WILEY SERIES IN BIOTECHNOLOGY AND BIOENGINEERING

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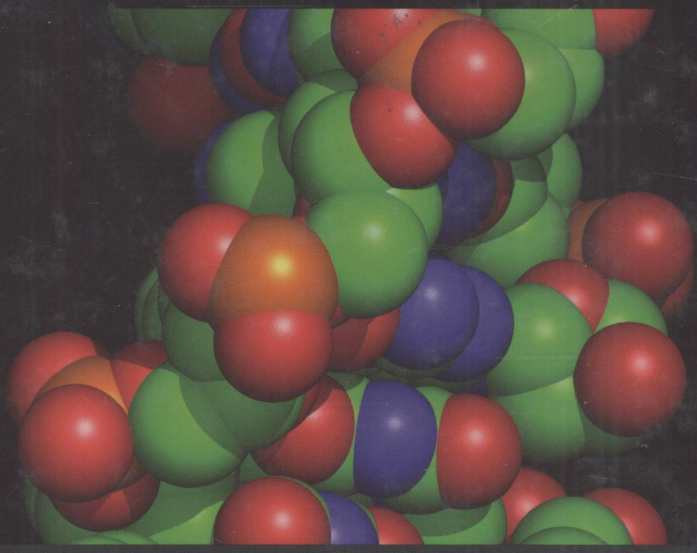
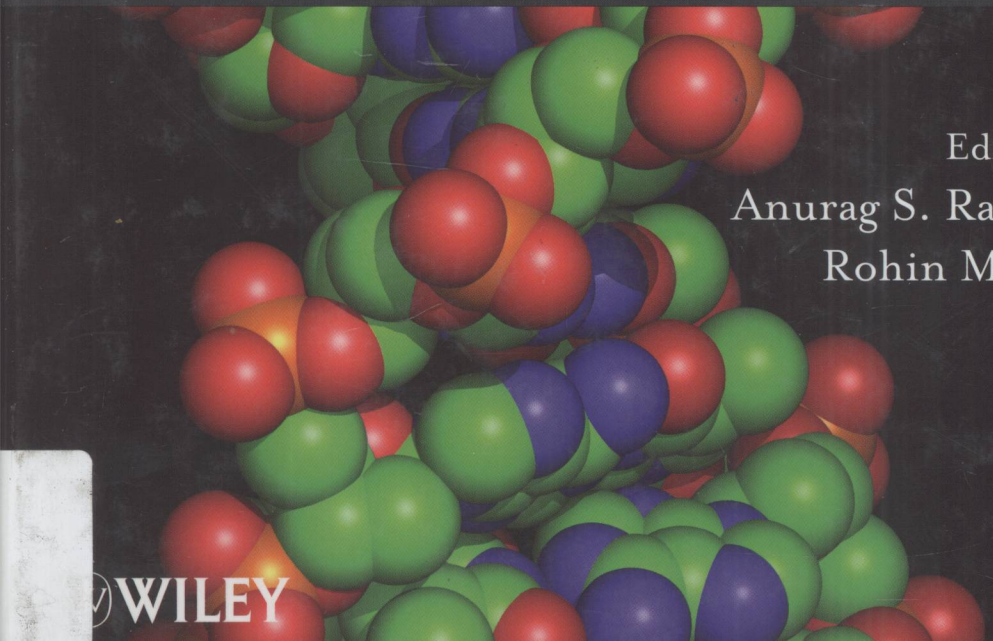


QUALITY BY DESIGN for BIOPHARMACEUTICALS

PRINCIPLES AND CASE STUDIES



Edited by
Anurag S. Rathore
Rohin Mhatre

WILEY

QUALITY BY DESIGN FOR BIOPHARMACEUTICALS

Principles and Case Studies

Edited by

Anurag S. Rathore and Rohin Mhatre

WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Rathore, Anurag S. (Anurag Singh); 1973-
Quality by design for biopharmaceuticals : principles and case studies / by Anurag S. Rathore and Rohin Mhatre.
p. cm.
Includes index.
ISBN 978-0-470-28233-5 (cloth)
1. Pharmaceutical biotechnology–Quality control. I. Mhatre, Rohin. II. Title.

RS380.R38 2009
615'.19–dc22

2008045484

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

QUALITY BY DESIGN FOR BIOPHARMACEUTICALS

To our family:
Bhawana, Payal, Parul, and Jyoti

FOREWORD

These are truly exciting times to be involved in the development of biopharmaceutical products. As the research community expands our understanding of the biological basis of health and disease, those who turn this knowledge into medical treatments are providing safer and more effective health care options. Over the relatively short history of biologically derived drugs, this trend is clearly apparent. The first biological products to be developed were natural products such as antisera and hormones purified directly from animal tissues. The development of hybridoma technology in the 1980s allowed the preparation of monoclonal antibody products and significantly reduced the structural variability characteristic of polyclonal antibody products. The molecular purity of these products allowed them to be extremely well characterized and also led to a much better understanding of the biological activities of their structural features. Subsequently, the application of recombinant DNA technology to biopharmaceutical development has allowed manufactures to design proteins with specific structural and functional characteristics that give them desired beneficial therapeutic properties and reduce their potential adverse reactions.

