



Corporate Regulatory Science

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December 20, 1999

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

**RE: Draft Guidance for Industry: BA and BE Studies for Orally
Administered Drug Products – General Considerations
[Docket No. 99D-2729]**

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people and serving customers in more than 130 countries.

Overall, we find the guidance document to be a thoughtfully prepared and balanced survey of the issues surrounding the design and conduct of bioavailability and bioequivalence studies. We have comments and suggestions on a specific section of the draft guidance as shown below.

Pages 15 and 16: The Draft Guidance states the following:

V. DOCUMENTATION OF BA AND BE

C. Immediate Release Products: Capsules and Tablets

1. General Recommendations

"For product quality BA and BE studies, where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study should be performed. In vivo BE..."

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Response:

For many drugs, single-dose studies conducted under fasting conditions provide the best assessment of BA/BE. There are, however, other drugs for which studies conducted under fasting conditions do not provide the best or the most clinically-relevant assessment of BA/BE. In general, this group will include drugs that have improved bioavailability when given under nonfasting rather than fasting conditions, and the approved labeling for such drugs will recommend that they be administered with food. While it may generally be true that studies conducted under fasting conditions provide the most rigorous test of BA/BE, with better power to discriminate between formulations, for this specific group of drugs, studies conducted under nonfasting conditions provide the most clinically-meaningful assessments of BA/BE.

When the BA/BE of a drug with these characteristics must be studied under fasting conditions, the absorption is substantially lower than would be observed under nonfasting conditions or in the clinical use of the drug. It is typical that this lower absorption under fasting conditions would also be more variable. The increased variability would increase the number of subjects required to have acceptable power for demonstrating bioequivalence, resulting in significant additional costs and exposure of healthy subjects to drugs for which they have no medical need.

Even if one dismisses the problems of cost and subject exposure associated with increased variability and the resulting increase in the required number of subjects, the question of clinical relevance remains. If the approved labeling of an immediate-release drug product states that the product should be taken with food, there is little apparent clinical relevance to administering the drug under fasting conditions in a BA/BE study. The plasma concentrations observed under fasting conditions would be much lower than the concentrations expected when the same dose is administered with food to patients. These unusual conditions and relationships could be difficult to defend to physicians who may wonder about the clinical utility of data generated at plasma concentrations which are much lower than those expected in their patients.

We suggest that an additional statement be added to the guidance which recognizes the utility of using nonfasting conditions. One suggestion might be:

BA/BE studies may be conducted under nonfasting conditions if bioavailability is significantly improved when the drug administered with food, and the sponsor agrees to recommend in labeling that the drug be administered with food.

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CLOSING COMMENTS

We recommend that the final promulgation and implementation of any proposed guidance should be undertaken in conjunction with an industry-wide educational effort due to the scope and potential implications relating to the design and cost of clinical trials. Finally, public seminars will serve to clarify regulatory expectations and interpretations.

Thank you for the opportunity to comment.

Yours truly,



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cc: Vinod P. Shah (HFD-350)