

**August 12, 2002**

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

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

Dear Sir or Madam:

On behalf of the Generic Pharmaceutical Association (GPhA), I submit the following comments on the Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. The issue of bioequivalence is of paramount importance to the generic industry as it continues to augment access to medicines by offering affordable, identical alternatives to brand name drugs. We applaud FDA's efforts to ensure that the best science continues to serve as the foundation for regulatory policy so that patients can be confident that their medicines are safe and effective.

**GENERAL COMMENTS:**

GPhA recommends adding specific instructions on how to conduct bioequivalence studies on orally disintegrating tablets, an oral dosage form that has become increasingly popular in recent years.

Given the proposed changes to delete the option of using individual bioequivalence criteria, GPhA recommends the corresponding deletion of the individual bioequivalence sections of the Guidance entitled "Statistical Approaches to Establishing Bioequivalence," dated January 2001.

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**SPECIFIC COMMENTS:**

GPhA also offers the following specific changes and recommendations:

**Page 7, Section III.A.4:**

Recent communications with the Division of Bioequivalence suggest that the Division currently recommends replicate design BE studies for active ingredients that are endogenous compounds, citing language in the "Statistical Approaches to Establishing Bioequivalence" Guidance. Based on recent experience, we believe that this view may more specifically apply only to endogenous compounds whose baseline blood concentrations appear at sufficiently high levels to warrant baseline correction. If, indeed the Division recommends a replicate design for such endogenous compounds, the present Guidance should be modified to state that fact explicitly. In fact, the plethora of issues surrounding the design and conduct of bioavailability and bioequivalence studies on endogenous compounds warrants a separate guidance on the subject.

**Page 16, 2. ANDAs: BE Studies, 3<sup>rd</sup> line:**

Change from:

“For modified-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, non-replicate, fasting study comparing the highest strength of the test and reference listed drug product, **unless the drug or drug product is highly variable in which case a replicate design study is recommended**; and (2) a food-effect, non-replicate study comparing the highest strength of the test and reference product (see section VI.A).”

to read:

“For modified-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, non-replicate, fasting study comparing the highest strength of the test and reference listed drug product and (2) a food-effect, non-replicate study comparing the highest strength of the test and reference product (see section VI.A).”

Rationale:

The additional recommendation regarding the replicate design for modified-release product is redundant. The acceptable study designs are presented earlier in the guidance stating that non-replicate design are acceptable for immediate release and modified release dosage forms with the option for using replicate design. Replicate design studies for highly variable drugs frequently do not offer any meaningful advantages over non-replicate designs. Therefore, the decision to select a replicate or non-replicate design for a highly variable drug should be left entirely up to the sponsor's discretion.

**Page 19, Section VI.B.1. (first and second bullet points):**

Change from:

"Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The metabolite data obtained from these studies should be subject to a confidence interval approach for BE demonstration. If there is a clinical concern related to efficacy or safety for the parent drug, sponsors and/or applicants should contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.

A metabolite may be formed as a result of gut wall or other pre-systemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not need to be measured. The parent drug measured in these BE studies should be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome."

to read:

The selection of the appropriate analytes to measure in BA and BE studies should be motivated by (1) whether the parent drug is adequately quantifiable over a reasonable period of time, (2) whether the parent drug contributes significantly to the safety/efficacy profile of the drug product, (3) whether the metabolite(s) contribute(s) significantly to the safety/efficacy profile of the drug product, (4) whether the metabolite(s) is (are) formed to any significant extent by pre-absorptive metabolism\*, and (5) whether the metabolic pathway is reversible (i.e., metabolite can be converted back into parent drug). The following principles should generally be followed:

Measure and apply acceptance criteria to the parent moiety if it is quantifiable and if it contributes significantly to the safety/efficacy profile of the drug product.

Measure and apply acceptance criteria only to the metabolite if the parent moiety is not quantifiable.

Measure and apply acceptance criteria only to the metabolite if the parent moiety is quantifiable but does not contribute significantly to the safety/efficacy profile of the drug product (i.e., the parent moiety is a prodrug).

Measure and apply acceptance criteria to both parent and metabolite only if both contribute significantly to safety/efficacy profile of the drug product, if the parent moiety

is quantifiable, and if a substantial proportion of the metabolite is formed pre-absorptively.

In cases where a metabolite is formed via a reversible process (i.e., significant conversion of the metabolite back to the parent may occur), consult with the appropriate review staff.

\*i.e., metabolic processes occurring at the gut wall or in the gut lumen

Rationale:

The wording in the current Draft Guidance does not clearly address all of the possible combinations of the critical factors of (1) pre-absorptive metabolism, (2) the ability to quantitate the parent drug, (3) the pharmacological activity of the parent drug, and (4) the pharmacological activity of the metabolite. The proposed revision was based on an examination of all of the possible combinations of those four parameters, together with the logical selection of analytes (i.e., parent and/or metabolite) in each case.

GPhA believes that pre-systemic metabolism, *per se*, should have no bearing on analyte selection, because if the pre-systemic metabolism is occurring after absorption (e.g., hepatic first-pass metabolism), then the parent drug will generally provide a more meaningful comparison between formulations. Pre-absorptive metabolism (i.e., metabolism that occurs in the gut wall or gut lumen) is a much more meaningful factor to employ for the selection of analytes.

