November 13, 2006

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Re: Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implication for Dosing and Labeling (Dockets No.:2006D-0344)

Japan Pharmaceutical Manufacturers Association (JPMA) has collected comments and suggestions regarding Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implication for Dosing and Labeling from the JPMA members in Japan. JPMA submits the comments and suggestions to CDER and hopes they are duly reflected in the Guidance.

Regards,

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

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JPMA Comments on

Draft Guidance for Industry:Drug Interaction Studies – Study Design, Data Analysis, and Implication for Dosing and Labeling

General: In this draft guidance, it seems that "in vivo study" means a clinical study in humans. Please make it clear (e.g., by writing as "in vivo human study"). General remarks regarding in vivo animal study would be helpful to understand the Agency's view.

Line 359–361: Conditions for dosing (dose and dosing interval) is missing only for strong CYP3A inhibitors. Please describe them as in the description about a moderate and a weak CYP3A inhibitor.

Line 445–446: The following sentence modification is preferable (addition of the under-lined phrase): "*When the above study shows significant interaction, further evaluation with weaker inhibitors may be necessary, <u>depending on the drug's exposure-response relationship.</u>*"

Line 556–557: Please show an example of drug whose clinical outcomes are related to AUC as shown for peak concentration (tachycardia in line 554–555).

Line 688–725 (Appendix A, Tables 2–4): Inconsistency in terms of listed substrates in Tables 2, 3 and 4 can be found:

- Duloxetine and alosetron are listed in Table 4 as sensitive substrates of CYP1A2, but not listed in Table 2.
- Budesonide, eplerenone, fluticasone, saquinavir and vardenafil are listed in Table 3, but not in Table 2

There are other inhibitors listed in both tables (e.g., omeprazole for CYP2C19).
Suggestion: All the substrates will be listed in Table 2 regardless of their sensitivity but with a specific symbol for sensitive substrate. Substrates with narrow therapeutic range will be listed in Table 3 for all the CYPs listed (Table 4 will be deleted instead).

Line 822–828: In this draft guidance, recommended method to identify contributing metabolizing enzymes is based on production of each metabolite. As an alternative, so called "substrate depletion approach" (e.g., Drug. Metab. Dispos. 34, 1433 (2006)) can be possible. Please add descriptions regarding this.

Line 842–852: Regarding contribution of CYP enzymes:

- Please show the conclusive scientific basis of “> 25 %” criteria.
- Please show the standard method to estimate the contribution of CYP enzymes to drug's clearance.

Line 890–891 (Appendix C-1, Table 2): Diethyldithiocarbamate is also known as a mechanism-based inhibitor, and should be pre-incubated before adding substrate (addition of "(2)" in the table).

Line 1044–1049: Please reconsider the definition of inhibitor concentration. In this guidance, C_{max} value for total drug (bound plus unbound) is used as inhibitor concentration. In general, unbound drug is considered to be better predictor of drug concentration around hepatic enzymes. Considering the fact that the inhibitor concentration can reduce in the actual situation and C_{max} represents an upper extreme of [I], additional extreme (i.e., total concentration instead of unbound) could result in too-conservative estimate for drug interaction potential.
Further, in the case of oral dosage form, a parameter "CuHi max (appr)" can be a useful as inhibitor concentration. This concept can be found in a Japanese guideline, “Methods of Drug Interaction Studies” (Jun 2001), page 16 (*http://www.nihs.go.jp/phar/material/material3/DiGlEngFinal011209. pdf.).

Please add descriptions that these approaches based on unbound fraction can be acceptable.

Line 1044–1074: What is the recommended approach to determine the inhibitory potency if time-dependent inhibition occurs in in vitro studies? In case of mechanism-based inhibitor, the potency can not be estimated by [I]/Ki ratio like reversible inhibitors.

Line 1190 (Appendix D): I In this section, in vitro evaluation method of P-gp was written in detail. Does this mean that P-gp-related evaluation should be conducted for all developed compounds? For CYPs, the enzymatic contributions to the clearance are taken into consideration, but not for P-gp.

Line 1142–1143: Please show the scientific besis for the criteria of 40%.

Line 1341: Please make it clear that "for 30 minutes" shows a typical example for incubation time as for concentraion (line 1339) and sampling time (line 1347).

Line 1425: For the LLC-PK1-MDR1 or MDCK-MDR1 cells, (R_{Ei}/R_{Ea}) represents the corrected efflux ratio (R_T/R_W) in the presence of inhibitor concentration (I) relative to that for the control without inhibitor as follows:

(R_{Ei}/R_{Ea}) = (R_T/R_W with inhibitor) / (R_T/R_W control)

Although the corrected efflux ratio may reflect the P-gp mediated transport more than the other parameters (ex. efflux ratio, net flux) from a theoretical point of view, it is still controversial among researchers which parameters should be used for the calculation of IC_{50} (and K_m).

In addition, it is uncertain whether reasonable IC_{50} values can always be obtained by using the corrected efflux ratio. For instance, the corrected efflux ratio for the typical P-gp substrate such as digoxin at the control level (in the absence of inhibitors) sometimes seems not large enough to obtain clear inhibition curves and appropriately estimate the IC_{50} values. In this term, more detailed criteria or conditions should be specified to select and use this parameter (R_{Ei}/R_{Ea}). Thus, at present, it seems better not to define the equation (3) as the only one for calculating IC_{50} values.

Line 1474 (Appendix D, Figure1): Determination of K_m value would be better before making decision of in vivo study to be performed. In the case of inhibitory compounds, this guidance recommends determination of IC_{50} (or K_i). Similarly, if compounds are substrate, K_m value would be helpful to judge whether in vivo study will be performed or not. Please add description that the decision based on consideration of Km (e.g., plasma or tissue concentration /Km ratio) can be possible.

Line 1554–1555: The definition of [I] should be written not only here as table footnote, but also in the text part in page 48. In addition to this, please consider the appropriateness of unbound drug concentration as [I].

Genera: The following typing errors are found;

Line 0352: "investigation" should be "investigational".

Line 0450: "more that one" should be "more than one".

Line 679: "ketocoanzole" should be "ketoconazole".

Line 1179: "Receprtor gene assays" should be "Reporter gene assay".

Line 1527: "Figure 1" should be "Figure 2".