Automated Drug Screening for ADMET Properties

MELVIN REICHMAN and HELEN GILL

1 INTRODUCTION

The pharmacological basis of therapeutics is comprised of two overarching scientific disciplines: pharmacodynamics and pharmacokinetics. It is often summarily stated: "pharmacodynamics is the study of what a drug does to the body; whereas pharmacokinetics is the study of what the body does to a drug." The latter studies the ***a***bsorption, ***d***istribution, ***m***etabolism, ***e***xcretion, and ***t***oxicology of drugs (ADMET). The survival and growth of the pharmaceutical industry relies on favorable, early clinical trial outcomes. Poor outcomes are commonly due to poor ADMET properties of new chemical entities (NCEs). The difficulty in optimizing ADMET properties of any NCE is universally recognized as an important factor responsible for the increasing cost of bringing a new drug to market. On the other hand, ADMET sciences in drug development can "rescue" drugs that otherwise would fail. While the list of marketed drug withdrawals continues to increase, it appears that significant progress has been made by earlier detection of ADMET issues through automated bioassays amenable to higher throughput screening paradigms. Higher throughput ADMET for drug lead qualification is deployed more commonly in the industry, as well as earlier rather than later preclinical development. There are data suggesting that the paradigm shift of deploying ADMET earlier in the R&D continuum has led to a marked decrease in drug failures. This article traces the development of automation in experimental ADMET to provide an overview of the assays that have been miniaturized to the microtiter plate format and automated on common or specialized laboratory workstations to enable higher throughput ADMET screening.

2 BACKGROUND

The term high-throughput screening (HTS) began regularly appearing in the scientific literature in the early 1990s (Harris *et al.*, 1991; Burch, 1993; and see Fig. 1). During

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad