Preface

In August 2002, the Food and Drug Administration (FDA) launched a significant initiative, "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century." This initiative, coupled with other subsequent regulatory publications, including ICH Q8–Q11, ushered in a risk-based and life cycle approach to process and product development. The initiative encourages manufacturers to capitalize on new technological advances and adopt risk-based approaches and quality system techniques. An increased emphasis has been placed on product and process understanding. This includes understanding the mechanism of action of the product, its safety profile, variability of raw materials, bulk and finished products, analytical method variations, relationships between process parameters and the product's critical quality attributes (CQAs), and the impact of CQAs on clinical responses and product quality. This enhanced product and process knowledge not only enables product quality to be built by design but also provides a basis for the development of robust control strategies.

A holistic approach, QbD begins in development and continues throughout the manufacturing life cycle. It involves defining desired clinical performance, identifying CQAs that have an impact on clinical outcomes, determining necessary raw material attributes and manufacturing process parameters to achieve the desired product attributes, and designing manufacturing controls to ensure consistent manufacturing. Furthermore, QbD enhances development capability, shortens development speed, and enables robust manufacturing. It also helps proactively prevent manufacturing failures. An additional benefit of QbD is that, in certain instances, it enables a manufacturer to make postapproval changes and scale-up operations without prior approval from regulatory authorities.

However, despite the plethora of opportunities to reduce manufacturing costs while ensuring product quality, implementation of QbD is often very challenging because of the large number of variables to consider, interactions among the variables, uncertainties in measurements, and missing data involved in product and process development. Such intrinsic complexities argue for advanced statistical methods in both study design and analysis. In fact, the preceding guidelines specifically call for use of such statistical tools. For example, ICH Q8 recommends the use of design of experiments (DOE) to aid the development of a design space, which is defined as the "multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." The successful determination of a design space makes continued process improvements within the design space possible, without overly regulatory oversight. Furthermore, the FDA guidance on Process Analytical

Technology specifically cites the use of multivariate tools for study design, data acquisition, and data analysis to aid quality assessment. In addition, the 2011 FDA process validation guidance recommends the use of a broad array of statistical tools, including DOE, acceptance sampling, multivariate modeling, and statistical process control. It has been widely recognized by both pharmaceutical manufacturers and regulators that novel statistical methods are key to delivering on the promise of the new pharmaceutical development paradigm.

In recent years, statistical science has made significant inroads in advancing the new product and process development paradigm and quality initiatives. As the entire pharmaceutical industry is adopting a QbD approach, statistics is likely to continue to play a central role in realizing the full benefits of QbD. However, no book so far has been written to discuss the QbD-related statistical advances. As such, a single book covering important biopharmaceutical development issues, relevant regulatory requirements, and associated statistical solutions would provide an invaluable resource for practitioners in biopharmaceutical development and manufacturing.

Drawing from the author's extensive drug research and development experience and published statistical works, this book is intended to provide a single source of information on emerging statistical approaches to QbD and risk-based pharmaceutical development. It combines in-depth explanations of advanced statistical methods with real-life case studies that illustrate practical applications of these methods in QbD implementation. The book is divided into four sections, consisting of a total of 12 chapters. Each chapter begins with a summary of the scientific issues, related regulatory requirements, and pitfalls of statistical methods either currently in use or recommended in regulatory guidance, followed by an introduction to and discussion of the advantages of the emerging statistical techniques used to address the scientific questions. The use of the statistical methods in practice is further illustrated through case studies. Each chapter concludes with a summary of key points and directions for possible extension and new applications of the statistical methods in future research. A brief description of each chapter follows:

Section I (Chapter 1) provides a background about the evolution of regulatory thinking and industry practice from "testing into compliance" to QbD. The chapter highlights challenges associated with the implementation of QbD and related statistical opportunities.

Section II (Chapters 2 through 4) is devoted to discussions of various statistical advances in analytical method development and validation, notably with focus on the validation of accuracy and precision, parallelism testing for bioassay, and validation of assay linearity.

Chapter 2 discusses a formal statistical framework for the validation of analytical methods, using QbD principles. The use of total error to control the risk of incorrect decision-making is summarized, including a new statistical

method based on the total error concept; the performance of the new method is compared with other statistical methods conventionally used.

Chapter 3 is concerned with an important issue of bioassay, namely, parallelism testing. Parallelism is a prerequisite for the estimation of relative potency in many bioassays. Implicit in parallelism is that the test sample is a dilution of the reference standard. In this chapter, various parallelism test methods are evaluated through simulation and receiver operating characteristic analysis. A new Bayesian test method, which overcomes the shortcomings of the current statistical approaches, is also discussed.

