LC/MS APPLICATIONS IN DRUG DEVELOPMENT

Mike S. Lee

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PREFACE

The combination of high-performance liquid chromatography and mass spectrometry (LC/MS) has had a significant impact on drug development over the past decade. Continual improvements in LC/MS interface technologies combined with powerful features for structure analysis, qualitative and quantitative, has resulted in a widened scope of application. These improvements coincided with breakthroughs in combinatorial chemistry, molecular biology, and an overall industry trend of accelerated drug development. The integration of new technologies in the pharmaceutical industry created a situation where the rate of sample generation far exceeds the rate of sample analysis. As a result, new paradigms for the analysis of drugs and related substances have been developed. Both pharmaceutical and instrument manufacturing industries have mutually benefited.

The growth in LC/MS applications has been extensive, with retention time and molecular weight emerging as essential analytical features from drug target to product. LC/MS-based methodologies that involve automation, predictive or surrogate models, and open-access systems have become a permanent fixture in the drug development landscape. An iterative cycle of "what is it?" and "how much is there?" continues to fuel the tremendous growth of LC/MS in the pharmaceutical industry. During this time, LC/MS has become widely accepted as an integral part of the drug development process.

It is clear that significant developments are happening in the analytical sciences and that future innovations will continue to positively impact the ability for industry scientists to create, share, and collaborate.

This book, based on an earlier review (Lee and Kerns, 1999), describes the utility of LC/MS techniques for accelerated drug development and provides perspective on the significant changes in strategies for pharmaceutical analysis. Specific examples of LC/MS innovation and application highlight the interrelation between the drug development activities that generate samples and the activities responsible for analysis. It should be noted that the extent of LC/MS applications within drug development is hardly complete, and therefore, this book is not intended to be encyclopedic. The goal was to provide an industry perspective on how and why LC/MS became a premier tool for pharmaceutical analysis. Frequently, the review of a specific methodology or technology creates a barrier of interaction with other disciplines. The applications described in this book are organized with regard to current drug development cycles (i.e., drug discovery, preclinical development, clinical development, manufacturing) to provide an enabling reference for a wide community of chemists and biologists. Future applications of LC/MS technologies for accelerated drug development and emerging industry trends that deal with sample preparation, chromatography, mass spectrometry, and information management are also discussed.

Mike S. Lee

ACKNOWLEDGMENTS

The inspiration, direction, and focus for this book were derived mainly through my pharmaceutical industry experiences. These experiences were fueled by the belief that analytical sciences play an integral and proactive role in the pharmaceutical industry. I am thankful that my first-hand experiences were, for the most part, pleasant. I do, however, acknowledge that the discovery, development, and manufacture of pharmaceuticals are extremely challenging endeavors. I believe that there is considerable reward for such a challenge. Obviously, there is a tangible reward that can be benchmarked by a cure for disease and/or commercial success of a drug. There is also a less-tangible reward that manifests itself in the form of accomplishment and enlightenment accrued over a period of time. I feel fortunate to have experienced many of the rewards that go with drug development. I am grateful that I was able to share these experiences with a diverse group of professionals. To have had the opportunity to participate in these activities is indeed noble. To have the opportunity to recount perspective on these activities is humbling. Interestingly, and perhaps predictably, I found that the reward is more fondly remembered in a nostalgic sense; recounting the experiences in real-time can be intense. The effort put forward for this project seemed to follow a similar path as input and suggestions from many individuals were required. Invaluable feedback and support was generously given by numerous people that included: Bradley

Ackermann, Tim Alavosus, Brad Barrett, Andries Bruins, Ben Chien, John Coutant, Dominic Desiderio, Ashok Dongre, Todd Gillespie, Edward Kerns, Steven Klohr, Zamas Lam, Ken Matuszak, Sara Michelmore, John Peltier, Kumar Ramu, Ira Rosenberg, Robyn Rourick, Charlie Schmidt, Marshall Siegel, Gary Valaskovic, Kevin Volk, David Wagner, Scott Wilkin, Antony Williams, Nathan Yates, and Richard Yost.

