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Introduction

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1.1 Quality by Design Overview

QbD emerged as a cultural change in the pharmaceutical industry, which promoted a scientific and risk-based approach to pharmaceutical product development and manufacturing. Historically, pharmaceutical development and manufacturing had emphasized checklist-based operations rather than scientific understanding. The high attrition rates of drug candidates during development and the high value of pharmaceutical products, along with extremely high regulatory burden, had led to business practices that minimized risk and restricted process changes and the implementation of new technology.

Traditionally, pharmaceutical process and product development utilized empirical and univariate experimentation and pharmaceutical processes operated at fixed process conditions with offline analytical testing (with a long feedback timeline) and end-product testing. In addition, it was typical of pharmaceutical companies to provide the regulatory agencies with minimal process and scientific information, and regulatory agencies responded with a wealth of detail queries.

QbD is a “systematic approach to pharmaceutical development and manufacturing that is based on science and quality risk management and begins with predefined objectives and emphasizes product and process understanding as well as process control” [1]. QbD emphasizes multivariable experimentation, design of experiments, process modeling, kinetics, thermodynamics, online analytical testing, and so on. In addition, it has become an improved regulatory paradigm in which the scientific understanding of the product and process has to be provided to the regulatory agencies. This new regulatory model is intended
to allow for higher transparency, higher quality, and the implementation of modern manufacturing techniques, such as continuous processing, as well as continuous improvement of commercial pharmaceutical processes.

1.2 Pharmaceutical Industry

The active pharmaceutical ingredient or drug substance is the active component of the pharmaceutical product, and typically small-molecule drug substances are produced by a multistep synthesis, which involves a sequence of chemical reactions followed by purification/isolation unit operations. Historically, drug substance pharmaceutical processes consisted of batch operations such as reactions, extraction, distillation, crystallization, filtration/centrifugation, drying, and milling.

The drug product is the pharmaceutical formulation that the patient receives and is often in the form of tablets or capsules; other common formulations are oral solutions, topical transdermal patches, and lyophiles or sterile solutions for injection. Historically, drug product processes also consisted of batch operations such as blending, granulation, drying, tableting, encapsulation, or filling depending on the final formulation.

The history of regulations [2, 3] shows an increase in regulatory control after catastrophes; one of the most tragic incidents in the United States was the elixir sulfanilamide incident of 1937 where diethylene glycol was used as a solvent in a pediatric cough syrup and resulted in more than a hundred deaths. This incident led to the Food, Drug, and Cosmetic Act, which increased the US Food and Drug Administration (FDA)’s authority to regulate drugs and required premarketing safety approval for new medications. Another tragic incident was the thalidomide disaster of 1961 where approximately 12,000 infants in over 50 countries were born with severe malformations. This incident led to the Kefauver–Harris Drug Amendment, which increased the FDA’s authority to require safety and efficacy prior to marketing (and tighter controls of clinical trials). These and other incidents led to tighter regulations and, in the 1960s and 1970s, to a rapid increase in national pharmaceutical regulations; simultaneously, many pharmaceutical companies were also globalizing.

The global harmonization of pharmaceutical guidelines across the developed economics was initiated in 1990 through the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use [4]. ICH is cosponsored by regulatory agencies and industrial organizations, as well as many observing organizations. These include the European Commission; the US FDA; Ministry of Health, Labour and Welfare of Japan; the European Federation of Pharmaceutical Industries and Associations; the Japan Pharmaceutical Manufacturers Association; the Pharmaceutical Research and Manufacturers of America; Health Canada;
Swissmedic; ANVISA of Brazil; Ministry of Food and Drug Safety of the Republic of Korea; the International Generic and Biosimilar Medicines Association; the World Self-Medication Industry; and the Biotechnology Innovation Organization. ICH has set a structure and process for the proposal, review, and implementation for efficacy, safety, and quality guidelines as well as dossier format requirements. The initial ICH guidelines set common structure stability, analytical methods, impurity control and drug substance, and drug product specifications requirements for drug substance and drug product, and the early ICH guidelines emphasized testing for quality.

1.3 Quality by Design Details

QbD was introduced through the “QbD tripartite” of ICH guidelines: ICH Q8 (R2) Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality Systems. ICH Q8 Pharmaceutical Development describes the principles of QbD, outlines the key elements, and provides illustrative examples for pharmaceutical drug products. ICH Q9 Quality Risk Management offers a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product. In addition, it states that “the evaluation of the risk to the quality should be based on scientific knowledge and ultimately linked to the protection of the patient” [5]. ICH Q10 Pharmaceutical Quality Systems describes a “comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organization quality concepts and includes applicable Good Manufacturing Practices” [6]. The fourth QbD ICH guideline (considered the drug substance equivalent of ICH Q8) for enhanced active pharmaceutical ingredient synthesis and process understanding, Q11 Development and Manufacturing of Drug Substances (Chemical Entities and Biotechnological/Biological Entities), was approved in November 2012 [7]. The fifth QbD ICH guideline (ICH Q12), Technology and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, is currently under development.

