AAPS Advances in the Pharmaceutical Sciences Series 26

Mario L. Rocci Jr.
Stephen Lowes *Editors*

Regulated Bioanalysis: Fundamentals and Practice

aapspress
Springer

AAPS Advances in the Pharmaceutical Sciences Series

Volume 26

The AAPS Advances in the Pharmaceutical Sciences Series, published in partnership with the American Association of Pharmaceutical Scientists, is designed to deliver volumes authored by opinion leaders and authorities from around the globe, addressing innovations in drug research and development, and best practice for scientists and industry professionals in the pharma and biotech industries.

More information about this series at http://www.springer.com/series/8825

Mario L. Rocci Jr. · Stephen Lowes
Editors

Regulated Bioanalysis: Fundamentals and Practice

Springer

Editors
Mario L. Rocci Jr.
Laboratory Services
ICON, Plc
Whitesboro, NY
USA

Stephen Lowes
Bioanalytical and ADME Labs
Q Squared Solutions
Ithaca, NY
USA

ISSN 2210-7371 ISSN 2210-738X (electronic)
AAPS Advances in the Pharmaceutical Sciences Series
ISBN 978-3-319-54800-5 ISBN 978-3-319-54802-9 (eBook)
DOI 10.1007/978-3-319-54802-9

Library of Congress Control Number: 2017933942

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my beloved wife and son, Donna and Mark Rocci for all the love, encouragement and support they've provided throughout my professional career.

—Mario L. Rocci Jr.

To Kathy, Thea and Elise Lowes—my loving family and all I hold dear.

—Stephen Lowes

Preface

Bioanalysis, simply described as the quantitative measurement of the concentration of a drug, its metabolite(s), or an endogenous compound present in a biological matrix, is essential to the discovery, development, and regulatory approval of new medicines. It is also key to modern pharmacokinetics (i.e., the study of what the body does to a drug) and, increasingly, to pharmacodynamics (i.e., the study of what a drug does to the body). Understanding these biological processes is critical to the practice of determining drug safety profiles and efficacy potentials as well as to establishing recommended dosage for new therapeutics that treat disease. Generating this important data to get safe and effective medicine to patients is the work of contemporary bioanalysts. It is the ingenuity of the bioanalysis team that enables development of robust assays to meet increased sensitivity and selectivity requirements across a wide range of chemical entities, from small molecule drugs to protein- or DNA-based therapeutics.

Once considered a branch of analytical chemistry, bioanalysis now spans biology and chemistry. It shows no sign of limitations in furthering drug development in, either the needs it can address or its potential to advance on those requirements. The advances in technology and strategies implemented in today's bioanalytical laboratory are in accordance with the challenges and opportunities presented by new drug therapies. Despite the developments in bioanalytical technology available to today's bioanalyst, an understanding of the fundamentals of this quantitative analytical science remains incredibly important. Whether setting up a new lab, reorganizing an existing lab, considering an investment in new technology or software, writing SOPs or defending data to an auditor, a firm grasp of the fundamentals will serve the bioanalyst well. While there is currently a wealth of information available on advanced bioanalytical approaches, the volume of material can be overwhelming to those new to or considering a career in bioanalysis. Add to this the evolving regulations guiding practice, and the need for a fundamental reference on modern bioanalysis arises, inclusive of the science, technology, and regulations. It is this need that prompted us to approach recognized bioanalysis experts and opinion leaders to write this book. With it, we aim to provide a comprehensive text that puts fundamental bioanalytical science in context with

current pharmaceutical bioanalysis practice, its challenges, and ongoing developments. It expands on existing texts on the subject by covering regulated bioanalysis of both small and large molecule therapeutics. We hope the content will be useful to a wide spectrum of readers: from those new to bioanalysis, to those developing their experience in the laboratory or working in one of the many critical supporting roles, to seasoned practitioners looking for a solid source of information on this exciting and important discipline.

Chapter 1 provides an introduction to the book. Chapter 2 is a primer on regulations affecting bioanalysis, describing what global health authorities require and expect of organizations generating bioanalytical data for new drug applications. An important foundation for the discipline, it also points to the challenge of drafting prescriptive and comprehensive guidance in a variable and rapidly evolving scientific environment. Chapter 3 summarizes the logistics and practice of establishing and running a bioanalytical laboratory. Chapter 4 discusses the documentation needed for such an endeavor. Chapters 5–7 focus heavily on small molecule bioanalysis and liquid chromatography-mass spectrometry (LC-MS) applications, including how LC-MS is now finding niche applications beyond small molecules, including for large molecule and biomarker bioanalysis. Ligand-binding assays (LBA) are noted as the go-to analytical approaches for peptide, protein, and other biomolecule work since the introduction of immunoanalytical techniques. With the surge in protein therapeutics entering pharmaceutical and biotechnology pipelines, we expect this trend to continue. Chapters 8 and 9, therefore, focus on LBA techniques, and also discusses where and how the regulations apply in light of the nuances of these approaches.

