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Dockets Management Branch (HFA-305)
Food and Drug Administration
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RE: Docket No. 02D-0258
Draft Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General considerations

Merck & Co., Inc, is a leading worldwide, human health products company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to support the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

In the course of developing our product candidates, Merck scientists regularly confront bioavailability and bioequivalence issues. We are, therefore, both interested in, and well qualified to comment on the recommendations addressed in this draft revised guidance on bioavailability and bioequivalence studies for orally administered drug products.

We commend the FDA for updating the October, 2000 "*Guidance for Industry on Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations*," to reflect the current thinking of the Agency on this important topic. In general, we welcome the revisions to this document. We have the following specific comments, however, for your consideration in preparation of the final guidance.

1. Page 4- II.C. first paragraph- "same molar dose."

It should be clarified whether potency adjustment for small variations in the assay of drug content between formulation batches should be carried out, or whether nominal dose potency should be used. Merck proposes adjustment.

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2. Page 4- II.C. first paragraph

The Guidance should define the terms *pharmaceutical equivalents* and *pharmaceutical alternatives*. In the CPMP Note for Guidance on the investigation of bioavailability and bioequivalence, July 2001(<http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf>), the terms are defined as:

Pharmaceutical equivalence - Medicinal products are pharmaceutically equivalent if they contain the same amount of the active substance(s) in the same dosage forms that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and /or absorption.

Pharmaceutical alternatives - Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc) of that moiety or in the dosage form or strength.

3. Page 7 – III.A.2. - Pilot Study

Please refer to the last sentence in the above referenced paragraph which states:

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.

- a. Is this statement intended to indicate that a pilot study with $n = 12$ may be “appropriate,” if adequately designed, to form a definitive regulatory BE conclusion?
- b. Please comment on the rationale of recommending $n=12$ for a pilot study to form a definitive BE conclusion. In addition, the sample size alone does not qualify a pilot study to be definitive. The batch size is also important (at least 1/10 of production scale or 100000 units, whichever is greater).

4. Page 8- III.A.5.- Study Population

The objective of a BE study is strictly to evaluate whether two products are bioequivalent. To best meet this objective, other confounding variables should be eliminated or tightly controlled. The more heterogeneous the study population in a BE study, the greater the likelihood of masking the ability of the study to achieve its objective. With a very heterogeneous study population in a study, the number of subjects powered for bioequivalence will probably be more than with a homogeneous population. Also, if a subpopulation requires dose adjustment (e.g. elderly), and if a study is needed on the highest weight multiple dose, that would not be possible with the mixed population. Further, there exist some drugs for which their pharmacokinetics varies with stage of menstrual cycle.

In the CPMP Note for Guidance on the investigation of bioavailability and bioequivalence, July 2001 (<http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf>), it was stated that: "The subject population for bioequivalence studies should be selected with the aim to minimize variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers. The inclusion/exclusion criteria should be clearly stated in the protocol. Subjects could belong to either sex; however, risk to women of childbearing potential should be considered on an individual basis". For the reasons stated above, we recommend the guidance to adopt similar language as in the CPMP.

5. Page 9- III. A.8.a. and Page 23- Attachment A - Partial AUC

More research on early exposure should be done before the agency adopts this approach.

6. Page 9- III. A.8.c. and Page 23- Attachment A.

Since both AUC_{0-t} and AUC_{0-inf} have been requested, the guidance should address whether both have to meet 90% CI limits 80 to 125%. It is our recommendation that it should be left to the sponsor to decide prospectively which AUC will be subjected to these limits when designing the protocol.

7. Page 11- III.D. – Dissolution method

It should not be required to supply both USP Apparatus I and II data. We recommend changing "and" to "or" in the following statement:

Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopeia (USP) Apparatus I (basket), and 50 to 100 rpm for USP Apparatus II (paddle).

8. Page 11- III.D. – Dissolution profiles for poorly soluble drugs

If the drug being considered is poorly soluble, it is not necessary to run surfactant dissolution at 3 different pH buffers, as implied by the statement:

Dissolution profiles generated on all strengths in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants should be used.

9. Page 11- III.D – FDA method

The meaning of the term “FDA method” in the following statement is not entirely clear and should be further explained.

