QUALITY BY DESIGN FOR BIOPHARMACEUTICALS

Principles and Case Studies

Edited by

Anurag S. Rathore and Rohin Mhatre

WILEY

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

CONTENTS

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,
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[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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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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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

biomolecules. As all these activities are the building blocks of QbD, the concept of QbD has in fact been practiced for the last few years and has in turn led to the development of highly efficacious biopharmaceuticals and robust manufacturing processes. The issuance of the ICH Q8 guideline was an attempt to formalize the QbD initiative and to allow manufacturing flexibility based on the manufacturer's intricate knowledge of the molecule and the manufacturing process. The concept of obtaining intricate knowledge of the molecule along with the manufacturing process and the resulting flexibility in manufacturing, the eventual goal of the QbD initiative, requires an understanding of the various elements of QbD.

The two key components of QbD are [4]

1. The understanding of the *critical quality attributes* (CQAs) of a molecule. These are the attributes of the molecule that could potentially affect its safety and efficacy profile.
2. The *design space* of the process defined as the range of process inputs that help ensure the output of desired product quality.

An overview of these components is discussed further in this chapter and elsewhere in this book.

1.2 CRITICAL QUALITY ATTRIBUTES

The starting point of QbD is developing a good understanding of the molecule itself. Biomolecules are quite heterogeneous due to the various post-translational modifications that can occur and have been commonly observed. These modifications arise from the glycosylation, oxidation, deamidation, cleavage of labile sites, aggregation, and phosphorylation, to name a few. As many of these modifications could impact the safety and efficacy of the molecule, defining the appropriate CQAs of the molecule is an important starting point in the development cycle of a biopharmaceutical. Although the understanding of the CQAs evolves during the life cycle of the product, understanding the CQAs at an early stage of the development of the molecule is clearly desirable. Studies conducted during the early research stages of development of a potential biopharmaceutical may entail evaluating various forms of a particular biomolecule in animal studies. The outcomes of such studies help "design" a biomolecule with the desired quality attributes so as to be safe and highly efficacious.

Since the CQAs can impact the safety and clinical efficacy of a molecule, data gathered in animal studies, toxicological studies, and early human clinical trails become the starting point for defining the CQAs. On the basis of the safety and efficacy readout of a clinical trial, one can start to define the product profile of a molecule. The assumption is that if the CQAs of the molecule are similar to those used in preclinical and clinical trials, the safety and efficacy will be comparable as well. Furthermore, historical data from clinical trials of similar molecules can also provide valuable insight into the CQAs. Evaluation of the *in vitro* biological activity via bioassays, reflecting the mechanism of action, can provide a good assessment of how the various product attributes could

potentially impact the *in vivo* activity of a molecule. The molecule can be altered by conducting stress studies to induce higher level of aggregation; oxidation, deamidation, and the glycosylation pattern can be varied as well. The impact of changes in the molecular structure on the biological activity can then be evaluated via various bioassays. This study is referred to as structure–activity relationship. The evaluation of *in vitro* activity is often the relatively easiest means of determining the CQAs. However, *in vitro* assessments can only provide an understanding of the potential changes in the activity of the molecule, and the correlation between this change in activity and the impact of efficacy in patients is often unclear. Further assessment of the molecule in animal studies to evaluate clearance, efficacy, and safety is often a good indicator of the behavior of the molecule in human trials and is a better tool for understanding the CQAs. Additional details of the determination of the CQA can be found in Chapter 4.

1.3 AN OVERVIEW OF DESIGN SPACE

After defining the CQAs, the next and more critical step is the development of a manufacturing process that will yield a product with the desired CQAs [4, 5]. During the process development, several process parameters are routinely evaluated to assess how they could impact product quality [6]. The design space for the process eventually evolves from such a study. For example, during the cell culture development, ranges for process inputs such as temperature, pH, and the feed timing can be evaluated to determine if operating within a certain range of temperature and pH has an impact on product quality. The design of experiments (DOE) is conducted in a manner so as to evaluate the impact of the multiple variables (multivariate) and also to understand if and how changes in one or more of the process inputs have an effect on the product quality and/or if a process input is independent of changes in other inputs.

