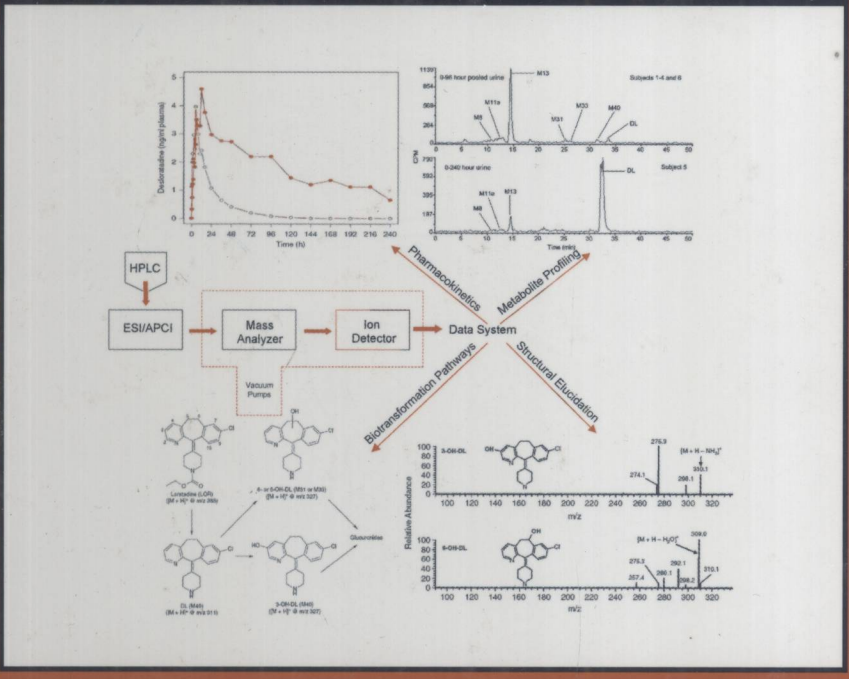
Mass Spectrometry in Drug Metabolism and Pharmacokinetics



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RAGU RAMANATHAN

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Mass Spectrometry in Drug Metabolism and Pharmacokinetics

Preface

Within the pharmaceutical industry, the mass spectrometer was long considered a useful and challenging analytical tool largely limited to the specialist user. The steady movement from specialist use to general use gained considerable speed in the 1990s, particularly due to the development of practical, sensitive liquid chromatography–mass spectrometry (LC–MS) interfaces and advances in the microelectronics. The rapid proliferation of quadrupole ion trap, linear ion trap, orbitrap, quadrupole mass filter, time-of-flight, and other types of mass spectrometers has impacted the industry from the earliest stages of disease determination through the final stages of clinical testing. This book, based on an American Society for Mass Spectrometry (ASMS) session, which I was fortunate enough to chair, will examine several of the ways in which mass spectrometry continues to have a profound influence on the direction and speed of drug discovery and development, especially in the area of drug metabolism (DM) and pharmacokinetics (PK).

To facilitate introduction to the topics contained in this book, the first chapter considers briefly the broader processes of drug discovery and development within the pharmaceutical industry. The specific roles of DM and PK, the applications considered throughout this book, are defined as well as major terms and concepts in mass spectrometry. Finally, the role of mass spectrometry in DM and PK is developed and the ensuing chapters introduced. For the experienced professional, this final section of the first chapter may represent the appropriate starting point in reading this book.