In Chapter 4, we focus on current statistical practices and emerging statistical methods in the validation of linearity, a key characteristic of analytical methods. Central to the discussion is a new equivalence test that compares the quality of a linear fit to that of a higher-order polynomial. By using orthogonal polynomial regression and generalized pivotal quantity analysis, the method allows for estimation of the probability of equivalence in either the assay response space or the dose concentration space. In addition, a simpler and more practical but theoretically rigorous alternative is also presented.

Section III (Chapters 5 through 8) concentrates on four major scientific issues related to biopharmaceutical process development, validation, and verification.

Chapter 5 concerns the assessment of oncogenicity and infectivity risk. It is well known that biological products manufactured in cells contain residual DNA derived from host cell substrates. Therefore, it is theoretically possible that the residual DNA could transmit activated oncogenes or latent infectious viral genomes to subjects receiving the product and induce oncogenic or infective events. A probabilistic model to estimate the risks due to residual DNA is discussed. The model takes into account the enzyme inactivation process and allows for more accurate risk assessment when compared to statistical methods currently in use. An application of the method to determine the safety factor for a vaccine product is provided as a case study. The model is further applied to establish acceptable limits of residual DNA that may differ from the current regulatory specifications. An extension of the proposed statistical method based on Bayesian inference is also discussed.

Chapter 6 discusses novel statistical methods in evaluating results of viral clearance studies. Statistical methods robust to both missing data and zero viral counts post process are presented along with results of simulation studies conducted to compare the performance of the current and new methods. These results provide practical guidance on the selection of statistical methods for assessing purification process capability.

In Chapter 7, we introduce a risk-based statistical approach to establishing prefiltration bioburden acceptance limits and alternative test volumes. The relationship between bioburden risk, prefiltration bioburden test limits, and sterile filtration process parameters, such as filtration volume, filter surface area, and microbial retention capacity of the sterilizing filter, is established

through statistical modeling. The method provides a sound rationale for justifying prefiltration bioburden test volumes and acceptance limits, as an alternative to the regulatory limit (10 colony-forming units/100 mL), without compromising sterility assurance.

Chapter 8 is dedicated to the latest statistical developments in adopting QbD principles in the life cycle approach to process validation. Various multivariate statistical methods to model relationships between process parameters and CQAs, to link CQAs to clinical responses, and to define a design space and set specifications are introduced and illustrated through examples. Also included in this chapter are methods for addressing key issues such as the number of lots used for process performance quantification and monitoring strategies for large dimensional data, with interdependent responses.

Section IV (Chapters 9 through 12) is devoted to quality control and assurance in manufacturing, in order to fulfill the requirements of the FDA's cGMPs. These chapters cover a wide range of important GMP topics, including specifications, environmental monitoring, stability study design and analysis, and the investigation of out-of-specification results.

Chapter 9 focuses on setting specifications for drug products, which are quality standards providing assurance that the product is fit for its intended use. While quality attributes may be correlated, specifications are often determined without taking into account any such interdependencies. Such practice may result in specifications that are narrower than the actual acceptable ranges of product performance, thus causing unnecessary out-of-specification investigations. Through multiple case studies, the chapter discusses how this issue can be avoided using multivariate statistical modeling and other advanced statistical techniques such as generalized pivotal quantity analysis.

Chapter 10 discusses statistical methods for trending environmental data of classified rooms. By modeling the excess of zeroes and overdispersion, caused by sampling population heterogeneity, the proposed statistical methods provide a clear improvement over the traditional approaches. Additionally, a new approach to constructing multivariate control charts for cleanroom environmental monitoring is presented.

Chapter 11 introduces a statistical framework for the evaluation of various commonly used shelf life estimation methods. In addition, through several case studies, it describes how novel statistical methodologies such as Arrhenius modeling, simulation, and Bayesian analysis can be effectively used in stability testing to achieve both quality assurance and cost reduction objectives.

Finally, Chapter 12 discusses current and new statistical methods for out-of-specification (OOS) result investigations and out-of-trend (OOT) result identification. Despite improved regulatory clarity on OOS investigations, how OOS results are evaluated and batches disposed continues to be a leading cause of warning letters issued by the FDA. Numerous working practices and various degrees of understanding of current expectations in this

area have led to many different statistical approaches to investigating OOS results. In this chapter, statistical methods for OOS investigation that represent good science and conform to current regulatory guidelines are presented. In addition, various statistical methods for identifying OOT results are also included in the chapter.

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