At many times during this project I found myself asking the question, "Why am I doing this?" In my attempt to answer, I would always seem to recount my positive experiences with the analytical sciences. Thus, I feel compelled to give thanks to those who were integral to my education in the analytical sciences and inspirations to my professional development. First, I thank the University of Maryland for encouraging me to pursue an education in the sciences. Second, I thank the graduate program at the University of Florida for providing me an opportunity to focus in the analytical sciences and teaching me how to formulate question and thought. Third, I thank Bristol-Myers Squibb for balancing my hunger for the application of analytical sciences with the need to experience collaboration, interaction, and growth. To each of the above mentioned institutions, I am grateful for the support and continued source of inspiration. To all the people at the above mentioned institutions, I will hold dear the friendships, relationships, and memories that are the result of success and failure. And finally, I wish to thank my loving wife and family for their continual encouragement and support for everything I do. For this, I am truly blessed.

CHAPTER 1

INTRODUCTION

Current trends in drug development emphasize high-volume approaches to accelerate lead candidate generation and evaluation. Drug discovery-based technologies that involve proteomics, biomolecular screening, and combinatorial chemistry paved the way, resulting in shortened timelines and the generation of more information for more drug candidates. The impact on the overall drug development cycle has been significant, creating unprecedented opportunities for growth and focus, particularly in the analytical sciences.

EMERGING ANALYTICAL NEEDS

Perhaps a major cause of these opportunities is the fact that the rate of sample generation far exceeded the rate of sample analysis. To put this factor in perspective, consider the following example that deals with combinatorial chemistry. Prior to the advent of combinatorial chemistry technologies, a single bench chemist was capable of synthesizing approximately 50 final compounds per year, depending on the synthesis. Today, chemists are capable of generating well over 2000 compounds per year, using a variety of automated synthesis technologies. If traditional approaches to analytical support were maintained, then analysts would outnumber chemists by nearly 40 to 1!

The reality of the situation has become evident: Without analytical tools that could keep pace with new benchmarks for sample generation, the advantages would not be fully realized. Thus, the relationship between sample generation and analysis is a major issue in the pharmaceutical industry. Clearly, traditional approaches for analysis are not capable of meeting specialized needs created by dramatic improvements in sample generation.

New technologies figure prominently in the success of drug development and directly impact pharmaceutical analysis activities. The integration of sample generation technologies such as combinatorial chemistry workstations, for example, created distinctly new requisites for analysis. Rapid, high throughput, sensitive, and selective methods are now a requisite for pharmaceutical analysis. Also, the ability to analyze trace mixtures, using an instrumental configuration compatible with screening approaches, emerged as an important feature.

As requirements for analysis rapidly adapted to breakthroughs in sample generation, a new scientific and business culture aimed at decreasing costs and accelerating development became entrenched in the pharmaceutical industry. These factors combined to produce more frequent, and perhaps, new demands on analysis. In particular, these demands underscored the importance of analytical instrumentation and the creation of novel analysis strategies. For example, to keep pace with emerging needs, the timely evaluation of new tools and applications appropriate for pharmaceutical analysis is essential. Once evaluated, the effective integration of these analysis tools represents an equally significant hurdle. The development of novel strategies for analysis has been an effective approach for introducing new technologies and for creating opportunities for streamlined drug development.

These trends have been complemented by the need to determine or predict molecular and physicochemical properties of an unprecedented number of structurally diverse molecules faster than previously required and at earlier stages in the drug development cycle. Prospective methods for investigating pharmaceutical properties were born, along with data-mining techniques to search large databases. Furthermore, new experimental approaches typically generated samples that contain small quantities of analyte in complex mixtures. This combination placed a tremendous burden on existing methods for pharmaceutical analysis.

Many industry initiatives feature the integration of sample-

generating and analysis activities, resulting in new paradigms for the discovery, evaluation, and development of pharmaceuticals. The basic idea of these initiatives is to do more with less. Invariably, *more* resources tend to be awarded to activities involved with sample generation, whereas *less* is received for analysis. As a result, a wide variety of analysis-based applications have been implemented. These applications emphasize *efficiency* and *throughput*. Three common themes arose from these activities:

1 An earlier availability of information leads to faster decision making.
2 Integration of instrumentation with information networks is a popular approach for combining high throughput analytical information generation with drug candidate screening.
3 Software is a powerful resource for the coordination of analysis events and the management and visualization of data.

