2 The Role of Pharmacokinetics in Drug Discovery: Finding Drug Candidates with the Greatest Potential for Success

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2.1 Introduction

Searching for new drugs is an extremely time-consuming and costly endeavor. Much of the time and cost is expended on clinical studies to obtain efficacy and safety data. Many drug candidates fail during these clinical trials. There are three main reasons for clinical failure, namely, lack of efficacy, serious side effects, and unacceptable pharmacokinetics. In a survey by PMA/FDA (1991), approximately 40% of clinical failures were attributable to poor pharmacokinetics, while lack of efficacy and adverse effects accounted for about 30% and 10%, respectively. Obviously, the ability to predict the efficacy, toxicity, and pharmacokinetics from preclinical and in vitro studies can reduce the high incidence of clinical failures and improve the success rate of drug candidates to reach the market. However, prediction of clinical efficacy
and toxicity is not easy; in most cases, they can be determined only by clinical experience. In contrast, prediction of human pharmacokinetics is relatively easy. There is an increasing body of evidence to suggest that a reasonable prediction of bioavailability and clearance in humans can be obtained when applying appropriate pharmacokinetic principles (Houston 1994; Iwatsubo et al. 1997; Lave et al. 1999; Lin 1999).

Today, all drug companies include early ADME (absorption, distribution, metabolism, and excretion) evaluation in the process of drug discovery, and employ pharmacokinetic principles to select lead drug candidates for further development. As a result, drug metabolism scientists within the pharmaceutical industry have emerged from their traditional role in drug development to provide valuable support in drug discovery efforts. In the early stage of drug discovery, drug metabolism scientists routinely provide information from pharmacokinetic evaluation for medicinal chemists to optimize and modify the chemical structure of compounds, and for pharmacologists to accurately interpret pharmacodynamic observations. Another important role of industrial drug metabolism scientists is to predict human pharmacokinetics of lead compounds to minimize the probability of unacceptable kinetics in clinical trials.

Recent advances in molecular biology and biotechnology have led to an improved understanding of the specific functions and regulation of enzymes and transporters. With these advances, many in vitro systems are now being used for ADME evaluation (Guengerich 1995; Suzuki and Sugiyama 2000; Tamai and Tsuji 2000). The use of such in vitro model systems will allow for a more accurate prediction of human pharmacokinetics. In parallel to the progress made in molecular biology, the commercial availability of sensitive analytical instrumentation and reliable robots have provided drug metabolism scientists with powerful tools for early ADME evaluation. The purpose of this paper is aimed at discussing the role that drug metabolism scientists play, and the limitations and problems that they face at various stages of the processes of drug discovery and lead candidate selection.