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Director
Scientific and Regulatory Affairs



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January 28, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Request for Comments on the Draft Guidance for Industry on Recommended Approaches to Integration of Genetic Toxicology Study Results [Docket No. 2004D-0493, Federal Register, Vol. 69, No.231/70153, December 2, 2004]

Dear Dr. Jacobson-Kram:

The attached comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA is a voluntary, non-profit trade association representing the firms that discover, develop and produce prescription drugs and biologic products. The large majority of new prescription medicines approved for marketing in the United States are produced by PhRMA member firms.

A PhRMA Joint Committee team has carefully reviewed the draft guidance and would like to take this opportunity to provide comments, which are attached.

Your consideration of these comments is appreciated. Please contact me if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads 'Michael Garvin'.

Michael Garvin, Pharm.D.

2004D-0493

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Pharmaceutical Research and Manufacturers of America

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To: Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: PhRMA response and comments to FDA CDER Draft Guidance for Industry:
Recommended Approaches to Integration of Genetic Toxicology Study Results

Reference to: Federal Register, Vol. 69, No. 231/70153. December 2, 2004.
Docket No. 2004D-0493

Date: 20 January 2005

Executive Summary:

We commend the Pharmacology Toxicology Coordinating Committee in initiating further discussions on this topic as well as the recently implemented tertiary review process (MAPP) (1).

- Overall, this draft guidance is consistent with ICH guidelines and therefore builds from a starting point routinely used within the industry. We commend the Committee for incorporating flexibility into the guidance for assessing the relevance of genotoxic hazard findings and the associated potential risks to clinical trials. We also welcome the clear statements on which circumstances are seen as appropriate for single-dose or multiple-dose clinical trials in normal volunteers.
- In keeping with the principle of maintaining flexibility, we recommend moving reference to the conduct of the fourth test in the ICH battery to Section A and consider it as part of the options that might be chosen to utilize a weight-of-evidence approach.

As requested, we also submit specific comments or responses for the Committee's consideration in formulating future revisions to the draft Guidance.

Specific Comments or Responses (organized by Draft Guidance section)

II. Background

-We seek clarification of the statement in lines 40-41, "*Administration of sustained-released preparations or agents with an in vivo half-life of greater than 12 hours can result in systemic exposure for greater than 24 hours*". It is not clear what is inferred by the statement on half-life. In our view, this scenario could also pertain to a "single-dose" clinical trial. Even investigational drugs administered once in standard formulations could have half-lives greater than 12 hours, but this would not be known until the initial clinical trial was completed

-We concur with the citation (lines 43-44) of ICH guidelines (including M3) and current CDER guidance pertaining to this subject matter as a starting point.

-We also concur with lines 47-48 that risk for carcinogenesis is usually determined in rodent assays *in vivo* (either 2-yr or short term alternative models) with the reference to the ICH S1B guideline, but we would like this FDA guidance to clarify that these are *in vivo* models and do not include *in vitro* models such as the SHE transformation assay (see comments on section C).

-We also concur with the option (lines 57-58) to initiate Phase I trials with results available from *in vitro* genetic toxicology studies as cited in ICH M3.

III. Integration of Genetic Toxicity Study Results

-We concur with the statement (lines 65-66) that compounds that "*give positive results in genetic toxicology assays but do not directly react with DNA do not always present a significant in vivo risk*". In principle we agree with the concept of understanding mechanism of action (MOA) in addressing possible risks of an identified genotoxic hazard. Elucidation of MOA can be a challenging goal in the context of drug development (especially during the early phases), and we submit that the emphasis should be placed on excluding a direct MOA (i.e., DNA reactivity) and where possible providing evidence of an indirect mechanism, and assessing relevance to anticipated *in vivo* conditions as a more practical alternative to support clinical trials.