A considerable growth in analysis methods resulted, with the primary focus being on accelerating drug development. New tools and strategies for analysis combined with technologies such as biomolecular screening, combinatorial chemistry, and genomics have positioned the pharmaceutical industry to *harvest* discovery and *manufacture* development opportunities.

INTEGRATION OF LC/MS INTO DRUG DEVELOPMENT

Liquid chromatography/mass spectrometry (LC/MS)-based techniques provide unique capabilities for pharmaceutical analysis. LC/MS methods are applicable to a wide range of compounds of pharmaceutical interest, and they feature powerful analytical figures of merit (sensitivity, selectivity, speed of analysis, and cost-effectiveness). These analytical features have continually improved, resulting in easier-to-use and more reliable instruments. These developments coincided with the pharmaceutical industry's focus on describing the collective properties of novel compounds in a rapid, precise, and quantitative way. As a result, the predominant pharmaceutical sample type shifted from nontrace/pure samples to trace mixtures (i.e., protein digests, natural products, automated synthesis, bile, plasma, urine). The results of these developments have been sig-

nificant, as LC/MS has become the preferred analytical method for trace mixture analysis (Figure 1.1).

An important perspective on these events, improvements in LC/MS technology and industry change, is just how LC/MS techniques became so widely accepted within every stage of drug development. It can be argued that the proliferation of LC/MS occurred not by choice but by need. For example, if a nuclear magnetic resonance (NMR)-based approach existed for the quick, sensitive, and efficient analysis of combinatorially derived mixtures in the early 1990s, then LC/MS would certainly have had a limited role in this area of drug development. However, at the time LC/MS provided the best performance without any rival or complement.

The significance of this fact is twofold. First LC/MS has, indeed, become the method of choice for many pharmaceutical analyses. Because the utilization of analysis technology in the pharmaceutical industry is highly dependent on perception, the breakthroughs and barriers that LC/MS has overcome provided opportunity for acceptance and a widened scope of application. Currently, LC/MS is widely perceived in the pharmaceutical industry to be a viable choice, as opposed to a necessary alternative, for analysis. Second, these events led to an increased understanding of LC/MS in such a way that practitioners and collaborators have become more diverse. The result of this diversity is a mutually shared sense of purpose

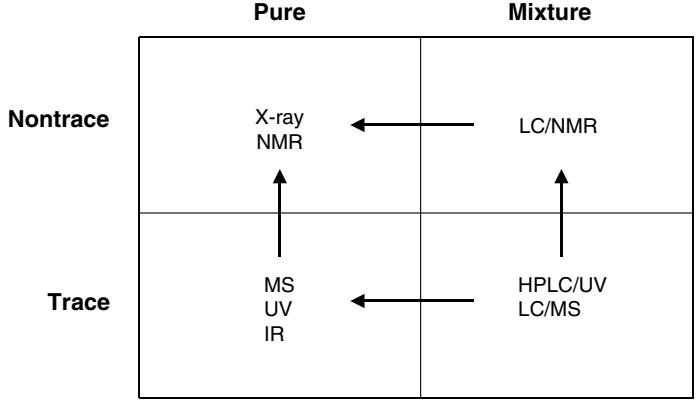

Figure 1.1 Structure analysis matrix that illustrates pharmaceutical analysis preferences for four specific sample types: nontrace/pure; nontrace/mixture; trace/pure; and trace/mixture. (Courtesy of Milestone Development Services, Newtown, Pa., USA.)

within the industry, inspiring creativity and generating new perspectives on analysis.

Along with timing and perception issues, four technical elements have been critical for the acceptance of LC/MS-based techniques in the pharmaceutical industry. The first is *separation sciences*. Simply put, the chromatographic method defines the pharmaceutical analysis. Chromatography provides analytical criteria to compare, refine, develop, and control the critical aspects of developing and manufacturing high-quality drug products. Thus, it is common in industry to see LC/MS methods distinguished by the chromatographic technology and features rather than by mass spectrometry performance and capabilities. Indeed, the effective combination of a wide variety of high performance liquid chromatography (HPLC) technologies and formats with mass spectrometry played a vital role in the acceptance of LC/MS. This achievement is significant because HPLC-based methods are a universally recognized analysis "currency," and perhaps, the first to be used throughout every stage of drug development.

