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

Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: Other
Comments on Draft Guidance for Industry: RECOMMENDED
APPROACHES TO INTEGRATION OF GENETIC TOXICOLOGY
STUDY RESULTS [Docket No. 2004D-0493]

Dear Sir or Madame:

Enclosed please find comments from GlaxoSmithKline on the draft 'Guidance for Industry on Recommended Approaches to Integration of Genetic Toxicology Study Results'. We appreciate the opportunity to provide stakeholder comments on this draft guideline. Members of the Genetic Toxicology Unit and Safety Assessment at GSK have reviewed the Guidance document, and in general, welcome the approach taken by the Center for Drug Evaluation and Research. However, there are several statements in the document where GSK would like to see further clarification, or where GSK would like to suggest alternative phrasing for consideration by FDA. Specific comments are provided on subsequent pages, organized under the same section headings as used in the draft guidance and cross-referenced by line number.

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

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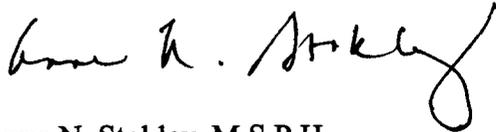
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Please contact me at (919) 483-6405 or my colleague Derek Newall, at (44 011) 192-088-3356, if you require clarification or have questions about these comments. Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "Anne N. Stokley". The signature is written in a cursive style with a large, looping final flourish.

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

Comments on Draft Guidance for Industry: Recommended Approaches to Integration of Genetic Toxicology Study Results

I. INTRODUCTION

It is acknowledged that the guidance pertains to pharmaceuticals only and **not** impurities, degradants, or human specific metabolites etc (which are informed by other, more appropriate, regulatory/guidance documents).

II. BACKGROUND

The pertinence of the sentence on Line 40 "*Administration of sustained-release preparations or agents with an in vivo half-life of greater than 12 hours can result in systemic exposure for greater than 24 hours*" is ambiguous and could be omitted or requires further clarification.

INTEGRATION OF GENETIC TOXICITY STUDY RESULTS

Lines 67-68 "*We recommend that evidence for the mechanism of genotoxicity and relevance of the mechanism to anticipated in vivo exposure be provided in such cases*"

When translating hazard identification into possible risk GSK would contend that evidence for an indirect mechanism of genotoxicity and/or the exclusion of DNA reactivity and relevance to the anticipated in vivo exposure be provided.

The sentence beginning on Lines 69-71 "*Drugs known to directly damage DNA may be permitted to be used in patients with debilitating or life-threatening disease, such as cancer, but should not be administered to healthy subjects*" appears to contradict Lines 81-82, "*In general, single-dose studies can proceed regardless of results in genetic toxicity studies, and any positive results are included in the investigator's brochure and informed consent form.*" Also, in Line 70 the document should refer to debilitating or life-threatening diseases.

The subject of the sentence in lines 76-77 "*If the results of the genetic toxicology tests indicate a lack of genotoxic potential, then single-dose or short-term repeat-dose trials can generally be undertaken in healthy subjects or patient populations...*" is somewhat ambiguous and requires clarification. Presumably, the document is referring to WOE tests (conducted either in vitro or in vivo) and an assessment of **the absence of** genotoxic potential in humans (as there would have been one or more positive genetic toxicology results which would not have been deemed biologically relevant in a WOE assessment to permit clinical development). It would be helpful if an idea of the maximum duration of the short-term repeat-dose trials permitted to be undertaken was given in the document.

The Guidance document appears overly prescriptive in recommending the mammalian CA assay to follow up an equivocal MLA finding (or vice versa) as an automatic default since the fourth test is not always appropriate: Lines 85-87 *"If any of the three assays in the ICH genotoxicity standard battery is positive, then we recommend completing the fourth test in the ICH battery. If a positive response is seen in one or more assays, sponsors should consider choosing from the following options (A, B or C)."* We would contend that additional testing, using the fourth or other supplementary tests (e.g. DNA adduct assays, gene mutation assays, DNA strand break assays etc.), with scientific justification, would provide the appropriate means to address the biological relevance of the original observation (i.e. a positive or equivocal result in one of the ICH genotoxicity standard battery of assays).

A. Weight-of-Evidence Approach

We would propose that the word "repeat" be inserted in Line 97 for clarification "...*(2) corroborating data from the same or complementary repeat assays.*"

B. Mechanism of Action

We would like to propose that the sentence in Lines 112-114: *"Agents that induce effects by indirect mechanisms, such as interference with metabolism of nucleotides and their precursors, damage to spindle proteins, inhibition of topoisomerase, may have thresholds for genotoxic effects."* is amended to include additional mechanisms, thus...*"Agents that induce effects by indirect mechanisms, such as interference with metabolism of nucleotides and their precursors, damage to cell division proteins, inhibition of DNA/RNA or protein synthesis and DNA topoisomerase enzymes, may have thresholds for genotoxic effects."*

Line 115: It can be very difficult, if not impossible, to provide direct experimental evidence of the existence of a threshold for genotoxicity. It would be more reasonable to provide evidence of an indirect mechanism(s) that is not expected to operate under in vivo exposure conditions in the clinic.

C. Additional Supportive Studies

Lines 140-150: We disagree that the SHE assay may be useful in making a WOE judgement. The SHE assay has not been adequately validated for regulatory use. There is no mechanistic understanding of the processes that induce morphological transformation or its relationship to rodent or human carcinogenicity and the assay does not discriminate between genotoxic and non-genotoxic mechanisms. Furthermore, the SHE assay it is not routinely available worldwide (there is currently only one commercial laboratory providing the SHE assay as a service). Moreover, this section of the Guidance document does not appear to reflect the outcome of the US EMS workshop organized by the FDA in 2004.