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EFFECTS OF THREE-DIMENSIONAL CULTURE ON THE DRUG METABOLISM GENE EXPRESSIONS IN HepG2 HUMAN HEPATOMA CELL LINE
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Evaluation of the safety of drug candidate compounds in each stage is very important for the drug development. Most of the in vitro safety evaluations in the earlier stages are done by using human primary hepatocytes, because of the species differences of drug metabolism and the deficiency of drug metabolizing activities in established human hepatoma cell lines. However, primary hepatocytes differ from one lot to others, reflecting inter-individual differences of the donors. Development of the in vitro systems which enhance the drug metabolism functions using human hepatoma cell lines is awaited to circumvent the difficulties involved in human hepatocytes. For this purpose, we are studying the effects of three-dimensional cell culture system on the drug metabolism gene expressions. HepG2 cells were cultured in the radial-flow bioreactor (RFB) for seven days, and the RNA was prepared. The RNA was also prepared from the HepG2 cells cultured in a cell culture plate. Gene expressions in each RNA sample were measured by quantitative real-time PCR and by Affymetrix GeneChip. More than a dozen genes, such as CYP2B6 and ABCCl, were upregulated in the three-dimensional culture (RFB) among the eighty-four drug metabolism genes measured. Induction of CYP3A4 gene by rifampicin was also improved in RFB. The global gene expression analysis by Affymetrix GeneChip indicated that the change of the cytoskeleton might be one of the causes of these gene expression changes. Further biological experiments run in the cell culture plate, which mimic the RFB culture effects, will be presented. Our results suggested that the culture environment is important for the drug metabolism functions of HepG2 cells.

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QUESTIONNAIRE SURVEY ON NON-CLINICAL ADME STUDIES PACKAGE
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The ICH guideline (M3) adopted (as a step 5 document) in November 1998 has shown that a phase I clinical (P1) study should start after completing evaluation of exposure data in animals. Further, information on inter-species comparison of metabolism should be made available by the time the P1 studies have been completed. However, there are not well-defined criteria or guidelines regarding when sponsors need to have ADME study data during R&D or what kind of data they need. Therefore, pharmaceutical companies need to establish their own policies regarding the types of ADME study should be done by first in human study. The contents of the ADME studies package thus depend on company's policy and also differ among regions.

Based on such a situation, questionnaire surveys concerning ADME studies for IND or NDA were conducted by sending to the 66 member companies of JPIA from January to February 2008. The surveys included both the timing of each study and the objectives in terms of efficacy, toxicity and clinical planning. The survey also questioned concerning the conduct of P1 study. The answers obtained from 54 companies were analyzed.

The results showed that pharmaceutical companies tend to conduct more in vitro studies than in vivo studies using radioactive compounds before P1 studies, especially in US/EU-capital companies. The environment that surrounds the drug development might have been dramatically changing, including the necessity of data package to start the clinical trial. This report will discuss what types of ADME studies are needed to support efficacy and toxicity studies and clinical planning, and will also propose a stage-appropriate approach for ADME studies.