This book was made possible by the dedication of the chapter authors. We are humbled by their generosity, both in time and effort, in sharing their valuable knowledge with the bioanalytical community. It is with deepest gratitude that we thank them for contributing excellent first drafts and for sticking with us through rounds of review. These thanks extend to their families, whom we know routinely accept this extra, uncompensated effort beyond the "day-job."

We also would like to thank Kathryn Henion, Ph.D., for her valuable proofreading edits. A third set of eyes and a masterful red-pen helped tremendously in pulling this book together. Finally, we would like to thank Springer Publishing for helping us through the process of bringing this book to fruition and into the hands of readers who, we hope, will benefit from the content. Thank you all.

Whitesboro, NY, USA Mario L. Rocci, Jr.
Ithaca, NY, USA Stephen Lowes

Contents

Editors and Contributors

About the Editors

Mario L. Rocci Jr. is Senior Vice President at ICON Laboratories and was formerly the CEO of Prevalere Life Sciences, Inc. He has held appointments in the Department of Medicine at Jefferson Medical College, and Pharmaceutics and Pharmacy Practice at the Philadelphia College of Pharmacy and Science.

Dr. Rocci has a B.S. in Pharmacy and a Ph.D. in Pharmaceutics. He is a Fellow of the American College of Clinical Pharmacology (ACCP) and the International Pharmaceutical Federation (FIP). Dr. Rocci is a past President of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and the American Association of Pharmaceutical Scientists (AAPS), where he received the AAPS Distinguished Service Award. He is a past Chairman of the Board of the Product Quality Research Institute (PQRI) and a past Board Member of the International Pharmaceutical Federation (FIP). Dr. Rocci also serves as Chair of the Dean's Advisory Council in the School of Pharmacy and Pharmaceutical Sciences at the University at Buffalo, where he received the Willis G. Gregory Memorial Award, and is a member of the External Advisory Board of the University of Kentucky's, School of Pharmacy.In addition to his accomplishments in the industry, Dr. Rocci has authored over 150 publications.

Stephen Lowes is a Senior Director at Q^2 Solutions. Dr. Lowes has over 25 years of experience in bioanalysis with a focus on LC/MS and regulatory requirements. He currently leads Q^2 Solutions' regulated LC/MS bioanalytical CRO laboratory, supporting drug development initiatives of global pharmaceutical and biotechnology sponsors.

Dr. Lowes received his bachelor's degree in Analytical Chemistry at Sheffield Hallam University (UK) and Ph.D. in Biochemistry at The Open University, Milton Keynes, (UK). He is a steering committee member and past-chair of the AAPS bioanalytical focus group, is a founding member of the Global Bioanalysis Consortium (GBC) and is an active contributor to the Global CRO Council (GCC). Dr. Lowes is a regular presenter, trainer and author of publications on regulated bioanalysis with emphasis on LC/MS approaches.

Contributors

Mark Arnold Burlington, NJ, USA

Surendra K. Bansal Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center New York, New York, NY, USA

Patrick Bennett PPD Laboratories, Richmond, VA, USA

Ronald R. Bowsher B2S Life Sciences, Franklin, IN, USA

Sheila Breidinger Merck Research Labs—PPDM Clinical Bioanalytics, West Point, PA, USA

Stephanie S. Cape Covance Laboratories, Inc., Madison, USA

Aleks Davis B2S Life Sciences, Franklin, IN, USA

Binodh DeSilva Analytical and Bioanalytical Operations, Bristol-Myers Squibb, Princeton, NJ, USA

Douglas M. Fast Covance Laboratories, Inc., De Forest, USA

Van Fitzgerald Radix BioSolutions, Georgetown, TX, USA

Eric Fluhler Washingtonville, NY, USA

Boris Gorovits Biomedicine Design, Pfizer Inc., Andover, MA, USA

Jack Henion R&D, Q Squared Solutions, Ithaca, NY, USA

Charles Hottenstein Bioanalysis, Immunogenicity and Biomarkers, GlaxoSmithKline, King of Prussia, PA, USA

