DRUG INTERACTION ASSESSMENT STRATEGIES: SMALL MOLECULES VERSUS THERAPEUTIC PROTEINS

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3.1 INTRODUCTION

Paramount to every small molecule drug (SMD) development program is the assessment of drug interaction (DI) liabilities involving metabolic enzymes or drug transporters. Generally, these assessments are undertaken to understand how one SMD (perpetrator) may affect the absorption, distribution, metabolism, and excretion (ADME) of another SMD (victim) and therefore determine the potential for drug–drug interactions (DDIs). The importance of DDI assessment during SMD drug development (generally in the context of pharmacokinetics-based interactions) has been highlighted in recent guidance documents and papers published by regulatory agencies worldwide, including the FDA[1–3] and the European Medicines Agency (EMA).[4] Many preclinical studies (mostly *in vitro* but also *in vivo*) have been developed over the last few decades to understand how a particular SMD may have a potential DDI risk and whether such a risk will translate into the clinic. In contrast, for therapeutic proteins (TPs), or biologics, recent concern has centered more around the ability of a TP to affect the ADME of a coadministered SMD (i.e., as a perpetrator only), although exceptions do exist. These types of TP-DI studies historically were not part of standard Biologics License Application (BLA) submissions. Table 3-1 gives a few examples of approved TPs for which DI assessment was performed and reported in the compound label.[5–10]

DDI risk assessment for a SMD often starts with well-established *in vitro* studies using human-derived models (e.g., human hepatocytes and microsomes). Inhibition (reversible, time-dependent, or mechanism-based) and induction studies of the

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