Minimizing the Potential for Drug Bioactivation of Drug Candidates to Success in Clinical Development

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1 INTRODUCTION

Toxicity problems, especially those that may only occur under unusual or idiosyncratic conditions during the late stages of drug development, are one of the most devastating surprises for pharmaceutical companies. Variations in human drug-metabolizing enzymes can produce subtle evidence of potential toxicity, or none at all, during preclinical safety studies. Such problems are also unlikely to show up in all but the largest clinical trials, but if the side effects are serious, can result in product withdrawal. There are indications that some substructures found in drugs can form reactive metabolites that are involved in toxicities in humans. These substructures include arylacetic and arylpropionic acids, aryl hydroxamic acids, oximes, anilines, anilides, hydrazines, hydrazides, hydantoins, quinones, quinone methides, nitroaromatics, heteroaromatics, halogenated hydrocarbons, some halogenated aromatics, chemical groups that can be oxidized to acroleins, and medium-chain fatty acids. Reactive metabolites are unstable, and are intermediates to more stable metabolites. Table 1 shows several examples of drugs that undergo metabolic activation and cause adverse reaction in humans, which have been withdrawn from the market or restricted in use with toxicity warnings. Clearly, a drug candidate that does, or may, metabolize to such substructures would increase the risk of failure or withdrawal.

1.1 Importance of Reactive Intermediates in Drug Discovery and Development

One key to success in clinical development is to minimize reactive intermediates in drug metabolism. There is a growing consensus that idiosyncratic drug reactions (IDRs) have enormous consequences for patients and the pharmaceutical industry. It is estimated that IDRs account for ~5% of all hospital admissions and occur in 10% to 20%

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