ICH Topic-M3 guideline:
Issues that had not been harmonized and the start of its revision

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There were following five issues that had not been harmonized in the ICH Topic-M3 guideline, "Timing of non-clinical safety studies for the conduct of clinical trials", when it was developed in 1997: 1) the minimum duration of rodent repeated dose toxicity studies for the conduct of Phase I and Phase II trials up to two weeks in duration (4 weeks in Japan and 2 weeks in US and EU), 2) the minimum duration necessary to evaluate male reproductive toxicity in rodent (4 weeks in Japan and 2 weeks in US and EU, and in US this issue may be neglected in case of single-dose trials for a screening purpose), 3) the minimum duration of repeated dose toxicity studies for the conduct of Phase III trials (there are complicated tables and notes of the tables in the guideline), 4) the allowance of single dose Phase I trials based on single dose safety studies (possible only in US), 5) the timing of each of the reproductive toxicity studies to conduct each Phase clinical trials. The issues 1) and 2) have been dissolved by a collaboration study by JPMA and MHLW, but other issues have not been harmonized yet. In addition, recent notifications of the Position Paper on microdose clinical trials by EU and the exploratory-IND guidance by US FDA stretched the differences in regulations among three regions. In Oct.-Nov. 2006, an ICH expert working group (EWG) has started to revise the Topic-M3 guideline. The EWG is expected to discuss all the disagreement issues including microdose clinical trials and exploratory-IND studies and to attain harmonization within the next year (2008).