The design space (process range) is then established for each of the above process inputs. This can be further explained using an example of a design space for a purification column. If a column used to purify a protein is expected to reduce the level of protein aggregate to 2%, the various column operating parameters such as flow rate, pH and strength of the buffer, load volume, and so on are evaluated such that operating within a certain range of these parameters yields an aggregate level of less than or equal to 2%. If it turns out that pH above 6 or below 4 results in aggregate levels above 2%, then the design space for the pH of the buffer is defined as between 4 and 6. One can similarly envision a design space for the flow rate and other inputs for the particular purification step. Eventually, the entire production process for a molecule will have a defined design space, and operating within that design space should lead to a product of acceptable quality. Operating beyond the design space of a particular process input may result in an unacceptable product quality.

Since the production process for a biomolecule entails multiple steps starting from the cell culture process to the final purification and eventually to the formulation and fill in the desired container, the development of a design space for a particular step is not usually independent of other steps in the production process. Since the output of one step becomes the input for the next step, the development of the design space for a process

should be evaluated in a holistic manner. One such approach may be to determine the desired product quality from the final process step and to work backward in the process to ensure that each step of the process delivers the required product quality needed for the next step to meet the quality target of the final step. To provide an example of this approach, we can revisit the above example of a desired level of 2% aggregate in the final drug product. In this particular case, design space should be developed for all parameters of the production process that can potentially impact the level of aggregate in the final drug product. The maximum level of aggregate resulting from each of the steps in the process does not need to be less than 2%, particularly steps that are upstream in the process such as the protein A purification, the first columns used in the purification of an antibody. The development of the design space including the design of experiments is discussed in detail in Chapters 5–7.

1.4 RAW MATERIALS AND THEIR IMPACT ON QbD

In addition to the design space and CQAs, other factors also play an important role in implementing QbD, and raw material is one such factor. Cell culture processes used to make recombinant proteins use complex growth media such as hydrosylates and also feeds such as vitamins for the cell. The understanding of how the various components of these complex raw materials affect the productivity of the cells and the quality of the product is not a trivial task. It requires a thorough analysis and quantitation of the various components of the raw material. Raw material analysis and correlation between raw material components and the productivity of cells and product quality is an area that has not been sufficiently explored by the biotechnology industry. However, the evolution of instruments such as high-resolution nuclear magnetic resonance spectroscopy, near infrared spectroscopy, and mass spectrometry has provided an opportunity to analyze complex mixtures of raw materials. In addition, the availability of sophisticated statistical tools for deconvolution and pattern matching of complex data sets has further refined the approach to analyzing raw materials. Once the correlation between the critical components of the growth or feed media and the performance of cells is understood, the ultimate goal of raw material analysis in the context of QbD would be to fortify the media as needed with the relevant component so as to ensure the desired productivity and product quality. Further details of analysis of complex raw materials are provided in Chapter 11.

1.5 PROCESS ANALYTICAL TECHNOLOGY

Since one of the goals of QbD is to maintain control of the process to achieve the desired product attributes, process analytical technology (PAT) is an important tool for QbD. PAT entails analysis of product quality attributes during the various stages of the manufacturing process of a biomolecule. The analysis is often conducted online using either probes inserted into the bioreactor to monitor critical components such as the cell density or sterile sampling devices to divert the stream from a purification column to assess the

product purity [7]. In either case, the online analysis enables operators on the manufacturing floor to make real-time adjustments to the process parameters so as to obtain the desired product profile at every stage of the manufacturing process. For example, a PAT tool to monitor a purification column would entail periodically sampling the elution stream from the column via a sampling device and diverting the sample to an online HPLC system [8]. The results of the online HPLC analysis, indicative of the product purity, would be used to determine the eluate volume that should be collected. In this particular example, the fraction of the eluate of purity below a predetermined criterion would provide a trigger to stop collection of the eluate and to divert the elution stream to waste. The advantage of such a PAT tool would be that the collection of the column eluate would be based on the required product purity and would help to ensure a consistent product quality for every production batch of the biomolecule [8]. Further applications of PAT can be found in Chapters 12 and 13.

