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**July 9, 2004**

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

**Re: Docket No. 2004D-0187; BMS ID No. 0495. Draft Guidance, Premarketing Risk Assessment (*Federal Register* May 5, 2004)**

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the Draft Guidance on Premarketing Risk Assessment. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. Our comments are set forth below.

**Summary of BMS Comments on Proposal**

BMS commends the FDA on the development of this comprehensive Draft Guidance. Overall, BMS concurs with the FDA's recommendations regarding premarketing risk assessment, requesting that sponsors pay careful attention from the outset of development to the overall design of the safety evaluations and refine and modify safety assessments as experience accrues. There are, however, several aspects of the Draft Guidance on premarketing risk assessment that cause concern for BMS.

The document could benefit from increased clarity in describing the settings for additional assessments and broader discussions of appropriate methodologies to utilize as tools for the issues described. BMS also recommends partnering as early as feasible with the FDA review division and other FDA working groups, e.g., representatives from the Office of Drug Safety (ODS) and from the division of Statistical Sciences, to maximally foster early and open discussions of safety concerns and relevant premarketing risk assessment.

**Specific Comments (Items that Need Clarification & Recommended Actions)**

Specificity of the Guidance:

As written, the Draft Guidance includes a number of assessments that are qualified as "may" or "should" be performed. If all were done, the development program would be, by necessity,

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substantially larger and less focused, lengthening time to market for new important therapies. The Guidance could be improved by guiding the reader more specifically as to the settings in which additional assessments should be made. The specific times for discussion of each potential assessment between the Agency and the sponsor, e.g., end of phase II meeting, should be included with each assessment.

FDA partnership:

The involvement of ODS during discussions of premarketing risk assessment is not specified. Can the sponsor request that ODS be present and provide input at key meetings with the FDA, e.g., end of phase 2 or pre-NDA meetings? These meetings involve critical plans for the timing of risk assessment and strategies for risk management, and the participation of ODS earlier would improve the sponsor's understanding of the Agency's overall thinking.

Role for pharmacoepidemiologic studies:

In what instances would the FDA find the use of pharmacoepidemiological studies appropriate? Potential situations may include:

- Section IV.A., line 215 discussing background rates of morbidity and mortality: No clear definition is provided as to what methods or study designs would be acceptable to the FDA to gather these data.
- Section IV.C., line 328 discussing drug interactions: The FDA does not indicate whether pharmacoepidemiologic studies could be used to address this issue rather than the more traditional approach of PK/PD studies.
- Section IV.D., line 376 discussing high background rates of adverse events: The FDA fails to clarify the approaches which are acceptable to obtain background rates of adverse events and whether epidemiologic analyses are acceptable in order to contextualize potential signals in the premarketing environment.

Sample size considerations:

BMS recommends that the sample size of large simple safety studies (LSSS) needs greater specificity. We suggest adding a statement that the sample size of a LSSS should be guided by the anticipated rate of occurrence for the event of interest. For example, to show an event rate is  $< 1/100$ ,  $< 1/1000$  or  $1/10000$  a study of  $\sim 600$ ,  $\sim 6000$  or  $\sim 60000$  subjects, respectively would be needed.

Safety database size is also discussed in Section IV.A. where circumstances in which the database may need to be larger than 1500 patients are outlined. One instance described (line 214) is when the benefit of a product is of "uncertain magnitude (e.g., efficacy determination on a surrogate endpoint)." The FDA should clarify for certain life-threatening diseases which specific surrogate markers have been validated and are acceptable without increasing the size of the safety database. These would include HIV, hepatitis and malignancies. Line 231 urges sponsors to "communicate early in the development program" regarding size of the database; the guidance needs to be more specific, i.e., at which meeting or in which IND document.

Definition of rare events:

In the section discussing LSSS (V.A., line 449), BMS recommends that a definition of “rare” be provided. BMS believes that control groups should be recommended to properly assess the

relationship of a rare event to drug or disease depending on the background rate of these events in the population being studied. This recommendation also applies to Section IV.B.1, lines 262-265.

Inclusion criteria:

Certain suggestions, while useful, are not practical in all settings. Regarding the suggestion for broader inclusion criteria (IV.B., line 281), further thought may need to be given to the potential effects on study design.

Long term safety measurements:

Requests for long-term safety measurements (Section VI.G., lines 879-881) do not address the limitations of obtaining this information in subjects with chronic disease who are off-treatment. These subjects most often receive follow-on treatment with additional therapies. Determining the relationship of events to study therapies is confounded by the use of prior and subsequent treatment.

Minimizing the potential for medication errors:

BMS supports the FDA’s goal of minimizing the potential for medication errors. Many elements of the analysis described in Section V.B, however, are beyond the control of sponsors of clinical trials. Moreover, although FDA suggests a number of premarketing assessment techniques that sponsors may employ to evaluate the risk of potential medication errors associated with the proposed product name, professional and patient labeling, and packaging (Section V.B.), BMS requests that more specific and validated methodologies be put forward in the Guidance. For example, the proposed general techniques may provide some indication of areas for potential confusion, but sponsors do not have access to large databases of other manufacturers’ packaging materials and are not privy to information related to other products under regulatory review. Additionally, such studies cannot anticipate all situations relative to outpatient use by broad populations or the chains of dispensing and administrative activities associated with inpatient administration across multiple institutions. Thus, sponsor-conducted assessments will be incomplete, and may not provide an accurate overview of the issues FDA is trying to address.

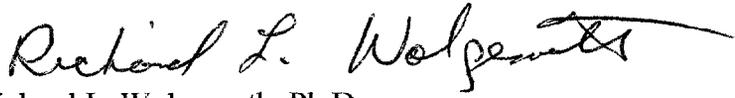
Specific evaluations:

- The collection of information on nutraceuticals (Section IV.C., line 345) is desirable; however, this information is frequently not disclosed despite direct questions.
- Addressing polymorphic metabolism in all new small molecule developmental programs is suggested in Section V.C., line 529. Guidance on specific methodologies acceptable to the Agency would be helpful.
- Exploring subpopulations for adverse event frequencies, e.g., frequencies by weight-adjusted dose (Section VI.C., line 737) has a high likelihood of producing false positive signals when events and populations are low frequency.

BMS appreciates the opportunity to provide comment and respectfully requests that the FDA give

consideration to our recommendations. BMS would be pleased to provide additional pertinent information as may be requested.

Sincerely,

A handwritten signature in black ink, reading "Richard L. Wolgemuth". The signature is written in a cursive style with a long, sweeping horizontal line extending to the right.

Richard L. Wolgemuth, Ph.D.  
Senior Vice President,  
Global Regulatory Sciences