Chapter 2 systematically defines some of the important PK parameters and guides the reader through the types of quantitative LC–MS experiments performed to elucidate the PK parameters necessary to move a drug through discovery, preclinical development, and clinical stages. Chapters 3, 4, and 5 respectively introduce the readers to quadrupole mass filters and liner ion traps, time-of-flight mass

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spectrometers, and Fourier transform (FTICR and Orbitrap) mass spectrometers and their applications in the area of DM and PK. The high-resolution LC–MS mass defect filter (MDF) approach is considered in Chapter 6. Today the MDF approach has been adapted by all the major mass spectrometer vendors to help accelerate drug discovery and development. Chapter 7 elegantly describes the utility of high-sensitivity radioactivity and mass spectrometry techniques for drug metabolism studies. While online electrochemical–LC–MS techniques available for generating metabolites are discussed in Chapter 8, Chapter 9 describes some of the LC–MS tools and techniques available for detecting and characterizing isomeric metabolites. Chapter 10 is dedicated to online sample processing and turbulent-flow LC–MS techniques. Finally, Chapters 11 and 12 present some of the laser desorption–based mass spectrometry applications in the DM and PK arena.

This book would have never been possible without the efforts and dedication of more than 35 co-authors and the editorial staff at Wiley. I am very grateful to Kevin B. Alton, Honggang Bi, Jimmy L. Boyd, Swapan K. Chowdhury, John R. Eyler, Michael L. Gross, W. Griffith Humphreys, Steven Michael, Richard Morrison, Noel Premkumar, Laszlo Prokai, Rasmy Talaat, Poonam Velagaleti, and Ronald E. White for their continued mentorship throughout my professional career. I am also very grateful to my parents, brothers, aunts, uncles, and grandmother for supporting my education and career. Finally, my deepest gratitude goes to my wife, Dil, and Vishan and Eshal for continuously supporting all my endeavors.

RAGU RAMANATHAN, PH.D.

New Jersey, USA
September, 2008

About the Editor

Ragu Ramanathan received a B.Sc. in Chemistry from the University of Southern Mississippi and a Ph.D. in Physical Chemistry/Mass Spectrometry from the University of Florida. His graduate research focused on coupling of electrospray ionization (ESI) to Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. After spending three years as a postdoctoral research fellow with Professor Michael L. Gross at the Washington University, St. Louis, Missouri, Dr. Ramanathan managed the Center for Advanced Mass Spectrometry at the Analytical Bio-Chemistry Laboratories, Columbia, Missouri. In 1998, Dr. Ramanathan joined Schering-Plough Research Institute's (SPRI) Drug Metabolism and Pharmacokinetics (DMPK) Department and completed his tenure as a senior principal scientist in 2008. While at SPRI, Dr. Ramanathan was involved in the application of LC–MS for profiling and characterization of metabolites of drug candidates in the preclinical development and clinical stages. Dr. Ramanathan was with Pfizer Global Research and Development from 1999 to 2002 as a group leader of the Ann Arbor site biotransformation group. Dr. Ramanathan is currently an associate director at the Bristol-Myers Squibb, Co. and is responsible for elucidating biotransformation pathways of development drug candidates. Dr. Ramanathan's accomplishments include 35 peer-reviewed papers, 10 book chapters, and over 60 oral/poster presentations. He also served as a chairperson for the North Jersey ACS Mass Spectrometry Discussion Group and as a chairman for DMPK sessions of the American Society for Mass Spectrometry and Eastern Analytical Symposium meetings.

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Evolving Role of Mass Spectrometry in Drug Discovery and Development

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1.1 ROUTE TO MARKET: DISCOVERY AND DEVELOPMENT OF NEW DRUGS

1.1.1 Industry Research and Development

The members of the modern biopharmaceutical industry are engaged in an on-going struggle to balance the needs of medicine and patient care with the demands of running a growing, profitable business. Moreover, new drugs must be proven to possess some combination of improved efficacy and safety compared with existing treatments. Success in drug research and development (R&D) is critical for meeting all of these objectives, and R&D efforts within the biopharmaceutical industry, as measured by spending, continue to grow steadily (Fig. 1.1). In recent years, the rate of annual growth in R&D spending has been between 5 and 10% in the United States, with the most recent data indicating that R&D spending in 2006 exceeded $50 billion (PhRMA, 2006).

