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GlaxoSmithKline

Management Dockets, N/A  
Dockets Management Branch  
Food and Drug Administration  
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**Re: NAS 0; Not Product Specific  
Response to FDA Request/Comment: Draft Guidance for Industry on  
Nonclinical Safety Evaluation of Drug Combinations  
[Docket No. 2005D - 0004]**

Dear Sir or Madame:

Enclosed please find comments from GlaxoSmithKline on the 'Draft Guidance for Industry on Nonclinical Evaluation of Drug Combinations.' We would like to thank the FDA Center for Drug Evaluation and Research for compiling this draft Guidance document and for the opportunity for comment by stakeholders. Members of Safety Assessment and Regulatory Affairs in GSK have reviewed the guidance document, and in general, welcome the approach taken by CDER. However, there are a several statements within the document where GSK would like to see further clarification from the Agency. Our specific comments are organized under the same section headings as used in the draft guidance and are cross-referenced by page and line number.

**Introduction, footnote 2**

The definition of adjunctive therapy is very broad; it could be inferred that combination toxicology studies might be required for any patient who receives incidental concurrent therapy. We do not think this is the intent of the guidance document and suggest the following clarification should be added to the footnote:

*Concurrent therapy is the incidental use of a drug product that may be administered during the course of a clinical study and is not excluded by the clinical study protocol. It differs from adjunctive therapy in that it is not intended that a specific drug product be administered in adjunct to the primary therapy to enhance efficacy or where the intent is the routine use of a second drug with the primary therapy, e.g. a hair restoration product following chemotherapy. In such cases combination toxicology studies are generally not required. In situations where a drug interaction is possible with a commonly used, concurrently administered compound, a clinical drug interaction study may be required.*

**III. Nonclinical Studies for a Combination of Drugs When One or More is Previously Marketed and One is a New Molecular Entity (Figure B)**

**A. General Toxicology Studies [page 6, line 201]**

The guidance document states: "Dependent on the duration of the proposed therapy, FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination in the most appropriate species." It would be helpful to elaborate on this point and to define the specific duration of combination toxicology studies needed to support a defined duration of clinical exposure. For example, would a 2-week combination study in the most sensitive species and 3-month toxicology studies with individual components permit clinical trials with the combination product of up to 3 months in duration? Alternatively, would one-for-one exposure be expected --- 3-month combination toxicology study to support clinical trials of 3-months?

**IV. Nonclinical Studies for a Combination of Two or More Drugs When Both are New Molecular Entities (Figure C)**

**A. General Toxicology Studies [page 7, line 254]**

The guidance states: "Dependent on the duration of the proposed therapy, a bridging study of up to 90 days should be conducted with the combination in the most appropriate species if the NMEs were evaluated as separate entities (which is preferred) and not as a combination." As above, it would be helpful to elaborate on expected duration of the combination toxicology study to support a specific duration of clinical study.

**II. Nonclinical Studies for a Combination of Two (or More) Previously Marketed Drugs (Figure A)**

**C. Combinations of Previously Marketed Drug Products: General Procedure [page 5, line 174]**

**III. Nonclinical Studies for a Combination of Drugs When One or More is Previously Marketed and One is a New Molecular Entity (Figure B)**

**B. Reproductive and Developmental Toxicology [page 6, line 218]**

In sections II. C. *Combinations of Previously Marketed Drug Products: General Procedure* and III. B. *Reproductive and Developmental Toxicology*, the guidance proposes that embryofetal development studies of the combination should be conducted unless one of the components is already known to have significant risk for developmental toxicity, because that risk will already be included in the product labeling. GSK would contend that where there are existing data, the need to perform embryofetal development studies on the combination should be based only on a scientific evaluation of the developmental toxicity of the individual components.

We are not aware of any case where two or more compounds that showed no developmental toxicity when tested as single entities, showed such toxicity when tested in combination. We would be interested in knowing if FDA has examples of this, that have contributed to the position expressed in this draft Guidance.

This submission is provided in electronic format according to the instructions provided at <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm?AGENCY=FDA>.

Please contact me at (919) 483-6405 if you require clarification or have questions about these comments. Thank you.

Sincerely,



Anne N. Stokley, M.S.P.H.  
Director, Policy, Intelligence & Education  
US Regulatory Affairs