



Bristol-Myers Squibb Company

David T. Bonk
Vice President & Associate General Counsel
Legal Division

P.O. Box 4000, Princeton, NJ 08540-4000
Tel: (609) 232-3114 Fax: (609) 232-0130
david.bonk@bms.com

July 28, 2004

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

Re: Critical Path Initiative [Docket No. 2004N-0181, 69 Federal Register, 21839 (April 22, 2004)]

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are pleased to comment on the Critical Path Initiative. Our comments are set forth below.

We applaud FDA's effort to address what some in the healthcare field have termed a "pipeline problem." More importantly, BMS agrees with the agency's overall goal of creating a new generation of performance standards and predictive tools that will provide better information about the safety and effectiveness of an investigational product at an earlier stage in the drug's development.

General Comments

As you are aware, HHS recently issued a call for comments on stimulating innovation in medical technologies. It appears that HHS is specifically interested in identifying ways in which its agencies can work together to facilitate the development and approval of new medical technologies.

Given this background, we would encourage FDA to work with other relevant health agencies, the pharmaceutical industry and the scientific community to develop a single, unified approach to critical path issues.

It is recommended that FDA collaborate in particular with:

- HHS generally
- the NIH Roadmap Initiative
- the European Medicines Evaluation Agency (EMEA)
- the Japanese Ministry of Health Labor and Welfare (MHLW)

2004N-0181

C14

- the pharmaceutical industry
- prominent investigators

Our comments on specific aspects of the Draft Guidance are set forth below.

Specific Comments

1) A Better Product Development Toolkit Is Urgently Needed

Figure 7: Industry - *FDA Interaction During Drug Development* (pg. 12) neglects discussion on post approval benefit/risk assessment. Systematic assessment is needed by therapeutic area or drug class, as to the scope of safety and efficacy evidence needed by regulators at the time of application submission versus what could appropriately be provided post-approval. Further, the process should include an ongoing review by therapeutic area to distinguish necessary Phase 4 studies from those that are informative but not required for the safe use of a drug. Absent this type of process, Phase 4 programs will continue to increase with little or no offsetting reduction in the Phase 3 testing requirements. Additionally, discussion and agreement of Phase 4 commitments earlier in the drug development process may help to facilitate this process.

The paper also discussed the “urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses.” Toward that end, the paper briefly describes FDA’s support of NIH’s Roadmap initiative, which is aimed at addressing important clinical research infrastructure problems. These efforts include giving more attention and creativity to disease-specific trial design and endpoints intended to evaluate the effects of medical products. BMS recommendations consideration of the following three points to assist these efforts:

Multiple efficacy endpoints: New drug approval in certain therapeutic areas including migraine, sleep disorders, fibromyalgia, antibiotics, and Alzheimer’s disease, increasingly requires statistically significant efficacy demonstration for more than one endpoint. Due to the fact that additional endpoint requirements can lead to increased study sample sizes, we suggest establishment of collaborative effort (e.g. a joint industry-FDA group) to analyze a review of multiple endpoint requirements by therapeutic area. Establishment of these data requirement norms may reveal opportunities to streamline clinical trial requirements.

Consensus on clinical endpoints: There is a pressing need for consensus both nationally and globally among regulators, physicians, and innovators as to appropriate clinical trial outcomes measures. Selecting a forum for stakeholders to discuss and agree on priorities, methods, sponsors, and conclusions is a necessary first step. The ICH process is a potential candidate for this forum since many procedures and relationships are already in place, but other multilateral agreement forums could also be structured. Means to facilitate incorporation of clinical outcome information, especially quality of life and health economics measures, into product labeling should be considered in this process.

Framework for Guidance Development: We also encourage the agency to continue, in other therapeutic areas, the framework it has established to address treatments for obesity, which includes the establishment of the Obesity Working Group, public meetings with discussion on obesity issues, development of a report/action plan that will facilitate development of more

medical products to treat obesity, as well as research to get a better understanding of consumer behavior and motivation.

2) Tool for Demonstrating Medical Utility

Towards a Better Effectiveness Toolkit

FDA writes (pg 23) that, “Additional biomarkers ...and additional surrogate markers... are needed to guide product development.” The paper also states that datamining and analysis may be all that is needed to confirm surrogacy of a particular marker. Finally, it states that for biomarkers that currently appear promising, a few specific projects need to be undertaken.

We agree with the agency that there is a tremendous need for the establishment of regulatory decision-making biomarkers. We suggest a joint industry-FDA-NIH task force be established to create a list of promising biomarkers. Following the establishment of this list the task force then needs to proceed to work on other related initiatives (e.g. pooling data for analysis by a third party and establishment of cross-institutional, multidisciplinary work groups to study the design and validation of biomarkers from the accumulation of sufficient data, preferably from multiple sources, to demonstrate a persuasive statistical or evidentiary case) to ensure acceptance of these biomarkers.

Additionally, development of validation processes (to include both algorithms and data quality) is a necessary first step, particularly for applications such as adverse event data mining. Decisions made without considering methods validation would be counter-productive.

The paper also talks about advancing the use of new imaging technologies in drug development (pg 24). Approval of novel imaging technologies could involve more than one Agency Center and so, consideration of methods to coordinate reviews across Centers should be a component of this project, with a goal to develop industry guidance.

3) Tools for Characterization and Manufacturing

We commend the agency for its efforts to date to incorporate the most up-to-date science into manufacturing regulations that enable and encourage manufacturing innovation. BMS also recommends the continuation of joint FDA-industry efforts to advance risk-based manufacturing regulations should continue to be aggressively pursued.

Again, BMS commends the agency for its continued efforts to try and assess and improve the regulatory decision-making processes and paradigms. We would be pleased to provide additional comment as needed.

Sincerely,



David T. Bonk