1.6 THE UTILITY OF DESIGN SPACE AND QbD

Prior to development of the design space, the questions to ask are the following: How would the design space be used? What is the advantage for a company of developing a design space for any of its products? What would be the driver for regulatory agencies to promote the concept of design space and QbD?

As seen in Fig. 1.1, limits that establish the acceptable variability in product quality and process performance attributes would also serve as the process validation acceptance criteria [4, 5]. After the design space has been established, the regulatory filing would include the acceptable ranges for all key and critical operating parameters (i.e., design space) in addition to a more restricted operating space typically described for pharmaceutical products. After approval, CQAs would be monitored to ensure that the process is performing within the defined acceptable variability that served as the basis for the filed design space. The primary benefit of an expanded design space would be a more flexible approach by regulatory agencies. Process changes are often driven by changes in the manufacturing equipment and raw materials, to name a few. At present, changes in the process require formal filings and approvals from regulatory agencies and often require a significant commitment of both time and resources for the industry and the regulatory agencies. The outcome of the design space development (as stated in the ICH Q8 guideline) would be that upon the approval of the design space for a particular product by a regulatory agency, process changes within the design space would not require additional regulatory filing and approval. This shift in the paradigm of using enhanced process knowledge to enable process changes with a limited burden of regulatory approval is clearly beneficial to both the manufacturer and the regulatory agencies. Chapter 2 further reviews the regulatory relief and implications of the QbD initiative.

Process improvements during the product life cycle with regard to process consistency and throughput could take place with reduced postapproval submissions. As manufacturing experience grows and opportunities for process improvement are identified, the operating space could be revised within the design space without the need

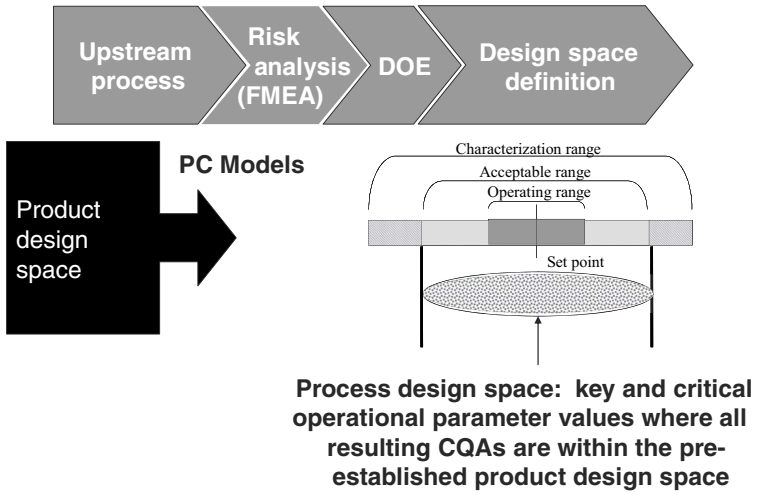

Figure 1.1. Illustration of the creation of process design space from process characterization studies and its relationship with the characterized and operating spaces. The operating range denotes the range in the manufacturing procedures and the characterization range is the range examined during process characterization. The acceptable range is the output of the characterization studies and defines the process design space. Adapted from Ref. [5], by permission of Advanstar Communications.

for postapproval submission. This is illustrated in Fig. 1.2, which shows that if the process creeps outside the design space, process changes may be required to be made and may require process characterization, validation, and filing of the changes to the approved process design space.