The second element that allows for industry acceptance of LC/MS techniques is *mass spectrometry*. The analytical figures of merit dealing with sensitivity and selectivity provide a powerful platform for analysis. However, it was not until these analytical attributes could be harnessed into a reliable, reproducible, rugged, and high throughput instrument that mass spectrometry techniques could be taken seriously as an integral tool for drug development. Though perhaps indirect, the pioneering work performed with LC/MS interfaces that featured moving belt (Smith and Johnson, 1981; Hayes et al., 1983; Games et al., 1984), direct liquid introduction (DLI) (Yinon and Hwang, 1985; Lee and Henion, 1985; Lant et al., 1985), thermospray ionization (TSI) (Blakely and Vestal, 1983; Irabarne et al., 1983), and electrospray ionization (ESI) (Whitehouse et al., 1985; Bruins et al., 1987; Fenn et al., 1989) approaches certainly played a significant role in the acceptance of mass spectrometry as a routine tool for pharmaceutical analysis. Furthermore, added dimensions of mass analysis provide enhanced limits of detection for the analysis of complex mixtures and unique capabilities for structure identification.

The third element is *information*. The rate of analysis and subsequent distribution of results has grown tremendously due to the increased use of LC/MS and other information-rich technologies. From strictly an analysis perspective, LC/MS has demonstrated a

unique capability for maintaining high quality performance and a rapid turnaround of samples. Yet, it is the accurate and efficient processing of information that has been essential for LC/MS use and acceptance. As a result, LC/MS has developed unique partnerships with tools responsible for sample tracking, interpretation, and data storage. Consequently, LC/MS has become an information-rich, information-dependent technology in the pharmaceutical industry. LC/MS is highly dependent on software to integrate key analysis elements that deal with sample preparation, real-time analysis decisions, and the distribution of results. The pharmaceutical industry has benefited from this trend and, as a result, the derived information has been easily translated into a form that many professionals can understand, interpret, and base their decisions on.

Finally, the fourth element is a *widened scope of application*. The fact that LC/MS is now routinely used during every stage of drug development is a powerful benchmark for acceptance. The increased performance of applications that incorporate LC/MS have, in turn, stimulated new performance levels for sample preparation, high speed separations, automated analysis, information databases, and software tools, to name a few. Motivated by unmet industry needs, the drive for new applications has stimulated tremendous growth in pharmaceutical analysis marked by invention and creativity.

PARTNERSHIPS AND ACCEPTANCE

What has happened in the pharmaceutical industry during this relatively short time span is truly remarkable. With the advent of advanced technologies responsible for increasing the rate of sample generation, there is strong motivation to respond with LC/MS-based analysis techniques. The understanding of principles, fundamentals, operation, and maintenance enabled researchers to improve analytical performance. The power of "seeing is believing" led to lower barriers of acceptance as well as to a new breed of practitioners.

Chemists, biologists, and other industry professionals are becoming more familiar and comfortable with LC/MS and its corresponding data as an everyday tool for analysis. The vast technical advances with LC/MS, along with a renewed emphasis on sharing, collaboration, and mutual understanding among disciplines, have helped researchers increase efficiency and overall productivity. At the same time, highly trained, highly skilled analysts are continually chal-

lenged with learning new principles in chemistry, molecular biology, and pharmaceutical development.

Of course, all of the previously mentioned successes would not have been possible without basic research and the ultimate design and manufacture of analytical instrumentation. Basic research and the manufacture of high performance instruments have each played a significant role in the drug development process. Continued relationship and partnership with universities and instrument manufacturers help to increase awareness and better understanding, and to bridge the gaps among research, discovery, and the development of high-quality pharmaceutical products.

The seven ages of an analytical method first described by Laitinen (1973) can be used to depict the important partnerships among academia, instrument manufacturers, and the pharmaceutical industry. These partnerships are responsible for the widened scope of application and acceptance of LC/MS in the pharmaceutical industry today. The *ages* of an analytical method are translated into *stages* of LC/MS events that lead to its routine use in the pharmaceutical industry (Table 1.1). The various stages represent a continuum for LC/MS advancement, beginning with basic research performed in universities, followed by the design and manufacture of instruments, and concluding with industry benchmarks for acceptance.