If a USP method is not available, the FDA method for the reference listed drug should be used.

10. Page 12 V. and Page 13- V. C.2. – Proportional formulations

With regard to the statements below regarding conditions that are necessary to permit waiver of in vivo studies for different strengths of a drug product, the guidance does not mention the manufacturing process. While it is generally understood that these conditions apply to proportional formulation only when the different strengths are manufactured by the same process, we recommend that, for completeness, this should be stated in the final guidance.

Waiver of in vivo studies for different strengths of a drug product may be granted under § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an acceptable in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test.

When the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the reference listed drug, an in vivo BE demonstration of one or more lower strengths can be waived to the reference listed drug based on dissolution tests and an in vivo study on the highest strength.

11. Page 15-17, V.D.1-4. – Consistency of use of the term “modified release”

Following the definition of modified release products, which includes both delayed-release and extended-release products, the guidance should be consistent in using modified release terminology to cover both categories.

12. page 16- V.D.1 – BA Studies for Modified-release Product

If the modified release tablet or capsule formulations are proportional formulations and have demonstrated linear dose proportionality, it is not necessary to conduct BA studies on all the strengths as recommended in the following statement from the draft guidance.

This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted as an NDA:

A single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules.

13. Page 18- VI.A.- Food-effect studies

The draft guidance includes the following general statement about food-effect BA and BE studies. Under what condition should BE study be conducted with food?

Coadministration of food with oral drug products may influence drug BA and/or BE. Food-effect BA studies focus on the effects of food on the release of the drug substance from the drug product as well as the absorption of the drug substance. BE studies with food focus on demonstrating comparable BA between test and reference products when coadministered with meals. Usually, a single-dose, two-period, two-treatment, two-sequence crossover study is recommended for both food-effect BA and BE studies.

14. Page 22- Attachment A

Under the paragraph describing the lots used in studies, the batch size for definitive BE studies should be mentioned: 1/10 of production scale or 100000 units, whichever is greater.

15. Page 23- Attachment A – Subjects with pre-dose plasma concentrations

The presence of drug in pre-dose samples could be due to various reasons, e.g., insufficient washout, interference, contamination. Please provide a rationale for not correcting pre-dose plasma concentrations if $<5\%$ of C_{max} . It might be better to let the sponsor deal with this issue using the best scientific judgment.

If the predose concentration is less than or equal to 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations.

16. Page 24- Attachment A - Rounding

The guidance recommends not to round. However, the example expresses confidence interval limits (%) in two decimals (i.e. rounding is still required). Instead of mentioning not to round off, the guidance should express the desirable CI decimal places.

Format comment:

Page 10- III.A.8.c. For computers without WordPerfect Greek Century font installed, the symbol tau in AUC0-tau is incorrectly displayed and printed.

For steady-state studies, the measurement of total exposure should be the area under the plasma, serum, or blood concentration-time curve from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the length of the dosing interval.

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Conclusion:

We commend the Center for Drug Evaluation and Research in its continued effort to provide up-to-date guidance to industry on its current thinking with respect to meeting regulatory requirements for the demonstration of bioavailability and bioequivalence. We welcome the opportunity to comment on this draft guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

A handwritten signature in black ink, appearing to read "David W. Blois". The signature is written in a cursive style with a large initial 'D'.

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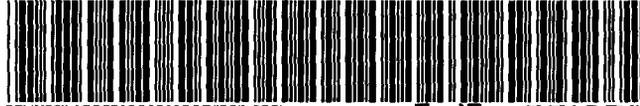
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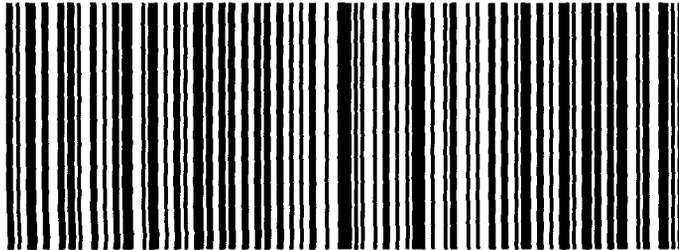
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