# *In Vivo* Metabolite Kinetics

ZHENG YANG

## 1 INTRODUCTION

Following the administration of a drug, the pharmacokinetics and disposition of the metabolite(s) that are formed can be described and modeled. Such information is important because any metabolite can be pharmacologically active and contribute to the overall efficacy of the drug of interest. For example, atorvastatin (Lipitor®) produces two active hydroxylated metabolites that are equipotent to the parent drug *in vitro* and contribute to the prolonged inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in an *ex vivo* assay (Christians, Jacobsen and Floren, 1998; Siedlik *et al.*, 1999). Another example is clopidogrel (Plavix®) whose pharmacological activity is due to the production of a reactive thiol metabolite that irreversibly blocks the ADP binding and receptor activation of the platelet $P2Y_{12}$ receptor (Savi *et al.*, 2000; Pereillo *et al.*, 2002). Information on active metabolites and their kinetics in the body is essential to comprehending the pharmacokinetic–pharmacodynamic (PK–PD) relationships of drugs and provides important guidance to their use in the clinic. With recent advancement in bioanalytical techniques, many of pharmacologically active metabolites can be identified and quantified in various biological fluids at the early stages of drug discovery. Understanding the pharmacological activity and pharmacokinetics of metabolites may provide useful insights into the PK–PD disconnect exhibited by a new chemical entity during *in vivo* efficacy testing. Moreover, the structural insights from active metabolites offer an excellent opportunity in the design of novel drug molecules (Fura *et al.*, 2004; Fura, 2006).

From a safety point of view, recent discussions on metabolites in safety testing (Baillie *et al.*, 2002; Hastings *et al.*, 2003; Smith and Obach, 2005, 2006; Davis-Bruno and Atrakchi, 2006) and the FDA Guidance on this topic also highlight the importance of understanding metabolite kinetics. In this context, it is imperative to make a distinction between a major circulating metabolite and a major metabolic pathway, and to understand the factors that determine the exposure of a metabolite in circulation and its appearance in excreta (e.g. urine and bile). In addition, knowledge of how metabolites distribute and accumulate in tissues is valuable to biotransformation-based

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