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May 12, 2008

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-D-0178. International Conference on Harmonisation; S2(R1)
Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human
Use

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) requests for comments on the International Conference on Harmonisation (ICH) draft *Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (the draft guidance).

BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial, and environmental biotechnology products.

General Comments

The purpose of the draft guidance is to update the existing ICH S2A and S2B guidelines pertaining to the genotoxicity testing of pharmaceuticals (the existing guidelines were approved in 1996 and 1997). The Expert Working Group for the S2(R1) guideline was charged to achieve several goals: reducing the number of animals used in routine testing; avoiding, or more adequately managing, irrelevant findings to reduce barriers in early drug development; clarifying the follow-up testing needed to address positive findings; and providing guidance in the interpretation of positive results. The draft guidance meets these goals and combines the two existing guidelines into a single revised guideline.

The draft guidance is a significant improvement over the existing guidelines. It incorporates much of the learning acquired during the 10 years since the approval of S2B. Additionally, genotoxicity assays developed since 1997 are included. Finally, the draft guidance allows sponsors more flexibility with regard to the choice of assays to use to evaluate molecules and to satisfy regulatory requirements by providing two primary options for the standard battery of tests needed to support submission. Our specific comments follow.

Specific Comments

Lines 20-22: BIO welcomes this statement regarding the scope of the guidance, which indicates that the primary focus of the guidance is “small molecule” drug substances rather than biologics as defined in the ICH S6 guideline (*Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*). This will eliminate the uncertainty around genotoxicity testing for biologics that resulted from not mentioning the ICH S6 guideline in the existing ICH genotoxicity guidelines S2A and S2B.

Lines 88-139: Please add information pertaining to the timing of testing. Specifically, we believe the intent is for sponsors to complete the *in vitro* tests prior to first human dose (FHD) when using Option 1 and to complete all testing prior to FHD when using Option 2, but this is not stated.

Lines 99-106: We request clarification of this section of the document. In Line 101, there is mention of assessing genotoxicity in two *tissues* while Line 106 indicates two *assays*. Please clarify that the draft guidance recommends evaluation of genotoxicity in two tissues rather than two endpoints, when integrating into repeat-dose toxicity studies. We note that while the former can easily be accomplished using the Comet assay, the latter is difficult. There is little information published regarding the combination of two genotoxic endpoints into treatment of a single animal. If the intent was to recommend evaluation of genotoxicity using two endpoints, we request that further details be provided regarding the conduct of combination tests (for example, references to published validated procedures).

Lines 267-271: We suggest deleting ‘including endoreduplicated’ from Lines 268-269. While an increase in polyploid cells may give an indication of the potential of a compound to induce aneuploidy as noted, endoreduplication is considered to provide an indication that the compound may interfere with cell cycle progression.

Line 337: The phrase ‘substantial sex difference evident in toxicity / metabolism’ should be reconsidered and clarified. Because the definition of ‘substantial’ will vary from individual to individual, it would be very helpful if the draft guidance provided specific examples of toxicity meeting this criterion, e.g. target organ toxicity present in one gender and not the other, different lesions present, etc. Furthermore, we suggest that the term ‘metabolism’ be replaced with ‘toxicokinetics’. 14C metabolism studies are typically performed only in a single sex unless there is a difference between sexes in the toxicokinetic results that is much greater than the interanimal variability. Therefore, the

wording should be modified so that it does not inadvertently imply that metabolism studies in both sexes are recommended.

Lines 411-414: As in our comments on lines 99-106, we request clarification of FDA's expectations for development and validation of procedures for combining two genotoxicity assays in the same animal, for example in the form of references to published validated procedures.

Line 691: We suggest the addition of a second reference*. This earlier publication on the use of young rats for the liver micronucleus test also includes a procedure for collecting bone marrow for micronucleus evaluation from the same animals and thus provides a method for assessing genotoxicity from two tissues in the same animal. Additionally, the paper includes a procedure for conducting a liver micronucleus assessment using formalin-fixed tissue.

* Parton, J.W., Garriott, M.L., "An Evaluation of Micronucleus Induction in Bone Marrow and in Hepatocytes Isolated from Collagenase Perfused Liver or from Formalin-Fixed Liver Using Four-Week-Old Rats Treated with Known Clastogens," *Environmental and Molecular Mutagenesis*, 29:379-385, 1997.

Lines 719-721: We suggest that the data be shown (cited) that support this statement.

Minor Comments

- Lines 154 and 161: N in "note" should be lower case.
- Line 328: The Kenelly et al reference in Section 8 was not found in the text. It could appropriately be included at the end of this line (and/or in line 683).
- Line 351: Change 'sample blood' to 'blood sample'.
- Line 369: The "Hayashi et al, 2005" reference cited is not included in the reference list (Section 8). This reference should be added in Section 8, or the date in line 369 should be changed from '2005' to '2000' or '2007', as appropriate.
- Line 374: Add a comma after '474)'
- Line 382: Add a second closed parenthesis, ie. '.....5)),'
- Line 403: Add a period after 'iv'
- Line 426: Letter 'a' in 'an' should be upper case.
- Line 517: Letter 'c' in 'coli' should be lower case.
- Line 561: Delete the second 'to' in the line.

- Line 570: ‘in vitro’ should be in italics.
- Line 578: The ‘Galloway et al, 1998’ reference cited is not included in the reference list (Section 8).
- Line 645: Delete second ‘l’ in ‘...-Volders et all, 2003’.
- Line 683: The Kenelly et al reference in Section 8 was not found in the text. It could appropriately be included after the word ‘assay’ (and/or in line 328).
- Line 762: The International Workshop on Genotoxicity Testing (IWGT) reference needs to be included in the reference list (or if it is already included, please clarify IWGT report referenced in this line).
- Lines 763-764: We suggest that the sentence would be clearer if it read ‘ ... few chemicals that were rodent carcinogens and that were positive in MLA ... ’
- Line 765: We suggest that the word ‘and’ be deleted, and that a new sentence begin at the “convincing”.
- Lines 782-787: We suggest moving the reference (Greenwood et al, 2004) to the end of the paragraph.
- Line 840: Please clarify the Tweats reference (e.g. at a minimum, add a space between ‘2007’ and ‘I’), and either delete ‘IWGT’ if it simply refers to Tweats et al, or add the separate IWGT reference to Section 8.
- Section 8. REFERENCES: Please add the specific page numbers cited to the Goodman & Gilman reference.

Conclusion

BIO appreciates this opportunity to provide input to FDA. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science and Regulatory Affairs

cc: Michael L. Garriott, PhD (Eli Lilly and Company), Biotechnology Industry representative to ICH S2(R1) Expert Working Group.