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Global Research & Development

January 31, 2005

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

Dear Dockets Management:

Re: **Draft Guidance for Industry on Recommended Approaches to Integration of Genetic Toxicology Study Results**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

Pfizer submits attached comments on the draft Guidance for Industry on Recommended Approaches to Integration of Genetic Toxicology Study Results, Docket No. 2004D-0493, 69 *Federal Register*, 70153, December 2, 2004.

Pfizer appreciates the opportunity to provide comments and commends the Pharmacology Toxicology Coordinating Committee for developing guidance on this topic, as well as, the recently implemented tertiary review procedure.[1]

Additionally, we would invite direct dialog with the Agency if you would consider the opportunity valuable.

Sincerely,

Warren W. Ku/plp

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General Comments:

This draft guidance incorporates the ICH guidelines currently used by the industry and allows for flexibility in addressing risk and relevance of genotoxic findings in the context of early human clinical trials. It also defines general guidance for progressing to both single- and multiple-dose clinical trials. We agree with the focus on a weight-of-evidence (WOE) approach to the analysis of genetic toxicology study results for relevance in support of the conduct of early clinical trials. Similarly, we commend the inclusion of the concept of a threshold mechanism of action (MOA) for genotoxins as part of WOE determinations. These are important concepts and represent the best use of available data especially in trials for patients with debilitating or life-threatening diseases. (lines 73-76). We suggest that, in keeping with the flexibility incorporated in assessing weight-of-evidence, the guidance should specify the conduct of the fourth test in the ICH battery as a possible <u>option</u> for integrating genotoxicity results. We also recommend additional clarity on what conditions warrant assessment of early carcinogenic potential as part of the weight-of-evidence (WOE) approach to support early clinical trials.

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.

Specific Comments:

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."* Clarification of this statement is needed within the context of the definitions proposed for single- and repeat-dose clinical studies. This statement could also apply to a single-dose clinical study, and our ability to discern half-life cannot be assessed until the initial clinical trials have been completed.

Lines 43-58. We agree that the ICH guidelines (including M3) and current CDER guidance pertaining to this subject matter are an appropriate starting point for determination of the conduct and timing of genetic toxicology studies. We also concur that risk for carcinogenesis is usually determined in rodent assays in vivo (either 2-yr or short-term alternative models) with reference to the ICH S1B guideline (lines 47-48). However, this guidance should make clear that the existing guidance documents discussing carcinogenicity testing refers to in vivo models and not in vitro models, such as the SHE transformation assay (see comments pertaining to section C). We also agree with the option (as cited in ICH M3) to initiate Phase I trials with results available from *in vitro* genetic toxicology studies (lines 57-58).

Lines 65-66. In principle, we agree with the concept of understanding mechanism of action (MOA) in addressing possible risks and we agree with the statement 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."* However, direct demonstration of MOA can often be challenging in the context of early drug development. As a practical approach to support clinical trials, we suggest 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.

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 that this statement be omitted. The choice of follow-up tests should be driven by the nature of the positive results seen in the ICH standard battery and supported by sound scientific rationale to address risk relevance. As noted above, we recommend that the selection of the fourth test in the ICH battery should be considered an option as warranted.

Lines 86-87. *"If a positive response is seen in one or more assays, sponsors should consider choosing from the following options."* We suggest that the sentence be modified to indicate that sponsors should choose from one or more of the following options proposed in the draft guidance, and that the choice(s) should be based on the nature of the positive effects seen and sound scientific rationale to address risk and relevance.

Lines 111-115. We agree with the inclusion of the concept of a threshold MOA in assessing WOE, consistent with previously published literature[2,3] and that generating sufficient evidence for an indirect MOA for a genotoxic compound should support progression to repeat-dose clinical trials. The guidance should also acknowledge that other indirect mechanisms are possible outside those mentioned.

Section C. Additional Supportive Studies. It is unclear in this section what conditions would warrant assessment of early oncogenic potential as part of WOE to support early clinical trials. When sufficient information exists to address WOE, or MOA, or the lack of *in vivo* relevance of an *in vitro* genetic hazard, an early assessment of carcinogenic potential (through either a SHE transformation assay or a p53 transgenic mouse assay) should not be required to progress to multi-dose clinical trials in normal subjects or patients.

Lines 140-150. In regards to the discussion on the SHE assay, it is unclear when, or for what purpose a sponsor would conduct this assay. This paragraph is contradictory in that it is acknowledged that for human pharmaceuticals, the

assay lacks good predictivity to detect putative human carcinogens, but also states that the assay may be useful as a WOE approach.

Lines 148-150. We suggest deletion of the last sentence stating that the assay measures an endpoint more akin to the health effect of concern. The mechanisms of transformation and relationship to human cancer are most often unknown. Additionally, human cells are much more difficult to transform than embryonic rodent cells.

While we would agree that sponsors may choose to use the SHE transformation assay for internal decision making purposes, and negative results may have some value, this assay does not represent a true assessment of carcinogenic potential and should not be used for that purpose.

References:

(1) FDA Center for Drug Evaluation and Research Office of New Drugs. Tertiary review of genetic toxicology studies resulting in a recommendation for a clinical hold or conduct of additional studies. CDER Manual of Policies and Procedures MAPP 7400.4, September 2004.

(2) Kirkland DJ and Muller L. Interpretation of the biological relevance of genotoxicity test results: the importance of thresholds. Mutat. Res. 2000:464; 137-47.

(3) Muller L. and Kasper P. Human biological relevance and the use of threshold-arguments in regulatory genotoxicity assessment: experience with pharmaceuticals. Mutat. Res. 2000:464; 19-34.