GPhA does not support the current recommendation for the measurement of an analyte solely for information or supportive purposes in BE studies. If an analyte is not sufficiently important to warrant the application of acceptance criteria, the analyte should not be measured at all. Measurement of additional analytes for information only adds unnecessary cost, may possibly increase the blood volume requirement, and may unnecessarily jeopardize analytical runs, requiring repeat analyses (e.g., if the extra analyte fails to meet QC or standard curve criteria). Analytes to be measured for information only are appropriate in the case of BA studies.

GPhA believes that the special case in which a metabolite is formed via a reversible process should be handled on a case-by-case basis.

GPhA's comments in this section specifically address BE studies. GPhA recognizes that the Agency may wish to apply somewhat different standards for analyte selection in BA studies. If so, the distinction in criteria should be made clear in the Guidance.

**Page 19, Section VI.B.2.:**

Please clarify the term "minor enantiomer." In the vast majority of cases, the two enantiomers are present in a drug product in exactly equal amounts. GPhA is aware of

several drug products that contain an excess of one enantiomer, but in each of these cases, the major enantiomer has the principal pharmacological activity. Presumably, the term "minor enantiomer" refers to that enantiomer with the smaller systemic exposure (i.e., AUC).

**Page 20, Section VI.C.:**

The current draft Guidance does not define the term "long half-life drug." GPhA recommends that the Agency define this term clearly, and further recommends that the definition be "any drug for which at least one of the analytes required to be measured in a BA/BE study has a mean terminal\* half-life of at least 24 hours."

\*observable in a single-dose study at dosage levels consistent with the reference listed drug product labeling. If a half-life of at least 24 hours is only observable at steady state, or with single doses exceeding the dose levels permitted in the product labeling, then the drug is not considered to be a long half-life drug.

The current draft Guidance discusses truncated AUC and  $AUC_{0-t}$  as if they were different entities, when, in fact, they are identical. GPhA recommends that the language of this section be revised to correct this.

Finally, regarding truncation at 72 hours post-dose, some compounds (particularly, some metabolites) do exhibit individual  $t_{max}$  values close to, or even later than 72 hours. Therefore a statement suggesting a later cutoff for such drugs may be helpful, to ensure that sampling would cover at least a reasonable portion of the concentration-time curve. The following wording is recommended:

Change:

"For drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours ( $AUC_{0-72 \text{ hr}}$ ) can be used in place of  $AUC_{0-t}$  or  $AUC_{0-inf}$ ."

to read:

"For long half-life drugs that demonstrate low intrasubject variability in distribution and clearance, an abbreviated sampling schedule ending at 72 hours (or later) may be used."

**Page 23, Attachment A, first bullet point:**

GPhA believes that if, for a given subject and period, the pre-dose level of parent drug (or one of its metabolites) exceeds 5% of the corresponding  $C_{max}$ , then that subject and period should be excluded from the statistical analysis of the parent drug and any of its metabolites. In the case of a combination drug product, however, GPhA believes that a

pre-dose concentration exceeding 5% of the corresponding  $C_{max}$  for one of the actives (parent or metabolite) should not trigger exclusion of the analyte(s) for the other active. Please also address the issue of pre-dose levels for endogenous compounds, for which pre-dose baseline levels may naturally exceed 5% of  $C_{max}$ . GPhA believes that brief mention should be made in this Guidance, as well as a more complete explanation in separate guidance on BA/BE studies on endogenous compounds.

**Page 23, Attachment A, second bullet point:**

This should be changed to allow, or even encourage, the removal of any subject who vomits (during the time interval within which absorption is expected to occur) from the study before bioanalysis begins. The "2 times median  $T_{max}$  criterion" is obviously only applicable after bioanalysis is complete. Also, the "2 times median  $T_{max}$  criterion" is currently ambiguous as to which treatment it should be calculated for. GPhA believes that it should be calculated for the treatment administered immediately before the emesis episode.

Therefore, GPhA recommends the following wording:

Change from:

"Data deletion due to vomiting:

Data from subjects who experience emesis during the course of a BE study for immediate-release products should be deleted from statistical analysis if vomiting occurs at or before 2 times median  $T_{max}$ . In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted."

to read:

"Emesis occurring during BE studies:

Any subject who experiences emesis during the course of a BE study may be removed from the study, prior to bioanalysis, at the discretion of the sponsor and/or principal investigator. If such a subject is not removed before bioanalysis, then the data from that subject/period should be deleted from statistical analysis if:

for an immediate release product, emesis occurred within 2 times the median  $t_{max}$ \* observed for any of the required analytes,

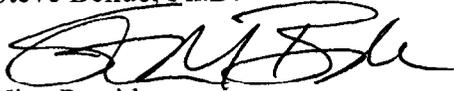
or

for a modified release product, emesis occurred at any time within the labeled dosing interval.

\*i.e., 2 times the median  $t_{max}$  of the product administered immediately before the emesis."

GPhA appreciates your consideration of our comments. Please contact me, if you have any questions or need clarification.

Steve Bende, Ph.D.



Vice President

Science, Professional and Regulatory Affairs