

Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs
January 28, 2002

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2383
215 652 5000

Dockets Management Branch (HFA-305) JAN 28 P1:13
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852



RE: Docket No. 01D-0488
Draft Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Merck & Co., Inc, is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates through comprehensive, state-of-the-art R & D programs that include basic research or discovery, developmental studies in animals, manufacturing quality assurance testing, and human clinical research. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists have long experience with issues of study design, data analysis, and labeling with respect to food-effect bioavailability (BA) and fed bioequivalence (BE) studies. Therefore, we are very interested and well qualified to offer the following comments on this draft guidance.

General Comment

This draft guidance is a revision of the October, 1997, draft guidance entitled *Food-effect Bioavailability and Bioequivalence Studies*. We commend the Food and Drug Administration (FDA) for its continued effort to provide guidance on its current thinking on how to meet the BA and BE requirements of 21 CFR 320, 314.50(d)(3), and 314.94(a)(7) for oral dosage forms.

Specific Comments

As requested in the guidance, to expedite FDA review of comments, the specific comments below are identified by specific line numbers from the PDF version of the draft guidance posted on the CDER web site at www.fda.gov/cder/guidance/4613dft.pdf.

1. Lines 79-83 (and elsewhere): The Agency states the belief that "...for many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) important food effects on BA are least likely to occur because absorption of drug substances in Class I is usually pH- and site-independent and insensitive to differences in dissolution." However, footnote 2 on page 3 indicates that this is an hypothesis which the Agency is currently studying at the University of Tennessee and that the results of this research will be considered along with literature and in-house data to test this hypothesis as the guidance is being finalized. Yet the draft guidance specifically excludes BCS Class I-

01D-0488

C 9

type compounds which dissolve rapidly from the recommendation to conduct a fed BE study for ANDAs (lines 134-136).

Comment

Bioequivalence studies are conducted to predict whether products that have not been subjected to direct clinical testing will have the same clinical effect as the originally tested product. The purpose is to assure that the “consumer risk” of being exposed to bioinequivalent products is extremely low. The validity of conclusions of equivalence based on data resulting from such studies depends on proven and accepted pharmacokinetic principles. Until a substantial body of information is available and has been reviewed and accepted by qualified experts as confirmation of the hypothesis that rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) are not subject to important food effects on BA, such products should not be categorically excluded from the recommendation to conduct fed BE studies. Given that the hypotheses is only now being studied, the agency’s proposal is premature.

2. Lines 45-49: It is proposed that the bioequivalence limits of 80-125% for the analysis of Cmax and AUC data (90% confidence interval (CI)) in food-effect BA studies be used as evidence of an absence of food effects and in fed BE studies to demonstrate the BE of a test and reference product.

Comment

(a) To improve the clarity of this bullet, the second sentence (beginning on line 46) should be rewritten as follows:

It proposes an equivalence limit of 80-125% for the analysis of Cmax and AUC data (90% confidence interval) both as evidence of an absence of food effects in food-effect BA studies and to demonstrate the BE of a test and reference product in fed BE studies.

As written, the second part of this statement seems unnecessary since test and reference products in a ‘fed BE’ study are given under the same fed condition (ie, one cannot determine the effect of food on either formulation).

(b) We disagree with the establishment of a standard difference of 20% or less as the cutoff for determining *the significance* of a food effect. This would appear to require a product to be labeled with a significant food effect because, for example, Cmax differed by more than 20%, even in the presence of phase 3 data that clearly show that such an effect is not clinically relevant. We favor selection of a more rigidly justified interval, pre-specified in the protocol, based on overall clinical criteria including dose and/or concentration-response data and safety/tolerance experience. In essence, NDA sponsors must make this determination during the drug development process in order to determine how an NCE will be dosed relative to food in pivotal clinical studies of safety and efficacy

3. Lines 115-118: For immediate-release products and lines 161-164 for modified-release drug products, the guidance indicates that BE should be demonstrated when there are changes

in components, composition, and/or method of manufacture (using SUPAC definitions) between the clinical trial formulation and the to-be-marketed formulation. Lines 123-126 and 160-164 note that these are generally conducted under fasting conditions but “When the fasting study does not establish BE, and food significantly affects the drug product’s performance *in vivo* (BA), it is important to determine food effects on the to-be-marketed formulation”.

Comment

This latter statement needs clarification since it seems to imply that one could fail to confirm bioequivalence, or could even show bioinequivalence, under fasting conditions between the to-be-marketed and clinical trial formulations and yet (presumably) go forward with the to-be-marketed formulation based on showing bioequivalence with the clinical trial formulation under fed conditions. Even if the product is labeled to be taken with food, a single bioequivalence study conducted with a high-fat breakfast would not provide assurance of bioequivalence under any and all other food regimens to which the ‘clinical trial formulation’ was exposed. Therefore we recommend that failure to confirm bioequivalence under fasting conditions should not be invalidated with demonstrating bioequivalence under fed conditions.

4. Lines 230 and 238 indicate that drug product should be taken with 240 mL of water in BOTH the fasted and fed treatments of a study. It should be noted (line 216) that the fed treatment ALSO includes 240 mL of additional liquid (milk) so that the total liquid load differs between fed and fasted regimens.

Comment

Consideration should be given to the potential for the difference in total fluid volumes between treatments to lead to a difference in gastric emptying times or patterns and, thereby, confound the interpretation of the differences in results as being due to a food effect.

5. Lines 305 –307 essentially states that for no food effect to be concluded, the food effect on T_{max} is also expected to be similar between the fasted and fed treatments.

Comment

It is common that food affects the time at which peak exposure occurs, but in many cases there are no important effects on C_{max} or AUC. Because it is unclear if a provision that T_{max} be “similar” between fed and fasted conditions is a clinically important part of determining a food effect for many drugs, we would favor a justification of any important T_{max} differences to be pre-specified in the protocol, based on overall clinical criteria including dose and/or concentration-response data, safety/tolerance experience, and the drug indication.

6. Editorial/technical issue: In the course of reviewing the draft guidance, we noticed that the PDF version of the document uses the Greek symbol for infinity in the subscript to indicate AUC to infinity (AUC_{0-∞}). We found that some printer drivers don't recognize this symbol

RE: Docket No. 01D-0488

Draft Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Page 4

and print it instead as the number “4” (AUC_{0-4}). A possible solution to this technical problem would be to substitute “inf” for the symbol in the expression of this term.

Conclusion

We commend the FDA for its ongoing effort to provide advice to industry on its current thinking on regulatory issues through the issuance of guidance documents and for seeking input from industry in their development. Overall, with respect to the “Draft Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling,” we recommend that the final guidance include greater recognition of the importance of clinical criteria (including dose, concentration-response data, and safety/tolerance experience) in addition to the results of food-effect bioavailability studies and fed bioequivalence studies with respect to product labeling.

We welcome the opportunity to comment on this draft guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,


for Bonnie J. Goldmann, MD
Vice President Regulatory Affairs Domestic

Bonnie J. Goldmann, MD
Vice President Regulatory Affairs Domestic