# PRACTICAL APPROACHES TO METHOD VALIDATION AND ESSENTIAL INSTRUMENT QUALIFICATION

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WILEY

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# PREFACE

This book is a complement to our first book, *Method Validation and Instrument Performance Verification*. As stated there, for pharmaceutical manufacturers to achieve commercial production of safe and effective medications requires the generation of a vast amount of reliable data during the development of each product. To ensure that reliable data are generated in compliance with current good manufacturing practices (cGMPs), all analytical activities involved in the process need to follow good analytical practices (GAPs). GAPs can be considered as the culmination of a three-pronged approach to data generation and management: method validation, calibrated instrumentation, and training.

The chapters are written with a unique practical approach to method validation and instrument performance verification. Each chapter begins with general requirements and is followed by strategies and steps taken to perform these activities. The chapters end with the authors sharing important practical problems and their solutions with the reader. I encourage you to share your experience with us, too. If you have any observations or solutions to a problem, please do not hesitate to email it to me at chung_chow_chan@cvg.ca.

The method validation section focus on the strategies and requirements for early-phase drug development, the validation of specific techniques and functions [e.g. process analytical technology (PAT)], cleaning, and laboratory information management systems (LIMSs). Chapter 1 is an overview of the regulatory requirements on quality by design in early pharmaceutical development and instrument performance verification. Instrument *performance verification* and *performance qualification* are used as synonyms in this book. Chapter 2 is an overview of the strategies of phase 1 and 2 development from the analytical perspective. Chapter 3 provides guidance on compendial method verification, analytical revalidation, and analytical method transfer. Discussed are strategies for an equivalent analytical

method and how that can be achieved. Chapters 4 and 5 cover method validation of specific techniques in PAT and near-infrared identification. Chapters 6 and 7 give guidance on cleaning validation and LIMS validation.

The instrument performance verification section (Chapters 8 to 16) provides unbiased information on the principles involved in verifying the performance of instruments that are used for the generation of reliable data in compliance with cGXPs (all current good practices). Guidance is given on some common and specialized small instruments and on several approaches to the successful performance verification of instrument performance. The choice of which approach to implement is left to the reader, based on the needs of the laboratory. Chapter 8 provides background information on the most fundamental and common but most important analytical instrument used in any laboratory, the balance. A generic protocol template for the performance verification of the balance is also included to assist young scientists in developing a feel for writing GXP protocol. Performance verification requirements for near-infrared, gas chromatographic, and high-performance liquid chromatographic detectors are described in Chapters 9, 10, and 11. Chapter 12 gives guidance on performance verification of particle size, which is very challenging for its concept. Chapter 13 covers the requirements needed for the specialized technique of total organic content. Performance verification of small equipment used in pipettes and liquid-handling systems is discussed in Chapters 14 and 15. Chapter 16 provides an overview of x-ray diffraction technique and performance verification of this instrument.

The authors of this book come from a broad cultural and geographical base—pharmaceutical companies, vendor and contract research organizations—and offer a broad perspective to the topics. I want to thank all the authors, coeditors, and reviewers who contributed to the preparation of the book.

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# 1

# OVERVIEW OF RISK-BASED APPROACH TO PHASE APPROPRIATE VALIDATION AND INSTRUMENT QUALIFICATION

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## 1 RISK-BASED APPROACH TO PHARMACEUTICAL DEVELOPMENT

In the United States, the U.S. Food and Drug Administration (FDA) ensures the quality of drug products using a two-pronged approach involving review of information submitted in applications as well as inspection of manufacturing facilities for conformance to requirements for current good manufacturing practice

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(cGMP). In 2002, the FDA, together with the global community, implemented a new initiative, "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach" to evaluate and update current programs based on the following goals:

- The most up-to-date concepts of risk management and quality system approaches are incorporated while continuing to ensure product quality.
- The latest scientific advances in pharmaceutical manufacturing and technology are encouraged.
- The submission review program and the inspection program operate in a coordinated and synergistic manner.
- Regulatory and manufacturing standards are applied consistently.
- FDA resources are used most effectively and efficiently to address the most significant issues.

In the area of analytical method validation and instrument performance qualification, principles and risk-based orientation, and science-based policies and standards, are the ultimate driving forces in a risk-based approach to these activities.

1. *Risk-based orientation*. To comply with the new guiding regulatory principle to provide the most effective public health protection, regulatory agencies and pharmaceutical companies must match their level of effort against the magnitude of risk. Resource limitations prevent uniform intensive coverage of all pharmaceutical products and production.
2. *Science-based policies and standards*. Significant advances in the pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. Although this knowledge has been incorporated in an ongoing manner, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.

Related directly or indirectly to implementation of the risk-based approach to pharmaceutical quality, the following guidance affecting the analytical method and instrument qualification had been either initiated or implemented.

*FDA 21 Code of Federal Regulations (CFR) Part 11: Electronic Records Requirements*. The final guidance for industry Part 11, Electronic Records, Electronic Signatures: Scope and Application, clarifies the scope and application of the Part 11 regulation and provides for enforcement discretion in certain areas. The guidance explains the goals of this initiative, removes

barriers to scientific and technological advances, and encourages the use of risk-based approaches.

*ICH (International Conference on Harmonization) Q9: Risk Management*. The goal of the guidance is to manage risk to patients, based on science, from information on the product, process, and facility. The level of oversight required is commensurate with the level of risk to patients and the depth of product and process understanding.

*FDA Guidance for Industry PAT: A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*. This guidance is intended to encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance technologies. The scientific, risk-based framework outlined in this guidance, process analytical technology (PAT), helps pharmaceutical manufacturers design, develop, and implement new and efficient tools for use during product manufacture and quality assurance while maintaining or improving the current level of product quality assurance. It also alleviates any concerns that manufacturers may have regarding the introduction and implementation of new manufacturing technologies.

*FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations*. One of the objectives of this guidance is to provide a framework for implementing quality by design, continual improvement, and risk management in the drug manufacturing process.

*FDA Guidance for Industry INDs: cGMP for Phase 1 Investigational Drugs*. This guidance recommended that sponsors and producers of phase 1 material consider carefully risks in the production environment that might adversely affect the resulting quality of an investigational drug product.

Implementation of a risk-based approach to analytical method validation and performance verification should be done simultaneously and not in isolation. It is only through a well-thought-out plan on the overall laboratory system of instrument performance verification that quality data for analytical method validation will be obtained. The laboratory will subsequently be able to support the manufacture of either clinical trial materials or pharmaceutical products for patients. Details of risk-based approaches to phase appropriate analytical method validation and performance verification are presented in subsequent chapters.

## 2 REGULATORY REQUIREMENTS FOR PERFORMANCE VERIFICATION OF INSTRUMENTS

System validation requirements are specified in many different sources, including 21 CFR Part 58 [good laboratory practice (GLP)], 21 CFR Parts 210 and 211 (cGMP) [1], and more recently, in the GAMP 4 guide [2]. GLP, and GMP/cGMP are often summarized using the acronym GXP. Current GXP regulations require