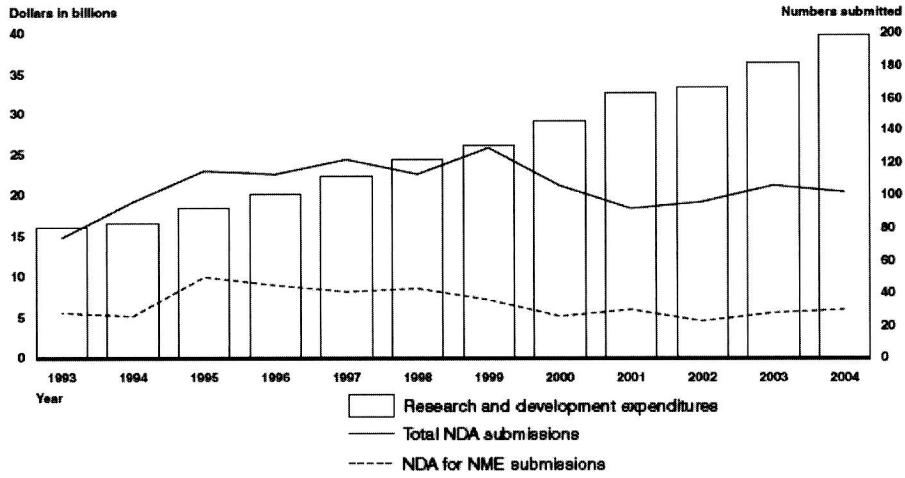

Figure 1.1. *1993–2004 Pharmaceutical R&D expenses, total new drug applications (NDAs), and NDAs for new molecular entity (NME) submission trends. [Reprinted with permission from the U.S. Government Accountability Office (GAO) 2006.]*

The many essential steps in the discovery and development of new drugs can be measured by two primary benchmarks. The first, the number of filed and approved investigational new drug (IND) applications, represents the threshold to human (clinical) testing. The second, the number of filed and approved new drug applications (NDAs), represents the threshold to marketing a drug. These numbers and their trends can represent the relative success of R&D efforts.

Given the typical 12–15 years required to discover, develop, and test a new drug (Fig. 1.2), the NDA submission and approval data will in part represent R&D

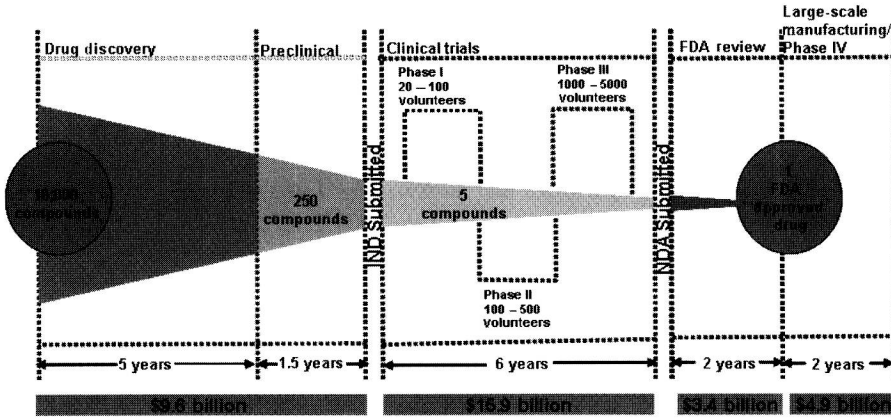

Figure 1.2. *Complex pathway of pharmaceutical R&D involved in bringing a new drug to the market. (Adapted from PhRMA, 2006.)*