Mohammad R. Koupaei-Abyazani Covance Laboratories, Inc., Madison, USA

Richard M. LeLacheur Agilux Laboratories, Inc., Worcester, MA, USA

Stephen Lowes Bioanalytical and ADME Labs, Q Squared Solutions, Ithaca, NY, USA

Min Meng Covance Laboratories, Inc., Salt Lake City, USA

Johanna Mora Analytical and Bioanalytical Operations, Bristol-Myers Squibb, Princeton, NJ, USA

William Nowatzke Radix BioSolutions, Georgetown, TX, USA

Mario L. Rocci Jr. Laboratory Services, ICON, Plc, Whitesboro, NY, USA

Gary Schultz Munson Technology LLC, Ithaca, NY, USA

Franklin Spriggs Ligand Binding Assays, AIT Bioscience, Indianapolis, IN, USA

Faye Vazvaei Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center New York, New York, NY, USA

Eric Woolf Merck Research Labs—PPDM Clinical Bioanalytics, West Point, PA, USA

Chapter 1
Introduction

Stephen Lowes and Mario L. Rocci Jr.

Abstract Bioanalysis spans nearly a century of practice enabling the widespread use of pharmacokinetics and pharmacodynamics to improve the rational use of existing drugs and the development of new drugs. While few universities and colleges offer formal programs in bioanalysis, there are several scientific degree programs that are good entry points into the field. The successful bioanalytical laboratory requires a high degree of scientific talent in addition to professionals capable of tackling operational and sample logistics, project and data management, quality control and quality assurance, metrology, instrument maintenance, information technology, and technical writing. These positions and others afford attractive career opportunities for those contemplating the field. Technology is developing at an amazing rate in the bioanalysis field and it is an exciting time to be engaged in this scientific discipline. Given this rapid pace of change, keeping current with the scientific literature, as well as active participation in professional organizations, focus groups, and scientific conferences and meetings germane to the field is crucial.

Keywords Bioanalysis · Bioanalytical career opportunities · Bioanalytical laboratory personnel · Bioanalytical information sources

S. Lowes (✉)
Bioanalytical and ADME Labs, Q Squared Solutions,
19 Brown Road, Ithaca, NY 14850, USA
e-mail: stephen.lowes@q2labsolutions.com

M.L. Rocci Jr.
Laboratory Services, ICON, Plc, 8282 Halsey Road, Whitesboro, NY 13492, USA
e-mail: Mario.rocci@iconplc.com

M.L. Rocci Jr. and S. Lowes (eds.), *Regulated Bioanalysis: Fundamentals and Practice*, AAPS Advances in the Pharmaceutical Sciences Series 26,
DOI 10.1007/978-3-319-54802-9_1

1.1 History, Background, and Status of Regulated Bioanalysis

Bioanalysis spans nearly a century of practice applied in pursuit of new medicines for human and animal use. The quantitative measurement of drugs and their metabolites in biological fluids, in addition to endogenous markers of drug effects, enabled the fundamentals of pharmacokinetics (PK) and later pharmacodynamics (PD)—two disciplines critical to the discovery and development of new drugs [1, 2].

Bioanalytical methods are developed and validated under very challenging conditions. Quantifying a drug, its metabolite(s) or endogenous analytes of interest is complicated by the biological sample itself, which often contains very high levels of structurally similar and naturally occurring endogenous compounds. Furthermore, these measurements must be made at very low levels and with a high degree of accuracy and precision. As drug development has evolved over the last few decades, the types of molecules undergoing development have become more diverse. Most notable has been the evolution of biotechnology which has changed the therapeutic landscape to include the development and use of protein therapeutics to treat diseases of all types. This has required bioanalytical science to broaden its reach to include the analysis of macromolecules in addition to small molecule drugs. As we will cover in several chapters in this book, different technology and approaches are necessary for analyzing low-molecular-weight, small molecule compounds compared to much larger, protein-based entities.

Today, bioanalytical assays are typically divided into two categories: chromatographic assays and ligand-binding assays (LBA). These categories can be further divided into the techniques used to perform them. While liquid chromatography–mass spectrometry (LC-MS) based techniques dominate chromatographic approaches, immunoanalytical techniques have enjoyed a tremendous renaissance in a wide range of LBA approaches. More recently, both LBA and LC-MS are being employed together in hybrid assays as a selective, sensitive, and adaptable approach for the bioanalysis of the latest (and, arguably, some of the more complex) drugs undergoing development. Commensurate with these technological advances are the evolving and increasingly more sophisticated methods for preparing samples prior to analysis. Pre-analytical activities and sample preparation (e.g., sample collection, extraction, and dilution) are integral to analyte quantitation and must be appropriate for the assay purpose and the detection technology being employed. Whatever the method or technology used, the goal remains the same: to obtain reliable measurements of the physiological concentrations of the analyte(s) of interest at the time of sampling.

