

# PHARMACIA

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Jenny Peters  
Director  
Global Regulatory Affairs  
Global Regulatory Policy & Intelligence

Pharmacia Corporation  
7000 Portage Road  
Kalamazoo, Michigan 49001

telephone: (616) 833-8141  
facsimile: (616) 833-0512  
jenny.i.peters@pharmacia.com

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 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*Draft Guidance for Industry on Food-  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*

Dear Sir/Madam,

As a company actively engaged in the drug development process, Pharmacia appreciates FDA's issuance of the draft guidance for industry, *Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling* (November 28, 2001, Federal Register, page 59433). The Clinical Pharmacology, Pharmaceutical Sciences, Statistics, and Regulatory divisions at Pharmacia have reviewed the guidance. Our specific comments are outlined below.

Note: Line designations below refer to the guidance document located at the Internet site: <http://www.fda.gov/OHRMS/DOCKETS/98fr/010488g1.pdf>. We noticed that there is another numbering of the guidance at <http://www.fda.gov/cder/guidance/4613dft.PDF>.

1. *Lines 50-53: It proposes an equivalence limit of 80-125% for the analysis of Cmax and AUC data (90% confidence interval (CI))....* When it can be demonstrated that AUC rather than Cmax is associated with activity, it should be stated that a less rigid criterion can be applied for Cmax.
2. *Line 233-235: General comment – There should be a recommendation for a vegetarian alternative.*
3. *Line 243-244: However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above....* There should be a recommendation for therapeutic indications and patient populations, e.g., oncology patients, where this meal is not applicable or could even be harmful.

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4. *Line 256: ...administration of the drug product immediately after the meal....*  
Consider putting a time frame for what is meant by immediately (within 5 minutes?).
5. *Line 266–267: It may be advisable to measure other moieties in the plasma....* This statement is vague. The BA/BE Guidance referenced in lines 268 – 269 is clear on when it is necessary to measure metabolites. Could the FDA link these two, i.e., metabolites should be measured in Food Effect BA studies if they have been identified as part of the development program to be relevant in line with the BA/BE Guidance?

General comment - When there is more than one metabolite, is it enough to establish BE with the one present in the highest amount, even when the others maybe active (also relevant to the BA/BE Guidance)?

6. *Lines 285-286: Peak exposure (Cmax), Time to peak exposure (Tmax)* The term "peak exposure" can be confused with total exposure. Peak concentration or maximal concentration is much more precise.
7. *Line 286 -288: The exposure measures Tmax, tlag, and t1/2 are encouraged; however,* there is no indication on how they should be analyzed.

The guidance mentions tabulating lag time for food-effect studies with modified release products. Is there a description of preferred procedures for estimating lag time in another guidance that could be referenced here?

8. *Line 288-289: Terminal elimination half-life and other relevant pharmacokinetic parameters* are listed as exposure measures for assessment of BA and BE. The analysis and role of these parameters is not discussed further in the guidance. We recommend that they be removed from the guidance.
9. *Line 295-296: For ANDA fed BE studies, the RLD administered....* With 3 acronyms, the sentence becomes difficult to understand.
10. *Line 311-312: ...the sponsor should provide specific recommendations on the clinical significance....* Suggest changing to "the sponsor should provide specific information on the clinical significance...." This information should form the basis for making label recommendations as indicated in Line 317. Left as is, the order of the paragraph is potentially confusing.
11. *Lines 332-333: ... that no food effect on BA is expected provided that Tmax values are also similar between fasted and fed treatments....* Use of the term similar is vague here. Additionally, the fact that this part of the guidance refers to both immediate release (IR) and modified release (MR) dosage forms is also problematic. For many MRs the profiles are very flat, so Tmax is not well characterized, and concentration-time profiles can be quite similar yet have very different Tmax values

in the absence of a significant food (treatment) effect. Indeed, if such a MR dosage form were given twice to same individual, you'd probably get different T<sub>max</sub>.

12. *Line 343: ...on log-transformed data, is contained in the BE limits of 80-125% for AUC and C<sub>max</sub>....* For consistency with lines 309 and 330, suggest changing to “on log-transformed data, is contained in the BE limits of 80-125% for AUC<sub>0-∞</sub> (AUC<sub>0-t</sub>) and C<sub>max</sub>.”
13. *Lines 344-345: ....the T<sub>max</sub> values for the test and reference products are expected to be comparable based on clinical relevance....* Again, what is meant by term comparable? Same issue as mentioned above in comment #11 with regard to T<sub>max</sub> for MR. Presumably in the absence of a good statistical test/criterion for T<sub>max</sub>, the guidance is making the point that there should not be a huge difference in T<sub>max</sub>. However, this opens the door for differing sponsor and regulatory views on what constitutes a difference.
14. *Line 345-347: Does this imply that if these criteria are not satisfied, that the test formulation might not be considered equivalent to and interchangeable with the RLD?*

We thank you for the opportunity to comment on this draft guidance. Please let us know if you have any questions on our review.

Sincerely,

A handwritten signature in black ink, appearing to read 'Jenny Peters', with a stylized, flowing script.

Jenny Peters

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