Assessment of Drug Metabolites

The guidance for safety testing of drug metabolites (MIST) from the FDA (2008) and the ICH (2009) has had significant impact on drug discovery and development. Before the MIST guidance, there were no regulations for drug metabolites. Nonclinical evaluation of drug safety is assessed by comparison between systemic exposure in nonclinical studies and in human studies; therefore, the nonclinical evaluation of drug metabolite safety based on a similar concept (comparison of systemic exposure of metabolites between nonclinical and human studies) may be reasonable. However, the requirement of further toxicological investigation of metabolites present at 10% of the parent drug’s exposure at steady state (FDA) or at 10% of total drug-related exposure (ICH) has led to much debate. There is no scientific consensus on the validity of the “10% criteria,” and a lot of debate around that. Under the MIST guidance, circulating stable drug metabolites are the basis of the criterion, whereas different categories such as the amount or duration of drug use or patient age from the viewpoint of pharmacologically based mechanisms of toxicity have been also proposed.

According to the MIST guidance, these assessments should be completed before beginning Phase III clinical trials. If disproportionate human metabolites that are present only in humans or are present at higher exposure in humans than in experimental animals are found, then the nonclinical safety testing of metabolites should occur; however, this additional safety testing may cause development and marketing delays. The safety of drug metabolites is currently receiving a lot of attention, but the relationship between drug metabolites and pharmacology or drug–drug interaction (DDI) potency should also be well characterized.

Pharmacologically active metabolites are known to have important roles contributing significantly to the overall therapeutic and adverse effects of drugs. If active metabolites significantly contribute to the efficacy in animal studies, we should consider their role in clinical studies. To consider this contribution, we need to predict the in vivo efficacy and pharmacokinetic profiles in humans. If the active metabolites can be predicted to exhibit important roles in clinical studies, we should incorporate the contribution of active metabolites when establishing the dosage and dose regimen.

The potential of drug metabolites to contribute to DDI should also be considered. The MIST guidance does not look at DDI. If drug metabolites have an effect on drug metabolizing enzymes or transporters, they may have the potential to change the exposure of parent or coadministered drugs and result in adverse events. Currently, there are no established examples of this type of DDI caused solely by metabolites. Usually, the evaluation of DDI potency is first assessed by in vitro studies, followed by in vivo DDI studies. To perform in vitro studies, we need reference standards of drug metabolites. However, the chemical synthesis of them is sometimes limited. In addition, the separate evaluation of in vivo DDI potency between parent and drug metabolites is difficult. Therefore, the limited availability of standards of drug metabolites and the difficulty in establishing the relative contributions may be the reasons for minimal recognition of the DDI potential of drug metabolites.

Up to now, screening tests for ADME at the discovery stage have focused on the selection of parent drugs. Although determination of the rate of metabolism of parent drugs is involved in these screening processes, the investigation of drug metabolite profiles is not. Metabolite profiles are usually established at a late stage, after selection of candidates. To assess drug metabolites, we usually conduct the following studies:

1. Qualitative structure elucidation of drug metabolites in vitro and in vivo in animals
2. Qualitative structure elucidation of drug metabolites in vitro using human tissues
3. Quantitative evaluation of drug metabolites in vivo in animals
4. Qualitative and quantitative evaluation of drug metabolites using Phase I samples
5. Human ADME study

Many DMPK researchers in the industry have proposed assessment procedures of drug metabolites to avoid delays in phase III clinical trials. At the preclinical stage, we can obtain useful information thorough studies of types 1–3. In vitro metabolism systems using microsomes and hepatocytes give relatively high predictability for the qualitative primary metabolic pathways, but the predictability of secondary metabolites is less reliable. Comparisons between in vitro and in vivo metabolite profiles in animals and comparisons between animal and human in vitro metabolite profiles also provide useful information about stable circulating drug metabolites. However, since drug metabolite exposure is related not only to the formation of drug metabolites but
also to their distribution and disposition in humans, the precise prediction of disproportionate (at 10% of the parent drug exposure) circulating drug metabolites in humans is difficult. Therefore, qualitative and quantitative assessment using human samples will be an important process (study type 4). For this assessment, the most problematic issue is the reliable quantitative evaluation of drug metabolites. In particular, the aforementioned preparation of standard drug metabolites is a formidable barrier; therefore, the industries have developed the assessment method without reference standards of drug metabolites.9–11

The assessment of drug metabolites is time-consuming work for DMPK researchers in industry with respect not only to safety but also to pharmacology and DDI. We should assess this issue with suitable timing and procedures for each candidate on a case-by-case basis.

**Reference**


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