Alongside its scientific developments and challenges, bioanalysis has become an area of drug development heavily scrutinized by regulators. This was not always the case. Prior to 1990, there was no specific regulatory guidance to ensure consistency within and between laboratories conducting bioanalytical work. While Good Laboratory Practices (GLP) provided an operational foundation for the discipline,

the performance characteristics of a given assay were left to the bioanalyst to define, demonstrate, and defend. Consequently, bioanalytical experiments and strategy varied among laboratories, resulting in a lack of consistency in drug approval submissions. The situation led several experts in bioanalysis, representatives of the US Food and Drug Administration (US FDA, FDA), and the American Association of Pharmaceutical Scientists (AAPS) to organize a workshop in 1990. Held in the Crystal City area of Arlington, Virginia, the meeting was subsequently referred to as the Crystal City workshop on bioanalysis, the first in a series of meetings that have followed. From the first workshop, a conference report was published in 1992 [3] that outlined a consensus view on what experiments and acceptance criteria should be employed when validating a bioanalytical method. While initially this paper did not meet everyone's expectations for bioanalytical method validation (BMV), it did gradually gain acceptance as a standard by both bioanalytical laboratories and regulators (particularly in the USA).

Ten years after the first Crystal City meeting, the bioanalytical community met again for the appropriately named workshop, "Bioanalytical Methods Validation—A Revisit with a Decade of Progress." The resulting workshop conference report [4] was essentially replicated in 2001 as a regulatory guidance issued by the US FDA [5]. Since that time, there has been a continual evolution in both laboratory practice and the expectations from regulators. Today, at least five global health authorities have released their own BMV guidances. While there is a general level of consistency among guidances, further opportunities for harmonization exist within and are desired by the bioanalytical community. Pursuit of such consistency is likely to continue into the foreseeable future, with the ideal objective being a single, globally recognized BMV guidance.

Because less-than-reliable methods can have significant implications with regard to drug safety and therapeutic efficacy, fully validated bioanalytical assays are a critical part of meeting the needs of pivotal PK studies such as bioequivalence (BE) and bioavailability (BA) trials. The critical nature of these assessments has led bioanalysts to adopt comprehensive method validation requirements for all bioanalytical methods used in the drug development setting, without regard to the purpose(s) for which the method is being used. More recently, scientists have instead directed efforts toward considering what level of method validation is suitable and sufficient for an assay's intended use(s). This is termed "fit-for-purpose" or "tiered" approaches.

It is worth noting that bioanalytical regulatory guidance was originally drafted around chromatographic assays, primarily LC–MS. While a section of the 2001 FDA BMV guidance [5] dealt with LBA, the content was insufficiently developed for practical use. Consequently, separate consortia and opinion leaders published highly regarded white papers on the development and validation of bioanalytical LBAs that in turn influenced common practice more so than the official regulatory guidance [6–8]. The Japanese Ministry of Health, Labour, and Welfare (MHLW) is the only global health authority to date to issue a separate BMV guidance for large molecule LBA assays [9, 10], while others follow the FDA's approach of a using separate sections of a common document. Despite continued development and new

releases of global health authority guidances, LBAs are still arguably underrepresented in the regulations. With an increasing percentage of biologic drug therapies filling pharmaceutical company pipelines, the call for agreement on what constitutes regulated LBA bioanalytical practice has reached a new urgency. The challenge here of course is that the accelerating pace of technology and science development makes comprehensive and prescriptive regulatory guidance a difficult expectation.

1.2 Roles, Responsibilities, and Career Opportunities in Regulated Bioanalysis

It is without doubt an exciting time to be in the field of bioanalysis. Technology is developing at an amazing rate for both chromatographic and LBA, as well as for hybrid methods that encompass both. Therapeutic drug classes are evolving similarly, creating ever-increasing bioanalytical challenges. Most recently, regulated bioanalysis has been applied to endogenous biomarker assays, further establishing a need for new strategies and approaches.