The first and second stages involve the *conception* of the fundamental principles and experimental *validation* of the analytical potential, respectively. The basic research conducted in universities during the 1970s and 1980s marked the conception stage of LC/MS methods. For example, the fundamentals of interfacing an HPLC with a mass spectrometer were studied (Arpino et al., 1974; Carroll et al., 1975; Arpino, 1982) and mechanisms of ionization were characterized (Thomson and Iribarne, 1979; Blakely et al., 1980; Whitehouse et al., 1985). The validation stage of the analytical method represents the convergence of interest among research, instrumentation, and potential application. The results and interest generated from the basic research that dealt with LC/MS led to significant investments in technology from instrument manufacturers. Applications dealing with pharmacokinetic (Covey et al., 1986) and biomolecular (Wong et al., 1988) analysis showed significant promise, insight, and direction. The market potential of an LC/MS instrument, providing expanded capabilities over gas chromatography/mass spectrometry (GC/MS) and HPLC methods for pharmaceutical analysis, was realized. The *availability* of commercial instruments

TABLE 1.1 The seven stages of the LC/MS analytical method that result from partnership within academia, instrument manufacturers, and industry

Stage	Event	Activity
Conception	Fundamental principles outlined	Basic research.
Validation	Analytical potential experimentally validated	Basic research; applied research; technology investments; product development; targeted pharmaceutical applications.
Availability	Instruments developed/manufactured	Commercial instruments sold; method development; applied research.
Foundation	A platform of performance established	Method development/refinement; analysis benchmarks; quantitative bioanalysis methods established; new product development.
Application	A widened scope of application	Unique methods developed to address sample generating technologies and traditional analyses for the identification of biomolecules, metabolites, and natural products.
Acceptance	Used as a routine, standard method	Development of fully automated methods for high throughput analysis; open access instruments; standard methods; outsourcing.
Senescence	Replaced by newer methods	Decline in applications, utility, and popularity?

Source: Courtesy of Milestone Development Services, Newtown, Pa., U.S.A.

provided the pharmaceutical industry with LC/MS capabilities plus training, service, and technical support. Applied research directed toward meeting current industry needs ensued, with active participation and collaboration from university- manufacturing- and pharmaceutical-led research groups (Covey et al., 1991; Weintraub et al., 1991; Aebersold et al., 1992; Weidolf and Covey, 1992). The ability to reliably develop and refine LC/MS-based methods helped to establish a solid fundamental *foundation* of this technique. The utility of LC/MS methods for quantitative bioanalysis was benchmarked as the industry standard in the early 1990s for performance and efficiency (Fouda et al., 1991; Wang-Iverson et al., 1992). New products were designed and developed exclusively for LC/MS performance. A widened scope of *application* occurred with the development of unique LC/MS-based methods for the analysis of novel pharmaceuticals. Analysis methods were easily developed and refined in the pursuit of opportunities created by the use of traditional, time-consuming procedures. Applications that deal with biomolecule analysis, drug metabolism and pharmacokinetics, natural products research, and combinatorial chemistry represent some important areas of LC/MS diversification and are discussed in the following chapters of this book. Perhaps the most significant benchmarks for industry *acceptance* of LC/MS appeared when fully automated methods were developed for high throughput analysis and when collaborators (i.e., sample generators) themselves became analysts via the purchase of instruments or routine use of open-access instruments (Taylor et al., 1995; Pullen et al., 1995). These methods and approaches were developed primarily in response to sample-generating technologies. And this step represents the present stage of LC/MS methods in the pharmaceutical industry.

Although the scope of application continues to grow, the routine use of LC/MS technologies are now embraced by pharmaceutical researchers. Standard methods that incorporate highly specialized features are routinely developed for a variety of novel applications. Furthermore, many LC/MS applications that deal with quantitative bioanalysis (i.e., pharmacokinetics studies) are frequently outsourced to contract analytical laboratories. Thus, the routine use of LC/MS is a benchmarked commodity for drug development.

The final stage, *senescence*, does not appear to be a prospect in the near future, but a decline in popularity and application will likely occur sometime. Perhaps the onset of this stage will be triggered by the divergence of academic, instrument manufacture, and industry

interests. However, the current industry trends highlight the tremendous challenge of drug development and an expanding need for tools that provide for fast, sensitive, and selective analysis of drugs and drug-related compounds.

