

Bristol-Myers Squibb  
Pharmaceutical Research Institute

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January 22, 2002

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

Re: Docket No. 01D-0488; Proposed Draft Guidance, "*Food-Effect Bioavailability and Fed Bioequivalence Studies : Study Design, Data Analysis, and Labeling*" (Federal Register Vol. 66, No. 229, November 28, 2001)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide 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 and 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For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance for Industry, "*Food-Effect Bioavailability and Fed Bioequivalence Studies : Study Design, Data Analysis, and Labeling*".

**Summary of BMS Comments on Proposal**

We commend the U.S. FDA for availability of the Draft Guidance on Food-Effect Bioavailability and Fed Bioequivalence studies. To enhance the clarity of the Draft Guidance, BMS respectfully suggests delineation of BA food effect studies and BE studies under fed conditions that are described in this Draft Guidance. In addition, since most drugs are administered repeatedly, multiple-dose food effect studies would be more relevant in a clinical setting than single-dose studies.

Specific comments related to the Draft Guidance are cited below.

**Specific Comments**

- (1) In the 'Introduction' section, the methods for assessments for 'rapidly dissolving' and 'similar dissolution' have not been described.

**Recommendation:** FDA should clarify which Guidance(s) should be followed for these assessments.

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- (2) In the 'Background' section, the Draft Guidance refers to BCS Class I drugs but does not specify exceptions (such as those described in the Guidance for Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000).

**Recommendation:** The Draft Guidance should include exceptions to BCS Class I drugs (e.g. narrow therapeutic index drugs), where the bioavailability and clinical outcome could be sensitive to differences in dissolution.

- (3) The Agency acknowledges ongoing clinical research studies that are designed to test the hypothesis of this Draft Guidance. Results from these studies have the potential to impact several of the provisions stated in this Draft Guidance.

**Recommendation:** Data from the ongoing clinical research studies and FDA in-house data must be distributed to the industry for review and comment prior to the finalization of this Draft Guidance.

- (4) It is not clear whether a BA study under fed conditions is required for an ANDA. If a BE study under fed conditions is required, then does this imply that no food-effect BA studies are needed? If the drug product is recommended to be taken with a light meal, can the BE study under fed conditions use a light meal instead of a high-fat meal? The Draft Guidance states, 'When the label of the RLD does not make any statements about the effect of food on absorption or administration.' It is unclear if this statement means that the innovators of the RLD conducted a food-effect study, which demonstrated no food-effect, or that the innovators did not perform a food-effect study.

**Recommendation:** Requirements for ANDAs should be clarified. In general, ANDAs *should* contain information on the effect of food on the test product.

- (5) In the 'Study Considerations' section, the statement of '... excipients are qualitatively the same..' is not clear. Does this mean 'proportionally similar' as described in FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations, October 2000?

**Recommendation:** Details for evaluation of excipient composition must be provided.

- (6) The 'Test Meal' section does allow the use of a meal that is 'significantly different' from the high-fat meal. Descriptions of other meals, e.g. a light meal which would be relevant to the cancer or AIDS population, should be provided. In addition, do the sponsors have to conduct studies to demonstrate that the drug product can be taken 1 hour before or 2 hours after a meal? In the 'Administration' section, the Draft Guidance recommends that the drug product be taken with 240 mL (8 fluid ounces) of water. Given that a subject will consume 8 fluid ounces of whole milk with a high-fat meal, the volume of total fluid intake appears to be excessive.

**Recommendation:** A description of a light meal should be provided. Recommendations for determination of timing of dose administration with respect to meal consumption should be included. Volume of total fluid intake should be revised.

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- (7) The 'Data Analysis and Labeling' section indicates that 90% CIs have to be reported for both  $AUC_{0-\infty}$  and  $AUC_{0-t}$  (paragraph 1). This requirement is inconsistent with paragraph 4, where either  $AUC_{0-\infty}$  or  $AUC_{0-t}$  is recommended. This inconsistency is also noted in the succeeding paragraphs where either  $AUC_{0-\infty}$  or  $AUC_{0-t}$  evaluation is considered to be sufficient or equivalence of both parameters is required to be demonstrated.

**Recommendation:** The Draft Guidance should clarify if evaluation of  $AUC_{0-\infty}$  and/or  $AUC_{0-t}$  is required to show an effect of food on BA.

**Elements Which Should Be Modified**

- (1) On page 5, line 167 (section entitled 'INDs/NDAs'), '... to-be-marketed formulation and the primary clinical trial...' It is recommended that the word 'primary' be replaced by 'pivotal'
- (2) On page 5, line 182 (section entitled 'ANDAs') , '... BE study under fed conditions is recommended for ...' It is suggested that the word 'recommended' be replaced by 'required.'

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

Sincerely,



Laurie F. Smaldone, M.D.  
Senior Vice President  
Global Regulatory Sciences

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