The successful bioanalytical laboratory requires talent with more than the fundamental science and technology skills. To be sure, an optimally functioning laboratory relies on multidisciplinary teams working in concert toward a common goal: establish robust methods that produce high-quality bioanalytical results. So what are the varied skills and roles that enable a regulated bioanalytical laboratory to thrive? First, is a need for creative bioanalytical scientists with strong scientific knowledge who can develop, validate, implement, and troubleshoot bioanalytical methods. Additional essential support functions are those tackling operational and sample logistics, project and data management, quality control and quality assurance, metrology, instrument maintenance, information technology (IT), and technical writing. In a successful bioanalytical laboratory, all of these professionals must work effectively, efficiently, and collaboratively, within a robust Quality Management System (QMS).

One concern within the modern bioanalysis community is insufficient "new-blood" joining the discipline to meet demand. The reasons for this may be speculated, but they likely relate to regulated bioanalysis being an analytical science niche, with unique requirements that do not fit well within conventional college course curricula or translate directly from other analytical sciences. Even at the graduate level, few research programs directly train and link the intricacies of quantitative bioanalysis with the regulatory requirements that guide this work. In response to this discrepancy, we present a discussion of which college programs of study might fit well with a future career in bioanalytical science. We then describe a few key professional roles within a regulated bioanalytical work environment, each of which provides a stimulating and rewarding career path for those interested in bioanalytical science and technology. These key roles are not inclusive of every

aspect of a modern bioanalytical laboratory and other roles offering rewarding career opportunities exist but are beyond the scope of this chapter.

1.2.1 College/University Programs of Study

While much of the education and training necessary for work in a bioanalytical laboratory comes from on-the-job training and experience, there are many programs of study within colleges and universities that can provide a solid foundation for entry into the discipline.

Programs in chemistry, and more specifically analytical chemistry, as well as the pharmaceutical sciences, will provide a solid knowledge base for working in the area of small molecule bioanalysis, which primarily involves quantitative PK assessments. The programs of study affording firm starting points for large molecule bioanalysis are broader given the many techniques and multiple assessments performed in this area. In addition to quantitative PK assessments, immunogenicity and neutralizing antibody assessments are required during the development of protein therapeutics (all of these assessments will be discussed in chapters that follow). As a result, programs in biology, molecular and cell biology, biochemistry, and pharmaceutical sciences are well suited for those interested in large molecule bioanalysis.

The chapters that follow provide a good introduction to bioanalytical sciences including current practice and ongoing advances in technology. We encourage those interested in careers in the field to consider where their education, training, and experience align with this information and where gaps in skill or knowledge exist that can be remediated through additional education or training.

1.2.2 Bioanalytical Laboratory Scientists

Those first being introduced to modern bioanalysis may be forgiven for thinking it is a discipline with rules and regulations that override the science. While bioanalysis does involve regulation, health authority guidance and comprehensive documentation, the foundation of bioanalytical methods relies on sound analytical science and scientists. Bioanalytical scientists are the lifeblood of the laboratory and no laboratory can be successful without progressive, creative, and highly productive scientists. There are a number of scientific roles required within the laboratory. Method development scientists are needed to develop methods from scratch or adapt existing methods, making them more suitable for their intended purpose. In many cases, method development scientists are developing methods for molecules that have never been measured in a particular biological matrix before. This process is extremely challenging, requiring a high level of creativity and scientific knowledge. Because each bioanalytical method is essentially a customized solution

to a given analytical need, bioanalysis presents both scientific and operational challenges on an ongoing basis. While common techniques, equipment, and instrumentation may be employed, each bioanalytical method is unique in the combination of steps developed to prepare and analyze samples. In many cases, early feasibility and development experiments need to be conducted to obtain a scientific understanding of the task. These should establish which specific bioanalytical skills will be required, including technique and instrumentation.

Each project starts with understanding the questions that need answering, including but not limited to

Why a particular analyte?

What is already known about the analyte?

What sensitivity of analysis is required?

How stable is the analyte in a collected sample?

What will be the biological matrix?

How will the data be used to make decisions on the development of a drug?

These questions must be answered, as they will influence the bioanalytical approach needed and lead to determining appropriate people, equipment, and time resources for the project.

Once a method is validated, to ensure it is fit for its intended purpose and that it will meet regulatory guidelines, bioanalytical scientists are then responsible for analyzing the thousands of samples generated from drug development efforts. This analysis should be highly efficient and of very high quality, as the data from many of the studies will be submitted to regulators for review as part of a marketing approval application [in the United States a New Drug Application (NDA) or, for a generic drug, an Abbreviated New Drug Application (ANDA)]. For particularly high-volume analyses, automated approaches may be validated and applied to good effect. Introducing automation in a bioanalytical method also requires additional skills and some unique operational specifics that will be covered in several chapters of this book.

