



GlaxoSmithKline

May 31, 2002

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Rm 1061
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Re: Comments on Draft Guidance for Industry - Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications [Docket 02D-0095]

Dear Sir or Madam::

Enclosed please find comments from GlaxoSmithKline on the draft guidance for industry entitled *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*. Notification of availability for comment on the guidance was published in the *Federal Register* on April 2, 2002, Vol. 67, No. 63, pages 15576-15577 (Docket No. 02D-0095).

GlaxoSmithKline endorses the development of this guidance and appreciates the opportunity to provide comments for consideration by the Agency.

These comments are provided in duplicate. If you have any questions regarding these comments, please contact me at (919) 483-3073.

Sincerely,

Mark A. Baumgartner, R.Ph.
Senior Director, Policy Development and Coordination
Regulatory Affairs

02D-0095

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**Comments on Draft Guidance for Industry - Exposure-Response Relationships:
Study Design, Data Analysis, and Regulatory Applications
[Docket 02D-0095]**

Lines 125-128: We suggest that critical studies should also have an appropriate sample size.

Lines 149-156: We suggest that this section be reworded to be consistent with ICH-E4's Section III, subsection 1 statements on the issue of multiple comparisons: 'In principle, being able to detect a statistically significant difference in pairwise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established using all the data. It should be demonstrated, however, that the lowest dose(s) tested, if these are to be recommended, have a statistically significant and clinically meaningful effect'. Guidance from the agency on control of regulatory risk (type 1 error) in this setting for multiple comparison testing is requested. Previous publications on the topic by agency staff may be helpful, e.g. Chi G, Hung J, Dubey S, Lipicky R (1994), 'Dose Response Studies and Special Populations', *ASA Proceedings*, 88-93. We believe that the agency should also consider implementation of ICH-E4's provision for the use of 'formally planned interim analyses' mentioned in ICH-E4 section III, subsection 1 and consider the impact on regulatory risk.

Line 291: An example from the Agency on the application of this technique in biologics would be helpful in evaluating its utility.

Line 367: Remove 'a misleading result'. Umbrella-shaped curves do occur in nature and can be meaningful - e.g. caffeine intake relative to attention to detail - too little coffee and there is the potential for insufficient attention; too much and the jitters interfere with attention.

Line 369: The reference should include '1991'.

Line 509: Mention of the use of models which account for variation in the exposure variable in addition to the usual models which account for variation in the response should be considered in this or an appropriate section of the guidance.

Line 580: Guidance from the agency on how to weight the evidence from multiple (possibly conflicting) endpoints is requested. Construction of a weighted or combined response that weighs each endpoint relative to clinical benefit may be helpful when interpreting such data.

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