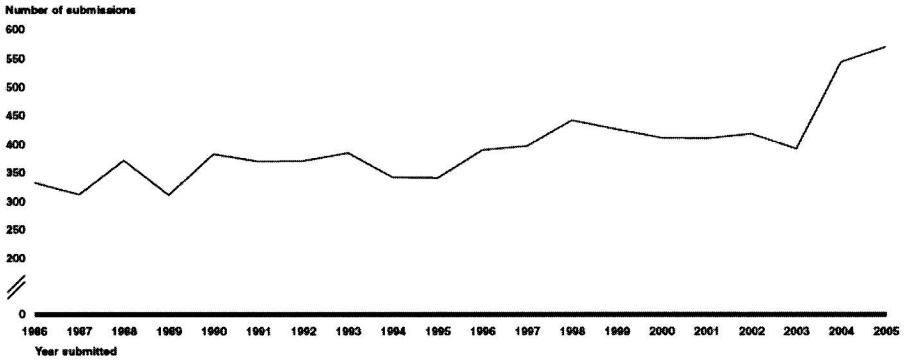

Figure 1.3. *Increase in INDs in recent years. Data are for commercial INDs. (Reprinted with permission from GAO, 2006.)*

progress from several years earlier. Since the late 1990s, the annual rate of NDA submissions and approvals has declined. A similar decline has been observed in the number of NMEs (GAO, 2006). Of the 93 NDA approvals for 2006, only 18 are considered to represent NMEs (*The Pink Sheet*, January 15, 2007). While both total NDAs and NMEs are important, the number of NMEs approved represents a particularly critical measure of overall R&D success.

The statistics of expenditure and NDA approvals can mask a major source of R&D cost and frustration in the industry: late-stage development and postmarketing failures. These types of failures attract significant unwanted publicity and only occur after hundreds of millions of dollars have been spent. Well-publicized examples have included the recent late-stage failure of torcetrapib (Tall et al., 2007) and the postmarketing withdrawals of fenfluramine-phentermine (Fen-Phen) and Vioxx (Embi et al., 2006).

Consideration of IND trends is more encouraging (Fig. 1.3). IND filings occur years before NDA filings and represent a more recent state of R&D success. The number of compounds in clinical testing has approximately doubled over the last decade to approximately 3000 compounds in 2005 in the United States alone. A recent tally of new treatments in clinical testing for various indications is summarized in Table 1.1 (PhRMA, 2006). It is encouraging to see this increase in clinical testing, but it is also important to remember that only about 8% of early-stage clinical testing drugs will produce an approved NDA (Caskey, 2007).

1.1.2 Drug Discovery and Development Process

The overall process of bringing a new drug to market is typically divided into two principal areas: drug discovery and drug development. Examples of summaries describing the entire process include the publication entitled "Drug Discovery and Development: Understanding the R&D Process" (PhRMA, February 2007) and a tutorial written by Jens Eckstein, recently available online at www.alzforurm.org/drg/tut/tutorial.asp.

TABLE 1.1. Treatments in Clinical Testing

Disease Area or Indication	Number of Compounds in Development
Oncology	682
Neurological disorders	531
Infectious diseases	341
Cardiovascular	404
Psychiatric	190
Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)	95
Arthritis	88
Asthma	60
Alzheimer/dementia	55

Source: PhRMA, 2006.

The following description very briefly summarizes some of the steps in drug discovery and development.

1.1.2.1 Drug Discovery The first step in discovering a new medicine is to identify a therapeutic target. Drugs in today's market as well as those in recent clinical testing target less than 500 biomolecules, with more than 10 times that many potential therapeutic targets waiting to be discovered and developed (Drews, 2000). More than 50% of the newly approved drugs result from R&D involving previously clinically tested and validated targets. Once a target has been validated (proven to be related to the disease process), high-throughput screening methods may be used to determine initial structural leads. Compounds are assessed for target affinity and for their "drug-like" properties, including absorption, distribution, metabolism, and excretion (ADME) using a series of in vivo and in vitro tests. The results of these tests are used to improve the structure and therefore the properties of the next round of test compounds, until ultimately one or more acceptable compounds are advanced forward in the process. This stage of discovery, which can be lengthy and difficult to predict, is generally referred to as lead optimization. The lead selection and lead optimization studies that are used to sift out the problematic compounds are summarized in Fig. 1.4.