1.2.3 Project Leaders and Project Managers

Bioanalytical project management is a multifaceted process. Once the scientific challenge is evaluated, the operational aspects of providing sufficient and appropriate resources become paramount. Personnel, equipment, and allocated time all influence the chances for project success. Experienced bioanalytical project leaders understand these needs and can plan accordingly, factoring in frequently required contingencies. Project leaders often graduate from the laboratory where they have experienced the challenges of developing, validating, and applying bioanalytical methods to study sample analysis. They are typically well organized and have

strong documentation and communication skills. Project leaders also need to have an ability to see the big picture and coordinate the efforts of multiple people and teams. Often project leaders juggle multiple projects simultaneously. This role usually involves direct communication with key stakeholders, the scientific teams, support functions, Quality Assurance (QA), and laboratory management.

Project leaders are the key to coordinating remediation efforts when issues arise. From scientific investigations of batch failure to addressing sponsor and QA observations and findings, the project leader is often the single point of control for a regulated bioanalysis project. Likewise, at times of QA audit or regulatory authority inspection, an effective project leader will greatly assist the process. Good project leaders are in high demand, as they are a key influence on the success and reputation of a bioanalytical laboratory.

Where multiple drug development protocols or programs are active simultaneously, it may be necessary to engage a project manager to handle the nonscientific aspects of a series of ongoing projects/programs. This helps ensure the logistical aspects of projects are reasonable, communication channels with all stakeholders are active, effective, and documented, and that satisfactory completion of the work is done according to agreed-upon timelines. In these instances the project leader(s) and project manager work in concert. The project leader focuses on the science, timing, and compliance aspects of the studies (or a subset of them if multiple project leaders are engaged). The project manager works to ensure that all logistics are in place to get the projects/programs completed on time and that communication of project status and issues that arise is quick and effective. Project managers can come from the laboratory or be professionals trained (and often times certified) for this role.

1.2.4 Laboratory Managers

The challenges presented to project leaders and project managers extend to the laboratory manager or management team. Laboratory managers also provide critical support to bioanalysis projects, though this is typically done by ensuring sufficient availability and appropriate allocation of resources. They are also responsible for maintaining an environment conducive to quality and regulatory compliance. When quality issues arise, it is the responsibility of laboratory managers, project managers, and project leaders to ensure that the issues are remediated, as appropriate, through Corrective and Preventative Action (CAPA) plans. Aside from these activities, managers are often responsible for meeting or exceeding their financial budgets or targets, as well as optimal laboratory performance as measured by a variety of metrics (e.g., as discussed later in Chap. 3).

For small, in-house bioanalytical operations, there may be only one laboratory manager coordinating people, equipment, and time allocation directly with the project leaders, project manager(s), or analysts. At the opposite end of the spectrum, within a large Contract Research Organization (CRO), separate departments may

exist for each specialized function, each led by a member of the management team. A potential danger here is the development of functional silos each focused primarily on its own interests. Companies cannot afford for this to happen because flexibility and adaptability are required to meet the requirements of varied internal and external stakeholders. It is imperative that laboratory management recognizes and remains sensitive to supporting interdependence among key functions such as sample management, bench scientists, metrology, IT, resource scheduling, and technical writing. This focus fosters collaboration and open communication across the different functions.

1.2.5 Quality Assurance

The QA organization in a regulated bioanalytical laboratory ensures compliance with applicable regulations and guidelines. Despite its importance, QA rarely gets addressed in scientific texts, but valuable and important careers can develop within this discipline.

QA must be kept independent from the operational and support groups within the laboratory. The GLP regulations require a reporting structure within QA that is separate from any personnel or functions that generate data. The role of QA is to ensure performed work complies with regulations where necessary, and to audit the work for compliance with the laboratory's standard operating procedures (SOPs) or any other documented plans, methods, and processes. QA also functions proactively and collaboratively with operational groups to provide input on how those teams might best resolve quality issues. It is therefore important that QA personnel have a basic understanding of the science as well as a deep understanding of the regulations that apply. In this way, remediation of quality issues can occur expeditiously. QA typically leads any external quality visits, audits, and inspections, including those conducted by regulatory authorities. For project-based audits or inspections, all phases of a bioanalytical project may come up for review. This includes review of organizational charts, the master schedule for GLP studies, SOPs, training records, facility records, instrument maintenance and calibration records, project data, archive facilities, and IT infrastructure. In contrast, system-based audits may take a more detailed look into one or more operational systems critical to the laboratory operation.