These changes in product development and expression system technology have driven, and relied upon, parallel advances in the manufacturing sciences. Biopharmaceutical manufacturers have always been faced with the challenges of finding ways to make living systems produce proteins with desired characteristics, purifying them from complex mixtures with economically feasible yields, and formulating them in to stable, medically useful products. These challenges are compounded by the variabilities in raw material quality, equipment components, environment within the manufacturing facility, and capabilities of operators. As those who have struggled with these issues know so well, the quality of biological products depends to a large extent on the design and control of the manufacturing process.

It is crucial to public health that the drugs upon which we depend are safe, efficacious, and of consistent high quality. Safety and efficacy determinations are based on toxicological data, clinical study results, and postmarketing evaluation-based performance. Because the quality of a drug product can have a major impact on its clinical performance, successful drug development and manufacturing must focus on quality. In this regard, the concept of quality is twofold. One aspect of product quality is the design of the drug itself as defined by specification of the characteristics it needs to have to treat a disease. This includes the structure of the pharmaceutically active molecule itself, as well as the formulation and delivery system that allow the therapeutic to reach its target. The other aspect of quality is the consistency with which the units of a batch or a lot of product

meet the desired specifications. As was alluded to earlier, within-batch variability and batch-to-batch variability depend, to a large extent, on the quality of the raw materials and the design of the manufacturing process and its control systems. Incorporation of these two aspects of quality into product and process development is the essence of quality by design.

To realize the full benefits of quality by design, one must develop a thorough understanding of the interrelationship between the attributes of the input materials, the process parameters, and the characteristics of the attribute of the input materials, the process parameters, and the characteristics of the resultant products. With this information in hand, it is possible to manufacture with a very high degree of assurance that each unit of product will have the desired quality. Of particular note in this regard is the quality control system known as process analytical technology (PAT) that has been applied with great success to manufacturing operations outside of the pharmaceutical industry. A cornerstone of PAT is the use of rapid analytical techniques and process control systems to monitor and control product quality during manufacturing. In 2004, the FDA published guidance for industry on PAT[1] to encourage the development and implementation of the agency's "Product Quality for the 21st Century Initiative," as PAT can provide the assurance of quality in a flexible manufacturing environment conducive to streamlined implementation of innovative technologies. The use of correlated metrics of quality, such as bioreactor conditions, within the process control system is quite familiar to biopharmaceutical manufacturers. However, future strides in rapid, real-time analytical technologies promise to make direct control of product quality during manufacturing a reality and open the door to efficiencies such as continuous processing and real-time release.

As biotechnology moves ahead, the concepts of William Edwards Deming and others that quality must be built into products will continue to be applied to the design of novel products and dose delivery systems as well as to the design and engineering of more effective and reliable manufacturing methods. Technological advances in this field will undoubtedly occur in an evolutionary manner, with successful systems serving as the foundation of even more valuable systems. However, this steady progression will, nearly as surely, be punctuated by revolutionary discoveries of magnitudes equal to hybridoma technologies that introduced monoclonal antibody production or the polymerase chain reaction that has made genetic engineering a relatively facile process. To ensure that we have the safest and most efficacious medications to treat today's disease, and those of tomorrow, we must not only continue developing innovative products and technologies but also take them to the manufacturing plant and the marketplace as quickly as possible. The sharing of ideas, information, and experience through books such as this is essential to the success of this endeavor.

Keith O. Webber
Deputy Director, Office of Pharmaceutical Safety, Food and Drug Administration

[1]FDA Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (September 2004).

PREFACE

Quality by Design (QbD) is receiving a lot of attention in both the traditional pharmaceutical and biopharmaceutical industries subsequent to the FDA published "Guidance for Industry: Q8 Pharmaceutical Development" in May 2006. Key challenges in successfully implementing QbD are requirements of a thorough understanding of the product and the process. This knowledge base must include understanding the variability in raw materials, the relationship between the process and the critical quality attributes (CQAs) of the product, and finally relationship between the CQA and the clinical properties of the product. This book presents chapters from leading authorities on a variety of topics that are pertinent to understanding and successfully implementing QbD.

Chapter 2 by Kozlowski and Swann provides a summary of QbD and related regulatory initiatives. Approaches to relevant product quality attributes and biotechnology manufacturing have been discussed along with some thoughts on future directions for biotechnology products.

Chapter 3 by Narum presents a case study where QbD principles have been applied to make significant improvements in the capacity of recombinant expression systems to produce malarial proteins by introducing synthetic genes for *Pichia pastoris* as well as *Escherichia coli*. It is shown that the use of synthetic genes not only makes possible the expression of a particular protein but also allows the gene designer to make appropriate modifications to increase product quantity and quality.

In Chapter 4, Schenerman et al. present a risk assessment approach for the determination of the likelihood and extent of an impact of a CQA on either safety or efficacy. Examples are used to illustrate how nonclinical data and clinical experience can be used to define the appropriate risk category for each product quality attribute. The attribute classifications then serve as a rationale for product testing proposals, associated specifications, and process controls that ensure minimal risk to product quality.

