

August 4, 2005



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

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Re: NAS 0; Not Product Specific
General Correspondence: Comments on Draft "Guidance for Industry:
Safety Testing of Drug Metabolites"
[Docket No. 2005D - 0203]

Dear Sir or Madame:

Reference is made to the notice published by FDA in the Federal Register on June 6, 2005, to invite written comments on a new draft guidance for industry ("Draft Guidance for Industry: Safety Testing of Drug Metabolites"). The purpose of this letter is to provide comments from GlaxoSmithKline on this new draft guidance.

GSK is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to lead longer, happier, healthier, and more productive lives. Members of the Safety Assessment and Drug Metabolism and Pharmacokinetics groups in GSK have reviewed the draft Guidance document and we appreciate the opportunity to provide our comments.

Overall, we support the Agency's efforts to provide guidance on this issue but we have some major concerns regarding the current draft, which are provided below. Given the nature of these concerns we feel it important that the Agency consider providing a 2nd draft for review and comment, prior to issuing the final Guidance.

- The first major concern is that the draft Guidance frequently refers to unique or major metabolites, whereas the flowchart implies unique and major metabolites. GSK assumes that the Guidance is intended to refer to unique and major metabolites only. It would be helpful if this was made clear in the text.
- The second major concern is with regard to the way industry will interpret Lines 72-73, "10 percent of drug related material (administered dose or systemic

exposure whichever is less)". To illustrate this major concern we provide the following example:

Compound A has a metabolite that represents only 5% of systemically circulating drug related material but 50% of the dose, and compound B has a metabolite that represents 50% of systemically circulating drug related material but only 5% of the dose. For both compounds the metabolite in question is poorly (significantly less than unity relative exposure) represented in the pre-clinical toxicology species either in terms systemic exposure or total dose. The question is would additional toxicological assessment of the metabolite be required for compound A or B, both or neither? The "whichever is less" wording in the text seems to suggest that in each case the 5% value could be chosen and no action is needed.

In addition, the Decision Tree (Line 354) refers only to the percent of dose that is represented by an individual metabolite, and not to the abundance of the metabolite in the systemic circulation, causing further confusion.

GSK considers it important that this ambiguity is resolved in the final Guidance. This should also take into account levels of metabolites in excreta (Lines 184-185).

- A third major concern is the criteria to be used for determining the maximum dose in toxicity studies designed to evaluate unique or major metabolites. Lines 235-237 refer to a dose that elicits frank toxicity or up to 2000 mg/kg/day. GSK considers that the purpose of these studies is to determine risk to humans and not to detect hazards. The use of such high doses would create clinically irrelevant exposure conditions both qualitatively and quantitatively. We propose that the maximum doses used in such studies should be at relevant multiples of human exposure, determined on a case-by-case basis.
- A final concern is that Lines 144-155 are open to different interpretations. It is GSK's interpretation that the Agency's recommendation that when a drug causes a potentially clinically relevant toxicity the metabolites be synthesized and directly administered to the appropriate animal species to determine their contribution to that toxicity, refers only to situations where there are animal specific metabolites. If this is the case, we would recommend that this guidance is inserted after the first sentence in Line 145. If it is not, please consider rewording Lines 144-155 to provide greater clarity.

Again, we thank you for the opportunity to provide comments. This submission is provided in electronic format according to the instructions provided at <http://accessdata.fda.gov/scripts/oc/dockets/commentdocket.cgm?AGENCY=FDA>.

Management Dockets

August 4, 2005

Page 3

Please contact me at (919) 483-6405 or my colleague Derek Newall at (44 011) 192-088-3356, if you require clarification or have any questions about these comments. Thank you.

Sincerely,

A handwritten signature in black ink, appearing to read "Anne N. Stokley". The signature is written in a cursive style with a large, looped "S" at the end.

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