During inspections, a laboratory tour allows the auditor to correlate practice with written processes and procedures. It is common for such lab tours to be hosted by QA and follow an imaginary sample from receipt through analysis and data reporting. As such, the QA representative must have a good understanding of bioanalytical science, the BMV guidances and associated interpretations of the regulations to manage the process.

1.2.6 Other Roles

The collective effort necessary for a well-functioning bioanalytical laboratory means that other, nonscientific support groups and individuals may benefit from an awareness and understanding of the topics covered in this book. To varying degrees, a working knowledge of regulated bioanalysis helps employees communicate and collaborate with one another. This knowledge builds team respect and appreciation among coworkers. It can also add to job satisfaction. While we do not suggest that every position requires a full understanding of the topics covered in this book, we hope readers from a broad spectrum of job functions across the pharmaceutical industry can find some of the content practical, valuable, and actionable.

Regulated bioanalytical laboratories usually employ some form of quality control (QC) in addition to and separate from QA. QC may vary from within-team peer review of documentation to a fully staffed QC department. In either case, effective QC can have a positive impact on data quality and compliance. It is always better to catch errors early versus later in the process. If the QC function is organized as a dedicated role, then knowledge and understanding of the science and regulations as described in this book will be an asset to job performance.

Similarly, those tasked with the technical writing of reports, research papers, and marketing material should also have a working knowledge of bioanalysis and regulatory expectation so that they may be better able to raise good questions and join dialogue on the topic area. Experienced and knowledgeable technical writers who can spot deficiencies and provide constructive input improve the final product and quickly become a valuable asset to the team.

Business Development (i.e., the group that sells bioanalytical services to new and existing clients) is a key area within CROs. Considering the direct interaction these professionals have with prospective and existing sponsors, it is a tremendous advantage if they can converse on a technical level. Doing so builds credibility and trust and helps ensure that accurate information gets to the bioanalyst.

Health and safety staff, facilities management personnel, and any persons involved in equipment metrology may be called upon during audits and inspections regarding the regulated aspects of their role in the laboratory. A firm understanding of the applicable regulatory requirements for their roles is critical and, in some cases, beyond the scope of this book.

Finally, IT departments face specific regulations (e.g., US 21 CFR Part 11 on electronic records and electronic signatures) requiring compliance in a regulated bioanalytical laboratory. IT staff members are often called upon during audits and inspections to defend practices that ensure the security and authenticity of information and data associated with a regulated bioanalysis project. We therefore advise organizations to train IT personnel in the regulatory requirements as outlined in this book.

1.2.7 Sponsors, Clients, and Data Customers—A CRO Perspective

Those in need of bioanalytical data benefit from understanding the basics of the work they commission a laboratory to perform. Even with the extensive regulations and health authority guidances, the specific nuances of any project call for agreement and communication between the sponsor of the work and the bioanalytical team performing it. While contracting bioanalytical work to a CRO may seem a straightforward process, experience pays dividends both on behalf of the sponsor and the CRO. As will be discussed in the following chapters, many factors contribute to a successful bioanalytical project. The more specific and relevant information a sponsor can provide during the initial contracting stages, the better chance there is for an optimum outcome. In the circumstances of a client outsourcing bioanalytical work to a CRO, experience and good communication skills on both sides of the partnership is especially important. A client who understands the key aspects of establishing and implementing bioanalytical methods, and who can contribute such experience to the project, is a significant advantage. As an independent entity, the CRO often relies on the client to provide key background information. When issues occur at the chemistry and biochemistry level during any phase of the project, the value of a strong client/project manager relationship becomes evident.

An often overlooked stakeholder in a bioanalytical project is the subsequent user of the final data. Typically this is the pharmacokineticist tasked with interpreting the bioanalytical data. Increasingly, it is important to interface with the PK scientist during the planning stages of the bioanalytical work. With bioanalysis now needing to address new compound classes, technology developments, and drug development strategies, it is important that the end-user of the data helps define, at the beginning of a bioanalytical program, what is needed from the method so that the data obtained is most useful for decision-making purposes.

1.3 Beyond This Book

1.3.1 Resources

This book is intended to offer an important foundation in bioanalytical practice. Once the reader acquires a basic understanding of the science, operational, and regulatory requirements on the subject, we encourage them to seek additional information continually in order to stay current.