-We concur with the proposed weight-of-evidence (WOE) approach (lines 73-76) that considers the spectrum of genetic toxicology tests conducted and the nature of the proposed clinical trial. We also concur with the concept that the risk is acceptable (in some cases without additional WOE) in clinical experimentation of drugs known to directly damage DNA in patients with debilitating or life-threatening disease (ex. cancer). This would especially apply to cases where the drug and genotoxic MOA are shared. The draft guidance does specify that such agents should not be administered to healthy subjects. To avoid a contradiction with the statement in lines 81-82: "*In general, single-dose studies can proceed regardless of results in genetic toxicity studies.....*", the guidance could be modified here to state that multiple doses of a directly DNA-damaging agent should not be given to healthy volunteers.

-We submit that it would be helpful for the guidance to be expanded (lines 81-82) to state that for micro dosing studies (e.g., PET tracer studies), single or multiple low doses could be given to healthy volunteers regardless of the genetic toxicology results.

-Regarding the statement in lines 84-86 "*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*" we recommend omission of this statement from this guidance section. We submit that the conduct of the fourth test in the ICH battery should be included with the options specified under sections A, B and C in the guidance, and should not be a standard recommendation. This choice should be driven by the nature of the positive

results in the ICH standard battery. There may be more relevant follow up tests that contribute more to WOE or MOA assessment. The most common scenario would be following up a positive result in either the mouse lymphoma cell mutation assay or the *in vitro* chromosome aberration assay, but since mechanisms that can lead to indirect or irrelevant positive results operate in both assays, this may not be the best way to add information useful in assessing potential risk relevance.

A. Weight-of-Evidence Approach

-We commend the proposed focus on a WOE approach to proceed to repeat-dose clinical trials, with sponsors' expectations to generate WOE as they see fit to support lack of risk relevance for the intended indication and objectives for early clinical trials.

-Regarding statement (lines 98-102): *"For example, a positive response seen in a short-term exposure without metabolic activation but not corroborated in the longer exposure at comparable levels of cytotoxicities would argue against the biological relevance of the positive result. Similarly, such a positive finding that is not corroborated by the matching exposure regimen of the mouse lymphoma assay could also call into question the significance of the positive finding."* We suggest adding to this statement the following:

It is important to recognize that both the in vitro chromosome aberration assay and the mouse lymphoma cell mutation assay are known to be prone to false or irrelevant positive results. Some of the mechanisms that lead to indirect/irrelevant positive results operate in both assay systems.

B. Mechanism of Action

-We commend the inclusion of the concept of a threshold MOA for genotoxins as part of WOE, as reviewed previously in published literature (2-6) and discussed at a recent joint PhRMA-FDA workshop (7). With an appropriate WOE profile for a compound with positive genotoxicity results (outside of weighing carcinogenic potential), this should not preclude progressing with repeat dose clinical trials.

-Regarding statement (lines 115-118): *"In such cases, we recommend presenting direct evidence of the existence of a threshold that would not be attained during the proposed clinical exposure. Positive responses that are satisfactorily explained by a MOA may allow repeat-dose studies to proceed without additional studies."* We suggest the omission of "direct" from the statement on *"direct evidence of the existence of a threshold..."*, as we foresee this to lead to complexities in definition and interpretation. Generating direct evidence for the existence of a threshold is not often attainable, even for the examples given here (interference with nucleotide metabolism, damage to spindle proteins or inhibition of topoisomerases).

-We also ask that the document (a) state more clearly that the thresholded mechanisms listed in lines 113-114 are not a restricted list but examples, (b) include reference to

inhibition of DNA synthesis as an indirect mechanism of action (reference 4) and (c) allow for the possibility of other mechanisms.

C. Additional Supportive Studies

-It is inferred from reading this draft guidance that a sponsor may choose option A, option B or option C to provide information adequate to support multiple-dose clinical trials in normal volunteers or patients. Thus, we suggest changing the title of section C to "Alternative Supportive Studies" and adding the following sentence to this section, perhaps instead of lines 158-160:

When appropriate evidence is available as outlined in sections A (weight-of-evidence) or B (mechanism of action), or additional studies support the lack of in vivo relevance (the first part of section C), available evidence shows that the likelihood of carcinogenesis mediated by genotoxicity is remote. Hence an extended early assessment of carcinogenic potential (such as the SHE transformation assay or a p53 transgenic mouse carcinogenicity assay) as outlined in paragraphs 3 and 4 of section C should not be required before progressing with multiple-dose clinical trials in normal volunteers and in patients.

