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November 10, 2006

Division of Dockets Management  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

**Re: Docket No. 2006D-0344**  
Draft Guidance for Industry titled Drug Interaction  
Studies – Study Design, Data Analysis, and  
Implications for Dosing and Labeling.;  
**Request for Comments**

Dear Sir or Madam:

Reference is made to the DRAFT Guidance for Industry on Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006).

Procter & Gamble Pharmaceuticals respectfully offers the following suggested changes for consideration.

General Comments:

1. Clarify the role of the previous guidance documents (listed below) on similar topics. Does the current DRAFT guidance supersede the previous documents or supplement them?
  - a. Drug Metabolism / Drug Interaction Studies in the Drug Development Process: Studies In Vitro (April 1997).
  - b. In Vivo Drug Metabolism / Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling (November 1999).
2. Wherever possible, appropriate references supporting recommendations should be included throughout the document

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Specific comments are listed below with the corresponding page and line number(s):

1. Page 5, lines 178, 183 and 195: Define the criteria for “do not metabolize”, “does not inhibit CYP1A2”, and “does not induce.”
2. Page 5, lines 199-202: Provide clarification on whether potential drug interactions with CYP2B6 need to be studied for all drugs or if there is a criteria that could be used to decide what drugs should be tested.
3. Page 6, lines 243-249; Include in this section any special considerations for study designs to evaluate drug interactions for highly variable drugs, or drugs with narrow therapeutic indices.
4. Page 8, lines 313-316: Include the reference citations that support the potential for drug interactions with apple or orange juice and vegetables from mustard green family since they are not as well known or documented.
5. Page 8, lines 320-331: The discussion on study population is missing potential considerations for gender effects in deciding the population for drug interaction studies, e.g., the effect of the menstrual cycle.
6. Page 9: Include the reference citations that support the classification of CYP3A inhibitors into strong, moderate and weak based on a particular fold increase in ratio of mean AUC.
7. Page 10, line 408: Clarify what is considered a “substantial” contribution to the overall elimination. Does 25% refer to a particular metabolic pathway or does it refer to the overall CYP related metabolism?
8. Page 11, line 443: Include “...poor metabolizers (*naturally or chemically induced*) versus...”
9. Page 11, line 455: Theoretically, the magnitude of change should not be predicted based on the product of AUC fold changes. It must be predicted based on clearance changes associated with the sum of each individual inhibitor. (e.g., if one inhibitor has 10% inhibition and a second has 20% inhibition, then the combined inhibition would be 30%).
10. Page 12, line 488: Use of ritonavir in healthy volunteers may pose ethical issues from IRB perspective.
11. Page 14, line 584: The suggested use of a ratio of geometric means of all PK parameters may not be statistically appropriate since all PK parameters may not have



a log-normal distribution. Some language around the appropriateness of transformation should be included for parameters other than Cmax and AUC.

12. Page 15, lines 620-625: If the classification of the inhibitors is based on a ratio of AUC of marker substance with and without the inhibitor present, shouldn't this approach be based on the ratios rather than confidence limits for equivalence?
13. Page 24, top box on the left: Define what is meant by a "major" contribution of the pathway.
14. Page 25, line 788: Define if "> 25% of a drug's total clearance" refers to a particular pathway or combined effects due to CYP enzymes.
15. Page 25, line 808: Instead of determining whether the metabolic pathways are parallel or sequential, it may be just as informative to determine the extent of metabolism via individual pathways. The other issue is whether it is feasible to obtain information on the parallel or sequential nature of metabolic pathways during the early part of the drug development process.
16. Page 26, line 824: Suggest replacing HPLC/MS-MS with "radiochemical detection and quantitation to account for all metabolites."
17. Page 26, lines 827-828: Suggest replacing this sentence with "Further analysis of the radioactive peaks by MS/MS, UV, fluorescence, etc., may provide structural elucidation capabilities."
18. Page 26, line 848: Include "If human *in vitro* and in vivo data...". It is unclear how > 25% contribution from a given pathway can be estimated without conducting in-vitro experiments first.
19. Page 27, line 857: Change to (1) specific chemical *inhibitors* or antibodies (delete "as specific enzyme inhibitors").
20. Page 27, line 859: Add (3) correlation analysis based on a bank of human liver...
21. Page 27, lines 865-866: Delete the sentence "For correlation analysis ..." since it is redundant with item #3 in line 859.
22. Page 29, line 912: If the clinical concentration exceeds Km, would it be more appropriate to use the clinical concentration?
23. Page 32, line 1014: Shouldn't this be >30% substrate depletion?



24. Page 33, lines 1048-1049 and Table 4: Please also add a corresponding statement to confirm that in situations where  $[I]/K_i$  is  $< 0.1$  additional studies would not be required.
25. Page 37, lines 1157-1187: Comments on the use of computer simulation as an additional method to identify and predict drug interactions should be included.

Thank you for the opportunity to provide comments. Please contact me if you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read 'Gary F. Galletta', with a horizontal line extending from the end of the signature.

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