There are several existing bioanalysis texts that supplement this book and provide additional detail of technology and technique. An online search will lead to

titles on principles of bioanalysis, or that focus on technology-specific applications. We view such books as complementary to what we have presented here, often providing additional compound-class case studies or in-depth assessment of instrument type. Several existing texts are focused on small molecule bioanalysis with LC–MS or other instrumental approaches. Others do not place emphasis on regulated bioanalysis and the associated disciplines. Currently, there is a lack of directly relevant books for those looking to advance their understanding of LBA in regulated bioanalysis.

There are several traditional journals that emphasize bioanalysis including *Analytical and Bioanalytical Chemistry* (Springer) and *Bioanalysis* (Future Science) that are tremendous resources for case studies and current developments within the field. Many other well-known analytical chemistry periodicals also publish papers on bioanalytical topics. There are also emerging open-access, peer-reviewed, online journals either focused in this area or with bioanalytical relevance.

We advise the reader to stay aware of ongoing developments through traditional peer-reviewed publications but also to conduct wider online searches of other information sources occasionally. Combined with participation in bioanalytical community discussion forums (see below), there is a wealth of constantly-emerging and valuable information available to the modern bioanalyst with access to the Internet.

The development of regulatory guidance is an ongoing process around the globe. Some of the most pivotal and interesting changes in bioanalytical practice have evolved from the interpretation of the BMV standards. Prior to a guidance becoming effective, a draft form is typically released for public comment. In addition to providing the bioanalyst the opportunity to contribute to the conversation by responding with comments about the draft guidance, becoming familiar with the expectations and requirements of guidances during their development helps the bioanalyst stay current and informed.

As with all fields of professional advancement and development, the Internet is a rich trove of information. There are some tremendously useful and effective online training courses dedicated to bioanalysis. These vary in quality, content, and accuracy, developed both by recognized and experienced opinion leaders and those with little tenure and few credentials. The convenience of online material is unquestioned and, as stated, some material is very helpful. Equally, some personal blogs, chat-rooms and other social media formats dedicated to bioanalysis can be excellent sources of current opinion and content. “User beware” applies here, though, and we recommend that new bioanalysts verify online-sourced information against peer-reviewed content. We expect that further advancement in online information and education will have a significant impact upon the future of bioanalysis. We encourage your participation with and support for the sources founded on accurate and helpful information.

1.3.2 Organizations and Focus Groups

There is now a multitude of nonprofit, professional organizations around the world that address bioanalysis areas. Regulated bioanalysis topics often feature heavily in the initiatives of these organizations as they seek to serve the interests of their members. Because these organizations are independent of pharmaceutical and biotechnology companies, these entities can often engage local health authorities on topics of bioanalysis. In recent years, groups such as the American Association of Pharmaceutical Scientists (AAPS), European Bioanalysis Forum (EBF), Japan Bioanalysis Forum (JBF), the Global Bioanalysis Consortium (GBC), and the Global CRO Council (GCC) have offered significant opportunities for bioanalysts to exchange ideas and interact with regulators. These and other professional organizations and their associated focus groups will continue to be a valuable asset to the bioanalysis community. We encourage bioanalysts to support and participate in the efforts of these groups. Opportunities to do so vary, from joining a local chapter to volunteering on programming and organization of meetings and conferences.

1.3.3 Conferences and Meetings

Through conferences, workshops, local meetings, and industry working groups, bioanalysts learn about and contribute opinions to the process of developing regulatory language, often interacting directly with representatives from regulatory bodies themselves. Many of the most popular and effective conferences are non-profit and conducted by the professional organizations referenced above. Others may have a for-profit structure but still offer valuable training and content. Rather than list all of the annual conferences with bioanalysis relevance, which are constantly changing in location and frequency, we encourage bioanalysts to participate in the community and follow its periodicals to learn of the regional, national, or international events worth attending.

Attendance at conferences and meetings is likely the most effective way for a bioanalyst to establish a personal bioanalysis network. As you will come to appreciate in the following chapters, information exchange is critical to a bioanalyst's professional development. The bioanalytical community welcomes new talent. As editors and years-long professionals engaging with this community, we can both attest to the value, collegiality, and enjoyment to be had working in this field. We hope you will join us in furthering the discipline and developing yourself as a professional bioanalytical scientist or supporter of the science so critical to bringing new drugs to the patients who need them.