

August 5, 2005

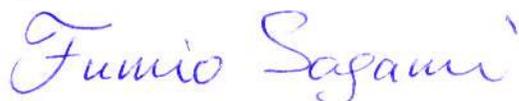
**Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

Dear Dockets Management:

**Re: Guidance for Industry: Safety Testing of Drug Metabolites
[Docket No. 2005D-0203, 70 Federal Register, 32839, June 6, 2005]**

Japan Pharmaceutical Manufacturers Association (JPMA) has collected comments and suggestions regarding Draft Guidance of Safety Testing of Drug Metabolites from the JPMA Members in Japan. JPMA submits the comments and suggestions to CEDR and hopes they are duly reflected in the Guidance.

Regards,



FUMIO SAGAMI, DVM, Ph.D.

**Chairperson
Non-clinical Evaluation Subcommittee
Drug Evaluation Committee
Japan Pharmaceutical Manufacturers Association (JPMA)**

**Eisai Co., Ltd.
1-3, Tokodai 5-Chome Tsukuba-shi,
Ibaraki 300-2635 JAPAN
Phone:+81-29-847-5605
Fax:+81-29-847-1006
E-mail: f-sagami@hhc.eisai.co.jp**

Comments,

Line 301-302: We request that “major metabolite” is more clearly and instructively defined, such as “a major metabolite is defined as one that account for greater than 10% of the exposure to circulating drug-related material as well as greater than 10% of the administered dose.

Line 28-30: Please indicate the typical calculation method of “% of drug in systemic exposure”.

Line 78: The above phrase should be changed to “one or more metabolites present at greater than 10 percent of the administered dose or systemic exposure.”

Line 210: Explain about the study method of “combined exposure” in detail please.

Line 224: How many species are required for the general toxicity studies, one or two?

Line 229: ICH Q3A may be more appropriate to refer instead of ICH Q3 (R).

Line 235-237: Does 2,000 mg/kg/day mean a dose of an isolated metabolite?

Line 235-237: Please define “frank toxicity”.

Line 235-237: The maximum dose selection is more appropriate based on the systemic exposure levels of a given metabolite (Ex. x 1, 5, 10 or 25 of therapeutic dose level) rather than dose level or toxicological appearance basis.

Line 239-241: Why is the intended clinical route of administration recommended? It is generally considered that oral administration of isolated metabolites is not suitable.

Line 256: Does FDA require two animal species for embryo-fetal development studies in accordance with ICH guidance?

Line 271-274: This sentence should be replaced to:

“We might recommend to conduct carcinogenicity study for a metabolite of drugs, if there is concern about their carcinogenic potential such as positive genotoxic findings, genotoxic or carcinogenic structural alerts, tissue proliferate effects (i.e., hyperplasia, preneoplastic lesions) identified in general toxicology studies as well as any other

relevant data. Generally, carcinogenicity studies might not be requested for nongenotoxic metabolites.” REASON: It is unclear whether the original sentence is written about metabolites or parent compound. Stance on necessity of carcinogenicity studies for nongenotoxic metabolites should be clarified in this paragraph.

Line 352: “Human only” leads to “H>10% Dose” only. An arrow should be projected from the box “Human Only” to “H=10% of dose”.

Line 352: It is confusing that the term ‘dose’ is used in appendix A, though the expression ‘ administered dose or systemic exposure whichever is less’ is used in the text.

Line 352: What does the abbreviation “H” stand for? The meaning of ‘H’ should be described in footnote.