-Regarding the second paragraph, lines 136-138: "DNA damage can be assessed in potential target tissues (e.g., DNA adducts or comet assays)...." We consider that the generic types of assays, rather than specific methodologies, should be cited. Thus, just as "DNA adducts" are mentioned without a method for measuring them, the wording "DNA strand breaks assays (including for example Comet and alkaline elution assays)" is preferable to limiting this to "comet assays".

-Regarding the 3rd paragraph, lines 140-150: The information cited on the SHE assay seems contradictory, in acknowledging the poor predictivity of the SHE assay for human carcinogenic risk (8), yet stating that it may be useful in making a WOE judgment. To clarify this distinction, we recommend changes to this paragraph as shown below. We have deleted the statement that "...transformation assays measure endpoints more akin to the health effect of concern (cancer)" since human cells are extremely difficult to transform while rodent cells transform readily and the mechanism of transformation is usually unknown.

We suggest the following revised 3rd paragraph:

The Syrian hamster embryo (SHE) transformation assay has been suggested as a follow-up assay in the face of positive in vitro genotoxicity results. Data in the literature suggest that the SHE assay correlates well with rodent carcinogenicity results for chemicals in general (Isfort et al. 1996). Results from an International Life Sciences Institute (ILSI) validation effort on human pharmaceuticals, although smaller in scope, suggest that the SHE assay is less predictive for human carcinogenic risk (Mauthe et al. 2001), since some rodent carcinogens that are putative human noncarcinogens are positive in the SHE assay. Nevertheless, negative results in this assay have value in

lessening concern about carcinogenic potential and can be a useful part of WOE assessment.

-Regarding additional supportive studies to address MOA/WOE, we welcome the inclusion of a forward thinking statement in this section of the guidance on the use of future alternative approaches that may emerge through new technologies and advancement of genetic toxicology science.

References:

- (1) Manual of Policies and Procedures. Office of New Drugs, FDA Center for Drug Evaluation and Research. Tertiary review of genetic toxicology studies resulting in a recommendation for a clinical hold or conduct of additional studies. September 2004.
- (2) Hilliard CA, Armstrong MJ, Bradt CI, Hill RB, Greenwood SK, Galloway SM. 1998. Chromosome aberrations *in vitro* related to cytotoxicity of nonmutagenic chemicals and metabolic poisons. *Environ. Mol. Mutagen.* 31:316-26
- (3) Galloway SM. (2000). Cytotoxicity and chromosome aberrations *in vitro*: experience in industry and the case for an upper limit on toxicity in the aberration assay. *Environ. Mol. Mutagen.* 35:191-201.
- (4) Galloway SM, Miller JE, Armstrong MJ, Bean CL, Skopek TR, Nichols WW. 1998. DNA synthesis inhibition as an indirect mechanism of chromosome aberrations: comparison of DNA-reactive and non-DNA-reactive clastogens. *Mutat. Res.* 400:169-186.
- (5) Kirkland DJ and Muller L. (2000). Interpretation of the biological relevance of genotoxicity test results: the importance of thresholds. *Mutat. Res.* 464:137-47.
- (6) Muller L. and Kasper P. (2000). Human biological relevance and the use of threshold-arguments in regulatory genotoxicity assessment: experience with pharmaceuticals. *Mutat. Res.* 464:19-34.
- (7) PhRMA/FDA Sponsored Workshop. Interpretation of positive genotoxicity data and follow-up testing. November 2003.
- (8) Isfort RJ, Kerkaert GA and LeBoeuf RA (1996). Comparison of the standard and reduced pH Syrian hamster embryo (SHE) cell *in vitro* transformation assays in predicting the carcinogenic potential of chemicals. *Mutat. Res.* 356:11-63