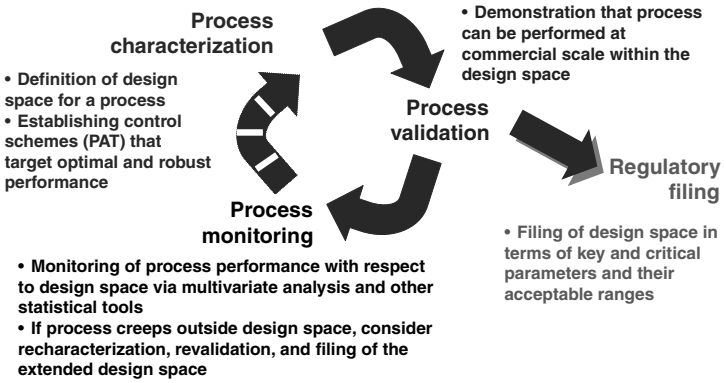

Figure 1.2. Application of the design space concept in process characterization, validation, monitoring, and regulatory filing. Adapted from Ref. [5], by permission of Advanstar Communications.

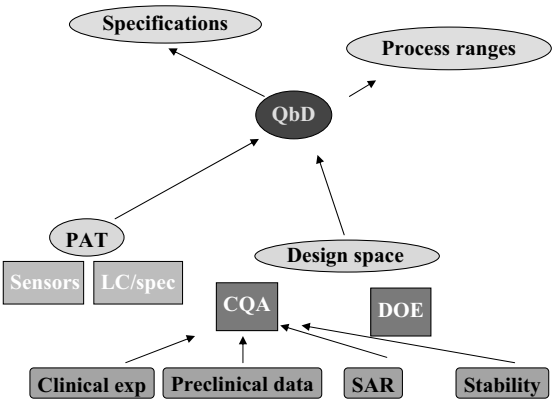

Figure 1.3. The various elements of QbD. The boxes in the bottom row show all the relevant information that is used to develop the critical quality attributes. The CQA and DOE data are then used to develop the design space. The design space and PAT tools help establish QbD.

1.7 CONCLUSIONS

Figure 1.3 depicts the various components of QbD discussed above and the correlation between the various components. As shown in the figure, the outcome of the QbD exercise is the establishment of the design space for the process and the operating ranges (ORs) that help achieve the desired product quality. As mentioned earlier, the reader is referred to the various sections of the book to gain further understanding of the various aspects of QbD. The editors hope that this book will help establish a good framework for any researcher to build Quality by Design into a manufacturing process for a biomolecule.

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2

CONSIDERATIONS FOR BIOTECHNOLOGY PRODUCT QUALITY BY DESIGN

Steven Kozlowski and Patrick Swann

2.1 INTRODUCTION

In August 2002, the Food and Drug Administration (U.S. FDA) announced a significant new initiative, pharmaceutical Current Good Manufacturing Practices (CGMPs) for the twenty-first century [1]. This initiative is intended to enhance and modernize pharmaceutical manufacturing and product quality. Specific areas of focus include facilitating industry adoption of risk-based approaches, technological advances, and modern quality management techniques. As part of this initiative, the FDA will use state-of-the-art pharmaceutical science in developing review, compliance, and inspection policies and will coordinate these activities under a quality systems approach.

Concurrently with the CGMPs for the twenty-first century initiative, process analytical technology (PAT), a system to improve pharmaceutical manufacturing was being discussed at the advisory committee of the Office of Pharmaceutical Science at CDER and at the FDA Science Board [2].

Process Analytical Technology is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality [3]. In 2004, the FDA published guidance on PAT [4] that

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described multivariate tools for design, data acquisition and analysis, process analyzers and controllers, continuous improvement, and knowledge management tools.

Systematic approaches to pharmaceutical manufacturing may be of benefit even if they do not use each of these specific tools. Although PAT may allow for greater flexibility, manufacturing may still be improved in the absence of real-time analysis of material attributes and without real-time linkage to process control. The term Quality by Design (QbD) [5, 6] is used to describe a more general approach to systematic pharmaceutical manufacturing. As described by Dr. Janet Woodcock, the desired state that drives all these manufacturing initiatives is a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight [7].