OVERVIEW

This book focuses on LC/MS applications in drug development. It examines the role of LC/MS in the pharmaceutical industry during the past decade and illustrates key elements for success that include significant advances in instrumentation, methodology, and application. The applications are highlighted with reference to the analysis opportunity and analysis strategy is implemented. Examples that depict unique advantages of LC/MS during specific stages of drug development are selected to capture the significant events and/or initiatives that occurred in the pharmaceutical industry during this time. In many instances, an analysis is provided to illustrate the result or development situation if LC/MS was not used. In these cases, the impact (number of samples) and value (cost) on drug development is highlighted independent of the technical features of LC/MS analysis. These unique industry perspectives offer an enabling "currency" and assist in understanding the events that resulted in the proliferation of LC/MS throughout the drug development cycle.

The book concludes with perspectives on future trends and some thoughts on the future direction of LC/MS applications in the pharmaceutical industry. New standards of analytical performance are discussed with regard to throughput and capacity. A prospective look at how higher standards of analytical performance in the pharmaceutical industry will effect relationships with academia and instrument manufacturers is featured. These sections extend the initial thesis of accelerated development to include new analysis bottlenecks and perspectives on analysis issues and industry needs.

CHAPTER 2

DRUG DEVELOPMENT OVERVIEW

Drug development may be defined as the series of specialized events performed to satisfy internal (i.e., competitive industry benchmarks) and external (i.e., regulatory compliance) criteria, to yield a novel drug. Much attention has been given to the various activities of drug development. These accounts primarily have a sample-generating perspective. For example, the timely review of innovations in automated synthesis stimulated new paradigms for drug discovery (Gallop et al., 1994; Gordon et al., 1994; Desai et al., 1994). The combined vision and depth of knowledge has had a profound affect on the pharmaceutical industry, helping to promote a greater understanding of technology and to develop new strategies for discovering novel lead candidates.

ANALYSIS PERSPECTIVES

The role of analytical technologies traditionally has been to *respond* to a pharmaceutical event, rather than to *lead* one. A complementary perspective from an analytical point of view can provide substantial insight into relevant drug development issues. This insight may not be intuitively obvious from a sample-generating (i.e., chemistry, biology) approach. And, when sample analysis activities are taken into consideration as an equal partner with sample-generating

activities, global, and perhaps, integrated strategies for drug development may be derived.

This view suggests that analysis insights provide unique perspectives and opportunities to contribute to the design, development, and manufacture of high-quality drug products. This statement does not intend to imply that this process does not occur in the pharmaceutical industry, only that there is opportunity for more such interaction and collaboration. With that said, sample analysis can be viewed as a dependent partner with sample generation. Without analysis, sample generation yields no information for satisfying drug development criteria, and vice versa. Therefore, no matter how quickly or efficiently samples are generated, the benefits are not realized unless they are analyzed in an equally efficient manner. Identical, or perhaps, matched criteria for performance (i.e., speed, throughput, compatibility) is, therefore, required for sample-generating and sample-analysis responsibilities.

THE FOUR STAGES OF DRUG DEVELOPMENT

Drug development has become more complex and highly competitive while the sample analysis contributions have become increasingly important. This perspective recognizes the impact of sample analysis activities and the corresponding information that must be accumulated throughout the various stages of development.

At present, drug development consists of four distinct stages: (1) drug discovery; (2) preclinical development; (3) clinical development; and (4) manufacturing (Table 2.1). Each development stage is geared toward the swift accomplishment of goals and objectives. Each stage culminates with a specific corresponding milestone: lead candidate; investigational new drug (IND)/clinical trial application (CTA); new drug application (NDA)/marketing authorization application (MAA); and sales. The IND and NDA are the required regulatory documents filed in the United States; the CTA and MAA are required in Europe.

For the successful completion of each milestone, a diverse array of analyses is required. The focus is generally unique to the specific stage of development and is a determining factor for criteria for analysis. For example, drug discovery approaches typically require rapid, high-throughput screening methods with the purpose of selecting a lead candidate from a large number of diverse compounds. Analyses that emphasize quick turnaround of results are