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

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**Re: Re: Docket Number 02D-0258, Comments on Draft Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products**

Dear Sir or Madam;

Enclosed please find comments from GlaxoSmithKline on the Draft Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. The comments are provided for consideration by the FDA. A general comment is listed first. It is followed by specific comments that are listed in order of appearance in the guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this guidance. I am submitting this document both electronically and by hardcopy. Therefore, you will also receive a copy of this letter and two copies of the comments by hardcopy through the USPS. If you have any questions about these submitted comments, please feel free to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

A handwritten signature in cursive script that reads "Mary Faye S. Whisler".

Mary Faye S. Whisler, Ph.D.  
Assistant Director  
New Submissions, North America

02D-0258

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### **General Comment**

The guidance document should explain the rationale for testing the “highest strength” dosage form as opposed to the lower dose strength (e.g., a starting dose strength).

### **Specific Comments**

#### Section III.A.8. Pharmacokinetic Measures of Systemic Exposure (Page 9)

This section should be rewritten. The text is confusing.

#### Section III.D. In Vitro Studies. (...dissolution method development for solid oral dosage forms for an NDA) (Page 11) Each topic is discussed individually.

**Agitation speeds:** The lowest speed possible should be tested first. If acceptable profiles are generated at the lower speed, evaluation at higher speeds is not necessary. If a higher speed is needed to generate an acceptable profile, then data at the lower speed(s) should be provided.

**Apparatus:** Dissolution profiles for both Apparatus I (basket) and Apparatus II (paddle) are unnecessary. Inclusion of data from Apparatus II is recommended. It is easier to automate and are usually more robust. “Discriminating ability” is only one factor in choosing the apparatus to be used.

**Dosage strengths tested:** Testing all strengths of the dosage form is unnecessary. Bracketing data using the low and high strengths should be sufficient for method development. Testing all strengths would only be needed after development of the final method.

**Dissolution media:** Dissolution media choice should be qualified. For a Class I drug with conventional excipients, different media is unnecessary. Also, the physico-chemical behavior of the drug in solution may preclude testing in different media (for example, poor stability at low pH or in the presence of buffer salts or pH dependent solubility that compromises the assessment of the data).

**Surfactants:** Surfactants should not be required because they can cause destabilization, flocculation, or can interfere with the analysis.

The statement for the NDA should be changed to the following.

- “The pH solubility profile of the drug substance.
- Dissolution profiles generated at the lowest discriminating agitation speed (e.g. 100 revolutions per minute (rpm) for U.S. Pharmacopeia (USP) Apparatus I (basket), and 50 rpm for USP Apparatus II (paddle)).
- Dissolution profiles generated on the lowest and highest dosage strengths in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) unless the physico-chemical behavior of the drug in solution precludes such testing (for example, poor stability at low pH or in the presence of buffer salts or pH dependent solubility that compromises the assessment of the data; in these cases, dissolution profiles in water will suffice). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants should be considered.”

The last statement in this section should be changed to the following (the word “three” is replaced with “relevant”).

“This guidance recommends that dissolution data from relevant batches for both NDAs and ANDs be used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms.”

Section V.B. Suspensions and C. Immediate-Release Products: Capsules and Tablets  
(Page 13)

The following statement should be added to each section.

“When an inactive ingredient, known not to affect absorption is removed or reduced in the formulation, a biostudy is not necessary.”

Section V.D.1. NDAs: BA and BE Studies (Page 15)

Clarify what is meant by “...drug product’s steady state performance is equivalent to a currently marketed noncontrolled release...”. This would imply that the IR and MR formulations meet BE standards. If that was intended or not, it needs to be clarified. It may be appropriate to reference the Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations.

(Page 16) In the statement “This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted ...” is not clear.

The statement should be changed to the following.

“This guidance recommends that the following product quality BA studies be conducted for an extended-release drug product submitted...”.

Section V.D.2. ANDAs: BE Studies (Page 16)

A study should be required to show bioequivalence across the dose range (or by bracketing the doses using the lowest and highest strengths of the product).

The last sentence in this section (“Because single-dose studies are considered...where non-linear kinetics are present.”) needs to be clarified as it conflicts with CPMP guidance favoring steady-state studies under appropriate circumstances.

Section V.E. Miscellaneous Dosage Forms (Page 17)

Delete the requirement for dissolution testing of chewable tablets.

This section should be changed to the following.

“Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for in vitro dissolution and in vivo BA and/or BE. Chewable tablets should also be evaluated for in vivo BA and/or BE.

Infrequently, different test conditions or acceptance criteria may be indicated for chewable and nonchewable tablets, but these differences, if they exist, should be resolved with the appropriate review division.”

Section VI.C. Long Half-Life Drugs (Page 20)

The recommendation for truncating the AUC at 72 hours needs to be changed. We suggest the use of the phrase “three elimination half-lives beyond T-max” rather than “truncation at 72 hours”.

Attachment A General Pharmacokinetic Study Design and Data Handling (Page 24)

The last bullet item, about confidence interval values expresses data to more than 3 significant figures. This should be limited to values reported to one decimal place to the right.

This statement should be changed to the following.

“Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80 to 125, the value should be at least 80.0 and not more than 125.0.”.