Over the last few years, there has been significant progress in moving forward with these initiatives for small molecules, including a pilot program for QbD submissions [8]. However, biotechnology products are a growing part of the drug development pipeline [9]. It is important to consider how to approach the "desired state" for more complex products, such as biotechnology products. The principles of Quality by Design should be applicable to all pharmaceuticals including biotechnology products [10].

2.2 QUALITY BY DESIGN

Quality by Design is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management [11]. Dr. Moheb Nasr has summarized QbD in a diagram [12] (Fig. 2.1). A systematic approach to pharmaceutical development should start with the desired clinical performance and then move to product design. The desired product attributes should then drive the process design, and the process design should drive the strategies to ensure process performance. This systematic approach may be iterative and thus the circular design as shown in Fig. 2.1. The inner circle interacts with many other specific measures of pharmaceutical manufacturing, such as specifications, critical process parameters, and so on. This QbD circle can be divided into two major semicircles, product knowledge and process understanding. A critical tool for enabling QbD manufacturing is a defined way of linking these two semicircles.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has bridged this gap using the concept of a design space. A design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality [3]. This is the scientific definition of a design space. Design space also has a regulatory definition. Movement within a design space is not considered as a change that requires regulatory approval. However, change within a design space does need oversight by the sponsor's quality system. Design space is proposed by the applicant and is subject to regulatory assessment and approval. A design space could potentially link process performance to variables such as scale and equipment. The design space is thus a very flexible tool that links process characteristics and in-process material attributes to product quality. A recent definition of product

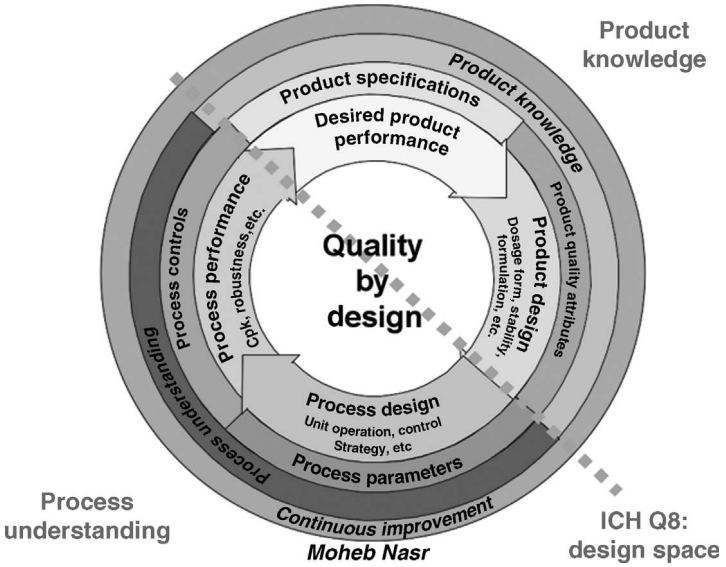

Figure 2.1. Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management (ICH Q8R1). Quality by Design begins by defining the desired product performance and also by designing a product that meets those performance requirements. The characteristics of the designed product are the basis for designing the manufacturing process, and the performance of the manufacturing process also needs to be monitored. Each of these steps may impact each other. For example, process performance may provide knowledge regarding manufacturability that could impact product design in an iterative manner. These steps also relate to specific quality measurements and tools. Product specifications should ideally be based on desired clinical performance. The product design should be defined in terms of product quality attributes. The criticality of these attributes and the relationship of these attributes to specifications may evolve over the product life cycle. Process parameters are important in defining the process, and process controls are important in ensuring process performance. This circle of QbD can be split into two general areas, product knowledge and process understanding. These two areas meet in the design space and the interaction of product knowledge and process understanding allows for continuous improvement. The QbD circle was developed by Dr. Moheb Nasr. (See the insert for color representation of this figure.)

quality was given by Dr. Janet Woodcock [13], "Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes." As indicated at the top of Fig. 2.1, QbD starts with the desired clinical performance.

2.3 RELEVANT PRODUCT ATTRIBUTES

In the draft annex to ICH Q8, ICH Q8(R1) [11], the target product profile is described as a starting point for Quality by Design. The target product profile is based on the desired