An Introduction to Metabolic Reaction Phenotyping

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1 INTRODUCTION

The role of drug-metabolizing enzymes (DMEs) and metabolic clearance in the overall determination of a drug's oral bioavailability and pharmacokinetics (PK) is well established and fully incorporated into the process of discovery, design, and development of new and better therapeutic agents. Given the very many different types, classes, and members of enzyme families known to metabolize drugs and other xenobiotics, the task of optimizing metabolic stability can appear somewhat daunting. Fortunately, certain enzymes feature more predominantly than others, and drug optimization often begins and ends with them.

In this chapter we will describe a few of the major enzyme families, the experimental and kinetic methods used to identify their role in the overall metabolic clearance of a drug (so-called "reaction phenotyping" or "enzyme mapping") and illustrate some concerns related to the contribution and interindividual variation of some notable enzymes. An attempt has been made to provide a useful and comprehensive outline of what is requisite for drug discovery, but an introductory text can only go so far. So for greater depth of analysis and discussion, the reader is referred to the many reviews published on bioanalysis, enzyme kinetics, substrates and biotransformation, drug–drug interactions (DDIs), adverse drug reactions, and *in silico* methods and pharmacogenetics, a few of which are listed at the end of this chapter.

2 DRUG METABOLISM

The membrane-bound hemoproteins that belong to the superfamily of cytochrome P450s (CYPs), by virtue of expression, number, diversity, and substrate promiscuity, dominate most other enzymes in their contribution to drug clearance. Members of three CYP subfamilies in particular (CYP1, CYP2, and CYP3) are responsible for the

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