

Bristol-Myers Squibb Pharmaceutical Research Institute

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

Re: Docket No. 02D-0258; Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations [Federal Register Vol. 67; No. 133: 11 July 2002]

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 2001 alone, Bristol-Myers Squibb dedicated \$2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and physicians 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 proposal to provide guidance for the pharmaceutical industry on bioavailability and bioequivalence studies for orally administered drug products.

Summary of BMS Comments on Proposal

We commend the U.S. FDA for assembling this thorough and well written document. In particular, we applaud the changes from the previous (October, 2000) version. However, there are a several points in the proposed guidance that we at Bristol-Myers Squibb respectfully request be given additional consideration.

02D-0258

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A Bristol-Myers Squibb Company

Specific Comments (Items that Need Clarification & Recommended Actions)

Page 5, Second paragraph of Section II. C. 1: The phrase “nondocumentation of BE” used twice in this paragraph is awkward and a bit misleading.

Recommendation: *FDA should consider replacing “nondocumentation of BE” by the phrase “failure to demonstrate BE”.*

Pages 6-9, Section III, A: This Guidance never mentions stable isotope methodology which has frequently been a useful technique for demonstrating BE.

Recommendation: *FDA should consider adding a section on using stable isotope methodology to demonstrate BE.*

Page 7, Last sentence of Section III. A. 2: “A pilot study that documents BE may be appropriate, provided its design and execution are suitable and a sufficient number of subjects (e.g., 12) have completed the study.” The reference to 12 being a sufficient number of subjects is unclear. The sufficiency of a sample size depends on a number of factors, primarily variability. Does the agency mean that the absolute minimum sample size on which BE could be documented is 12 subjects?

Recommendation: *FDA should clarify what it means by “a sufficient number of subjects” and whether a sample size of 12 subjects is the minimum with which to document BE.*

Page 7, Section III. A. 4: The clearly stated recommendation to use nonreplicate study designs seems contradicted by the subsequent list of advantages of replicate designs. There may be particular cases (e.g., highly variable drugs) where the replicate design would be superior to the otherwise recommended nonreplicate design.

Recommendation: *FDA should provide guidance as to when a replicate design might be preferred to a nonreplicate design.*

Middle of Page 11, Section III. D: The third bullet item of the list of information generally included in the dissolution method development report for an NDA is “Dissolution profiles generated on all strengths in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer).” The same three dissolution media (pH 1.2, 4.5, and 6.8 buffer) are recommended in Section V.C.2.a. (bottom of page 13), and in V.D.3.b. (middle of page 17). However, there are cases in which the three listed pH buffers are insufficient.

Recommendation: *FDA should consider adding a phrase like “or other media, as appropriate” to the three citations of this list of recommended dissolution media: i.e., “...three dissolution media (pH 1.2, 4.5, and 6.8 buffer, or other media as appropriate).”*

Middle of Page 11, Section III. D: Reference to “the best discriminating ability” in “The agitation speed and medium that provide the best discriminating ability, taking into account all the available in vitro and in vivo data, will be selected” seems to require more than is necessary.

Recommendation: *FDA should consider rewording “best discriminating ability” to “meaningful discriminating ability”.*

Middle of Page 12, second bullet in Section V: Recommendation: *The phrase “the ratios of inactive ingredients” should be changed to “the changes in the ratios of inactive ingredients”.*

Middle of Page 14, Section V.C.2b: The section on “NDAs and ANDAs: Postapproval” does not refer to biowaivers for higher and lower strengths such as that described in the previous page under “Waivers for In Vivo Studies”.

Recommendation: *The Guidance should include information on postapproval biowaivers for higher and lower strengths.*

Middle of Page 15, first paragraph of Section V. D.1: It is possible for the originator of the first modified-release formulation of a drug product to develop a reformulation. In that case, does the statement that “Subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product should be submitted as ANDAs.” apply to original drug innovators as well as generic substitutes?

Recommendation: *FDA should clarify whether an ANDA or SNDA would be required for subsequent modified-release formulations from the originator of the first modified-release product.*

Page 18, Section VI. A: Recommendation: *Since this paragraph deals with food effect studies, it should reference the corresponding Guidance for Industry on that subject. Moreover, since food effect and BE studies are so similar in design, conduct, and analysis, the FDA should consider combining these two Guidances into a single comprehensive Guidance.*

Page 22, Attachment A, first bullet under Study Conduct: Recommendation: *The phrase “under fasting conditions, unless the study is a food-effect BA and BE study” should be “under fasting conditions, unless the study is a food-effect BA study or a BE study with food”.*

Bottom of Page 23, Attachment A: The Guidance calls for statistical analysis (90% confidence intervals) of both AUC_{0-t} and $AUC_{0-\infty}$, as well as C_{max} . However, AUC_{0-t} and $AUC_{0-\infty}$ are such highly correlated endpoints that they are essentially two measures of the same thing. Requiring both AUC_{0-t} and $AUC_{0-\infty}$ to pass the BE criterion increases the overall chance of a type II error (concluding inequivalence when the formulations are, in fact, equivalent). Analyzing both, but requiring only one of AUC_{0-t} or $AUC_{0-\infty}$, to pass the BE criterion increases the overall chance of a type I error (concluding equivalence when the formulations are, in fact, not equivalent).

Recommendation: *The Guidance should call for the analysis of C_{max} and one of either AUC_{0-t} or $AUC_{0-\infty}$, as pre-specified in the study protocol.*

Bottom of Page 24, Attachment A: The Guidance correctly admonishes against rounding off the confidence limits used to test BE. However, the extra two decimal places in the statement “to pass a CI limit of 80 to 125, the value of should be at least 80.00 and not more than 125.00” suggests that rounding 79.999 to 80.00 or 125.001 to 125.00 would be acceptable, whereas rounding 79.99 to 80.0 or 125.01 to 125.0 would not.

Recommendation: *The Guidance should call for sufficient decimal places to be*

reported in order to clearly indicate whether the confidence limits fall below or above the specified equivalence limits.

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,

A handwritten signature in cursive script that reads "Laurie Smaldone".

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