

# Procter & Gamble

The Procter & Gamble Company  
Health Care Research Center  
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

6 August 2002

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket No. 02D-0258  
Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations

Dear Sir or Madam:

Reference is made to the Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. Submitted herewith, are comments from Procter & Gamble Pharmaceuticals regarding the draft guidance document. We appreciate the opportunity to respond to the Agency's request for comments.

## Comments

**Section III.A.1.** Regarding the reference to using urinary excretion data to assess bioequivalence (BE), linearity of renal clearance ( $Cl_R$ ) should be established to support the use of urinary data.

**Section III.A.8.c.** With respect to measurement of total exposure, please clarify whether the last "measurable" concentration should be "observed" or "predicted" at the time of the last quantifiable concentration.

Please add a statement indicating that extrapolation of the area from the last time point ( $C_t$ ) to  $AUC_{0-\tau}$  is necessary when concentrations fall below the LOQ during the dosing interval.

**Section V.C.1.** P&GP recommends revising this section to reflect that the product labeling should be used in making decisions on whether BA and BE studies should be performed with food or under fasting conditions. For instance, if the drug product is labeled to be administered with food, then the BE studies should be conducted in the fed state.

**Sections III.C. and VI.E.** P&GP recommends these sections be revised to clarify that comparative clinical trials only be done in situations where plasma and/or urine assays are not feasible.

**Section III.D. (For an NDA), 2<sup>nd</sup> bullet.** With respect to dissolution method development (i.e., dissolution profiles generated at different agitation speeds), please add the following statement, "If dealing with multiple strengths, the above should be performed using the highest strength."

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**Attachment A, 3<sup>rd</sup> bullet.** With respect to use of half-lives to determine the washout period, P&GP recommends using 97% of the Total AUC instead of 5  $t_{1/2}$  since this more adequately addresses drugs with multi-compartmental disposition.

**5<sup>th</sup> bullet.** Please provide an explanation for the requirement to “abstain from alcohol for 24 hours before each study period and until after the last sample from each period is collected” for all drugs studied versus those cleared metabolically.

**6<sup>th</sup> bullet.** Regarding use of half-lives to determine sampling period, P&GP recommends using 90% of the Total AUC instead of 3  $t_{1/2}$  since this more adequately addresses drugs with multi-compartmental disposition.

**11<sup>th</sup> bullet.** P&GP requests removing the recommendation to provide  $\lambda_z$  information from submissions since  $t_{1/2}$  is already provided and is more commonly understood and used.

Thank you again for the opportunity to provide comments. If you have any questions regarding the above, please contact the undersigned by telephone at 513.622.5278, or by facsimile at 513.622.5363.

Sincerely,



Wendy M. Sauber  
Section Head, U.S. Regulatory Affairs

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ACTUAL WGT: 1 LBS SCALE

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ROCKVILLE MD 20857



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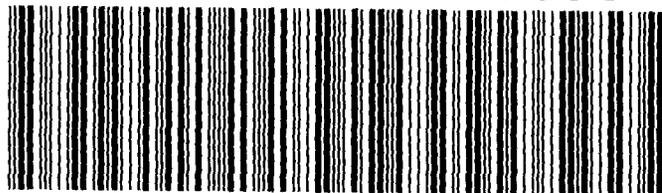
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