Chapter 5 contributed by Hoek et al. presents a case study involving a cell culture step. All operational parameters were examined using a risk analysis tool, failure mode and effects analysis (FMEA). The prioritized parameters were examined through studies planned using design of experiments (DOEs) approach. Qualified scale-down models were used for these studies. The results were analyzed to create a multivariate model that can predict variability in performance parameters within the "design space" examined in the studies. The final outcome of the effort was identification of critical and key operational parameters that impact the product quality attributes and/or process consistency, respectively, along with their acceptable ranges that together define the design

space. Chapters 6 and 7 define approaches to establishing design space for a filtration and chromatography unit operation, respectively.

Sofer and Carter present a strategy in Chapter 8 for applying QbD principles for virus clearance. It is concluded that implementation of the proposed strategy will require an extended and coordinated effort, primarily by manufacturers and regulators. The mutual investment in moving to a QbD approach holds promise of better understood, and therefore better controlled, unit operations. The QbD design space describes a full range of manufacturing conditions within which changes may be made with relative ease and modest regulatory oversight, freeing both manufacturers and regulators' limited resources. Intrinsically, enhanced process control and process understanding represents a benefit to the patient population.

Chapter 9 by Ng and Rajagopalan presents the different considerations to remember while designing a formulation process. Some of the key steps include identification of target commercial drug product profile; preformulation and forced degradation studies to characterize molecular stability properties, impact of formulation variables, and other factors; preliminary stability risk assessment with emphasis on direct impact on the activity based on preformulation and forced degradation studies results; initial formulation risk assessment to establish the cause–effect relationship of different factors and solution formulation stability via Ishikawa (Fishbone) diagram; multivariate DOE studies to optimize the formulation composition and define a robust design space to meet the expected shelf life of 24 months at 5°C; establishing formulation design space based on DOE results and stability properties projections; and finally selection of commercial solution formulation based on design space, molecule knowledge, and risk assessment.

In Chapter 10, Singh et al. present case studies illustrating a systematic work process for application of risk-based approaches to formulation development for biologics.

Lannan addresses the application of multivariate data analysis (MVDA) to analysis of raw materials in Chapter 11.

Chapter 12 by Molony and Undey provides a review of various PAT tools and applications for the biopharmaceutical industry. Finally, Chapter 13 by Low and Phillips provides the background for PAT and also how it relates to QbD.

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Thousand Oaks, California
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March 2009

PREFACE TO *THE WILEY SERIES ON BIOTECHNOLOGY AND RELATED TOPICS*

Significant advancements in the fields of biology, chemistry, and related disciplines have led to a barrage of major accomplishments in the field of biotechnology. The *Wiley Series on Biotechnology and Bioengineering* focuses on showcasing these advances in the form of timely, cutting-edge textbooks and reference books that provide a thorough treatment of each respective topic.

Topics of interest to this series include, but are not limited to, protein expression and processing; nanotechnology; molecular engineering and computational biology; environmental sciences; food biotechnology, genomics, proteomics, and metabolomics; large-scale manufacturing and commercialization of human therapeutics; biomaterials and biosensors; and regenerative medicine. We expect these publications to be of significant interest to the practitioners both in academia and industry. Authors and editors are carefully selected for their recognized expertise and their contributions to the various and far-reaching fields of biotechnology.

The upcoming volumes will attest to the importance and quality of books in this series. I thank the fellow coeditors and authors of these books for agreeing to participate in this endeavor. Finally, I thank Ms Anita Lekhwani, Senior Acquisitions Editor at John Wiley & Sons, Inc., for approaching me to develop such a series. Together, we are confident that these books will be useful additions to the literature that will not only serve the biotechnology community with sound scientific knowledge but will also inspire them as they further chart the course of this exciting field.

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January 2009

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1

QUALITY BY DESIGN: AN OVERVIEW OF THE BASIC CONCEPTS

Rohin Mhatre and Anurag S. Rathore

1.1 INTRODUCTION

The premise of Quality by Design (QbD) is that the quality of the pharmaceutical product should be based upon the understanding of the biology or the mechanism of action (MOA) and the safety of the molecule [1]. The manufacturing process should then be developed to meet the desired quality attributes of the molecule, hence the concept of "design" of the product quality versus "testing" the product quality. Although testing the product quality after manufacturing is an essential element of quality control, testing should be conducted to confirm the predesired product attributes and not to simply reveal the outcome of a manufacturing process. The ICH Q8 guideline provides an overview of some of the aspects of QbD [2]. The guideline clearly states that *quality cannot be tested into products*; that is, *quality should be built in by design.*

Although the task of designing a complex biological molecule such as a monoclonal antibody may seem daunting, the experience gained in the past roughly 30 years of the biotechnology industry history has laid the foundation for the QbD initiative [3, 4]. The industry has come a long way in identifying and selecting viable drug candidates, in developing high-productivity cell culture processes, in designing purification processes that yield a high-purity product, and in analyzing the heterogeneity of complex

Quality by Design for Biopharmaceuticals, Edited by A. S. Rathore and R. Mhatre