- Provide clarification for the request to add “discontinuations” in the Clinical Studies section in addition to the current policy of including these data in the Adverse Reactions section.
- Although we agree that there may be circumstances when it may be beneficial to provide information on the “run-in periods or other distinct phases”, when this information does not materially add to the understanding of the drug’s effects it should not be routinely included.

#### 2. Treatment Effects

“Uncertainty of Treatment Effect:” We agree that the confidence interval is typically more informative than the p-value. However, section II.C of the Appendix says, “Differences should be accompanied by the appropriate measure of uncertainty (confidence interval or p-value).” Please explain this apparent contradiction.

#### 4. Demographic Subgroups

*Compelling results from analyses of other subgroups of established interest should also be presented, with a caution statement, where appropriate, about the inherent risks of unplanned subgroup analyses.*

- With respect to this issue of “unplanned subgroup analyses”- the guidance should identify that usually age, gender and race are not powered to measure differences. In addition, the caution statement should apply across all subgroups and remove the term “unplanned”.

**D. Presenting Data for Different Types of Outcomes** (Guidance page 8):

*I. Categorical Outcomes (e.g., success or failure):*

- Dropouts because of adverse events are usually presented in the Adverse Reaction section not in the Clinical Studies section. We request clarification whether it is necessary to present them in both sections.

**E. Advertising and Promotional Considerations** (Guidance page 9):

*...Therefore, the CLINICAL STUDIES section should be carefully scrutinized to ensure that its content does not suggest or imply claims for indications, doses, regimens, or comparative effectiveness that are not adequately supported”...*

- We note that information pertaining to design and results of clinical studies provide the basis for understanding the products clinical profile. Therefore, we would be concerned if information pertinent toward to this end is be omitted from the package insert.

**F. Updating the Clinical Studies’ Section** (Guidance page 10):

*“The CLINICAL STUDIES section should be updated when new, important information becomes available. Outdated information should be promptly revised or replaced.”*

- We feel that the FDA should clarify the type of information that would be considered “outdated”.
- In addition, changes to the clinical studies section do not always result in “prompt revision and replacement”. We feel that this terminology should be reserved for changes based on the postmarketing collection of adverse events and is not applicable to the Clinical Studies Section.

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,



Laurie Smaldone, M.D

Senior Vice President

Regulatory Sciences & Outcomes Research

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