Mass spectrometry enters into all phases of drug discovery (Feng, 2004; Lee, 2005). Early in the discovery, target proteins are identified and characterized by MS following LC or two-dimensional gel electrophoresis separation (Kopec et al., 2005; Deng and Sanyal, 2006). The make-up of an isolated protein is determined by enzymatically digesting the protein and then analyzing the peptides by MS (Link, 1999; Kopec et al., 2005; Köpke, 2006). Once a target is validated, compounds generated from any one of the following strategies are evaluated against the target: total synthetic process (33%), derivative of natural products (23%), total synthetic product with natural product mimic (20%), biological (12%), natural product (5%), total synthetic product based on a natural product (4%), and vaccine (3%) (Newman et al., 2003; Newman and Cragg, 2007). In almost all pharmaceutical

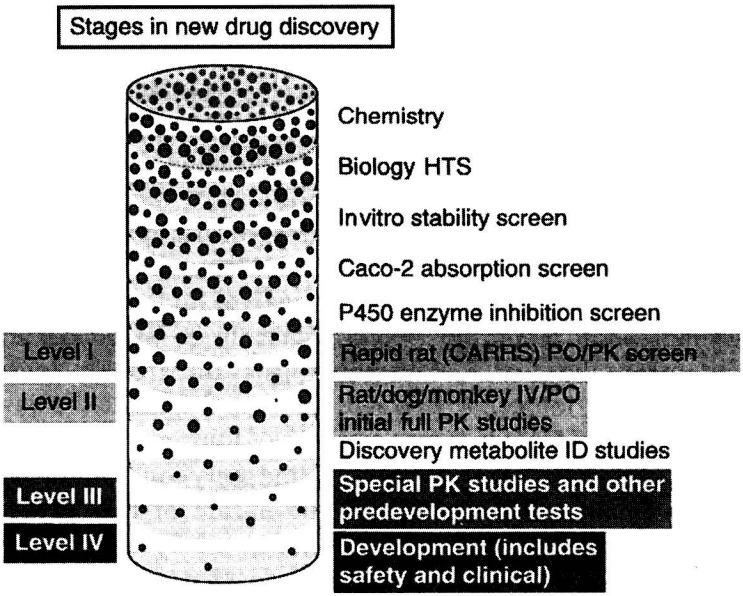

Figure 1.4. *NCE/NME progression scheme showing the various discovery stage liquid chromatography–mass spectrometry (LC–MS) and LC–tandem MS (LC–MS/MS) assays used for selecting NME/NCE to advance into development. (Reprinted with permission from Korfmacher, 2005.) (CARRS, Cassette accelerated rapid rat screening; IV, Intravenous administration; PO, Oral administration; NCE, New chemical entity)*

companies, open-access MS laboratories have been set up to allow medicinal chemists to confirm and assess the purity of their synthesis or isolated products (Chen et al., 2007). Once the compounds or compound series are confirmed, high-throughput screening (HTS) assays are used to weed out compounds that do not show any activity toward a host [protein, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), etc.] (Fligge and Schuler, 2006). Mass spectrometric approaches also have been used to study noncovalent complexes involving protein–drug, DNA–drug and RNA–drug to identify structural details of the drug-binding sites (Benkestock et al., 2005; Siegel, 2005; Hofstadler and Sannes-Lowery, 2006; Jiang et al., 2007).

Compounds or compound series selected using HTS are further filtered using in-vitro-based solubility, chemical stability (Wilson et al., 2001), permeability (Bu et al., 2000a,b; 2001a–d; Mensch et al., 2007), and metabolic stability (Lipper, 1999; Thompson, 2000, 2005) assays before the lead selection/optimization stage (Lipper, 1999; Thompson, 2000, 2005). Most of these in vitro assays are faster, more efficient, and more sensitive due to unsurpassed involvement of the LC–MS (Thompson, 2001; Mandagere et al., 2002; Pelkonen and Raunio, 2005; Thompson, 2005). Results from such high-throughput in vitro assays are used to select compounds for additional in vitro tests and finally for in vivo testing in preclinical species (mouse, rat, dog, monkey, etc.). Similar to the early discovery stage high-throughput assays, LC–MS and LC–MS/MS assays are the methods of

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