Proper Number of Subjects and Study Design for Evaluation of Ethnic Difference of Oral Clearance: Use of Inter-individual and Inter-study Variability Obtained from Meta-analysis

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Objectives: Ethnic difference in pharmacokinetics is one of the most critical concerns in the international new drug development. However, statistical detectability and proper number of subjects of clinical studies for evaluation of the ethnic difference have not been fully investigated. This is probably because variability of the oral clearance (CLoral) is highly variable, and is hence unpredictable. Previously, we have performed a meta-analysis of CLoral of 80 drugs reported in 662 clinical studies to elucidate the ethnic difference in CLoral between Japanese and Western subjects considering clearance pathways. In this study, proper number of subjects and study design for evaluation of the ethnic difference are considered based on outcomes of the meta-analysis.

Methods: For the meta-analysis of ethnic difference, CLoral values of 80 drugs in Japanese and Western subjects were collected mainly from literatures and product labels. Drugs were classified by their clearance pathways (eight groups) based on contribution ratio (CR) determined in vivo. Ethnic difference of CLoral, inter-individual variability, and inter-study variability were estimated by Gibbs sampling method. Based on outcomes of the meta-analysis, statistical powers to detect ethnic difference were calculated for various conditions.

Results: In addition to inter-individual variability, significant and consistent inter-study variability was detected in the meta-analysis. When the observed variability was considered, it was estimated that significant ethnic difference might be detected in 22% of studies incorrectly (i.e. false-positive) for drugs cleared by hepatic metabolism. On the other hand, ethnic difference can be detected as significant if the difference is more than 2.5-fold, although this degree of difference does not exist for usual type of drugs. In order to detect ethnic difference reasonably, it is suggested that sufficient subjects of both reference and target ethnicities need to be included from this study.