INTRODUCTION
The mechanisms of drug interactions are divided into pharmacokinetic interactions and other interactions (pharmacodynamics etc). The Japanese Guidance on Drug Interaction Studies (draft), which was presented in April 2000 mainly refers to pharmacokinetic interactions and extensively covers all stages of drug development, including non-clinical, clinical, and post-marketing studies.

On the other hand, drug interaction guidances have already been introduced in other regions in the world, and there are significant differences between Japan and the rest of the world. Therefore, there is a need for worldwide harmonization (without taking up as a theme by the ICH).

Taking the above background into account, the Pre-Clinical Evaluation Subcommittee of the Drug Evaluation Committee of the JPMA (Japan Pharmaceutical Manufacturers Association) established a working group in the fourth division (responsible for ADME) to coordinate opinions of the pharmaceutical companies in cooperation with Clinical Evaluation Subcommittee. At the same time, we compared the Japanese Guidance with the guidances of other regions and have already submitted the results to the regulatory authorities through the Japan Federation of Pharmaceutical Organizations (NICHYAKUREN).

This presentation discusses the issues that may be encountered in the actual process of drug development and differences from the other regions impacting international harmonization. It should be noted that although these perspectives are based on information obtained through objective review by JPMA, it also contains personal views which may not necessarily reflect the views of JPMA (or the consensus of all pharmaceutical companies in Japan).

USEFULNESS OF ANIMAL STUDIES AND THEIR LIMITATIONS
The other regions have recognized that the application of drug interaction studies in animals should be limited to pharmacodynamic interactions. In contrast, the Japanese Guidance (draft) takes the standpoint that some drug interaction studies in animals will be useful for pharmacokinetic interactions.

In predicting from animal study data to humans, species differences in drug metabolizing enzymes and transporters, differences in systemic exposure (unbound drug), and ratio of total body clearance by metabolic route through which interactions occur need to be addressed carefully, and it is dangerous to conduct discussion based only on change in blood concentrations in animals. It is, however, not often the case that animal studies can clear these hurdles and be scientifically meaningful, especially when the objective is prediction to humans.

According to research by the JPMA, the majority of pharmaceutical companies consider in vitro studies using human tissue-derived material are more useful for prediction to humans than animal studies if limited to interactions related to metabolism including enzyme induction. It is also true that there are opinions that the usefulness of animal studies should not be completely ignored. However, this may be due to the social circumstance particular to Japan; that is, materials derived from human tissues are not available locally and must be imported.

Even taking into account existing circumstances, the Guidance should not insist on the usefulness of animal study for such a negative reason as there being no other choice. The cases where animal studies are regarded useful should be indicated specifically as special cases.
IMPORTANCE OF CLINICAL STUDIES

The guidances of other regions are generally skeptical of prediction to *in vivo* (humans) from *in vitro*. For example, the EU Guidance mentions that *in vitro* data should mainly be used qualitatively. It is also mentioned in the US Guidance that the overall experience to date is not extensive enough to allow reliable conclusions about prediction from *in vitro* to *in vivo*. Furthermore, the US Guidance declares that *in vivo* studies remain the primary source of information for enzyme induction.

On the other hand, the Japanese Guidance (draft) tends to over-emphasize the importance of prediction from *in vitro* to *in vivo*, and it's basic stance is that "**It is important to select safe drug candidates for which conducting drug interaction studies in humans is not necessary**" (quoted from the Guidance). In addition, as one method to make possible prediction to *in vivo* from *in vitro*, the Japanese Guidance (draft) describes in great detail the prediction of degree of interaction in humans from the relation between the maximum concentration of the unbound inhibitor in the metabolizing organ (C\text{I, max}) and the inhibition constant (K\text{i}) obtained from *in vitro* study. However, it cannot be said that global consensus exists on this at the present time.

The common view of the three regions is that if no inhibition is observed against representative marker drugs in a *in vitro* study using materials derived from human tissues, no further study of interactions is necessary at least for interactions related to the mechanism involved. Therefore, what is called for in *in vitro* studies is qualitative judgment on whether or not interaction can occur in humans. Even if a semi-quantitative (equivocal) prediction is given, i.e., that interaction can occur in humans but degree is low, clinical confirmation studies (to estimate the degree of interaction) must be conducted.

However, prediction of degree of interaction from *in vitro* studies will be helpful for the assurance of safety of subjects in clinical studies.

CRITERIA OF DRUG INTERACTION

In the Japanese Guidance (draft), one way mentioned to determine the lack of drug interaction from clinical study is "**if the 90% confidence interval for the ratio of pharmacokinetic parameters falls between 80-125%, pharmacokinetic drug interaction is considered negative**" (quoted from the Guidance). However, the Guidance makes no mention of flexibility of the acceptance range of the confidence interval taking into account clinical significance and just proposes a uniform criteria, which makes it different from the guidances of other regions.

For instance, the EU Guidance accepts that the "acceptance range" of the confidence interval can be wider (or narrower) than the interval of 80-125%, taking into account causal relationship between therapeutic effect and blood concentrations. It also calls for the necessity of analysis focused on increased variability in blood concentration due to interaction in the case of drugs with a narrow therapeutic index. The US Guidance also calls for deciding on "no effect boundaries" based on dose and/or concentration-response relationships, PK/PD models, and other available information and using a default no effect boundary of 80-125% in the complete absence of such information.

In actuality, it is not frequent that clinical studies are conducted to determine the lack of interaction (clinical studies are usually planned only when expression of interaction is highly possible). It is more often the case that clinical studies are planned to determine the degree of interaction assuming that interaction predicted from *in vitro* studies will appear *in vivo* (in humans). In this sense, it is desirable that practical guidance be established dealing with clinical study data from comparatively few subjects, evaluation methods taking into account clinical significance, and details of concrete methods for description in package inserts.

CONCLUSION

I have given an outline of some points at issues regarding the Japanese Guidance on Drug Interaction Studies (draft) from my role in coordinating opinions of pharmaceutical companies as a part of JPMA activities. I will be happy if this presentation will contribute to discussions of the Forum to achieve harmonization between the three regions (proposals for ICH Guidance).