The QbD approach begins with Quality Target Product Profile, which is a prospective summary of the quality characteristics of the pharmaceutical product that ensures the desired quality, safety, and efficacy, and works backward through the drug product and drug substance processes establishing a holistic understanding of which attributes are linked to patients’ requirements and functional relationships of these attributes.

The next step in QbD is a systematic approach to determine the aspects of the drug substance and drug product manufacturing processes that impact the Quality Target Product Profile. A risk assessment is conducted to identify the quality attributes and process parameters that could potentially impact
product safety and/or efficacy, utilizing prior scientific knowledge gained from first principles, literature, and/or similar processes.

The output of the risk assessment is a development plan, in which multivariate experiments, kinetics, and/or modeling is typically utilized. The goal of the plan is to establish a holistic understanding of how attributes and parameters are functionally interrelated throughout the entire drug substance and drug product processes. The result is control strategy, which links parameters and attributes to the Quality Target Product Profile.

This approach provides a comprehensive understanding of the critical quality attributes, which is a “physical, chemical, biological, or microbiological property or characteristic that should be in an appropriate limit, range or distribution to ensure the desired product quality,” and of how the process parameters are related to the quality attributes and how probable they can impact quality.

The enhanced understanding of products and processes, along with quality risk management, leads to a product control strategy, which might include a design space (that is optional in ICH Q8/11), which is “the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.” The control strategy is a planned set of controls, which can be process parameters, process attributes, design space, facility and equipment operating conditions, and process testing that ensures process performance and product quality.

The regulatory QbD landscape continues to evolve, and AIChE conferences and sessions will continue to provide a platform to discuss and debate the latest QbD concepts and implementations.

1.4 Chapter Summaries

The contributions in this book can be divided into three sets: Chapters 2–6 address the role of key technologies, process models, process analytical technology (PAT), automatic process control, and statistical methodology, supporting QbD and establishing associated design spaces. Chapters 7–13 present a range of thoroughly developed case studies in which tools and methodologies are used to support specific drug substance and drug product QbD-related developments. Finally, Chapter 14 discusses the needs for initial efforts toward systematic data and knowledge management to support QbD and related activities. More specifically:

Chapter 2, An Overview of the Role of Mathematical Models in Implementation of Quality by Design Paradigm for Drug Development and Manufacture (Chatterjee, Moore, and Nasr), reviews the categories of mathematical models that can be exploited to support QbD and presents literature examples of various types of model formulations and their use. The authors
emphasize that models are valuable tools at every stage of drug development and manufacture. Examples presented span early-stage risk assessment, design space development, process monitoring and control, and continuous improvement of product quality.

Chapter 3, *Role of Automatic Process Control in Quality by Design* (Braatz and coworkers), outlines how robust automatic control is an important element in actual implementation of QbD. Using phenomenologically based or data-driven models, automatic control strategies provide the active mechanism that maintains the operation of the manufacturing process within the design space despite the disturbances that inevitably arise. The authors illustrate the use of feedback control methodology combined with online process measurement for controlling critical quality attributes such as polymorphic form and particle-size distribution in batch crystallization operations.

Chapter 4, *Predictive Distributions for Constructing the ICH Q8 Design Space* (Peterson and coworkers), reviews the reported applications of response surface methodology for constructing design spaces and identifies risks associated with the use of “overlapping mean response” constructions, which are typically used in building multivariate design spaces. The authors outline two predictive distribution approaches that overcome these risks by taking into account the uncertainty associated with the experimental results used in building the response surfaces as well as the correlation that may exist among the responses. A Bayesian and a parametric bootstrapping approach are presented and illustrated with examples.

Chapter 5, *Design of Novel Integrated Pharmaceutical Processes: A Model-Based Approach* (Roman-Martinez, Woodley, and Gani), builds on model-based development of design space advanced in Chapter 2 to present a systematic strategy for identifying the best design of a process for developing an active pharmaceutical ingredient. The strategy employs a library of unit operation models and physical/chemical property prediction tools, which are used as components within a process synthesis strategy that employs mixed integer nonlinear optimization methods. This optimization-based strategy generates the optimal selection and sequence of reaction and separation unit operations as well as the associated design space. A case study is reported involving the synthesis of neuraminic acid.

Chapter 6, *Methods and Tools for Design Space Identification in Pharmaceutical Development* (Boukouvala, Muzzio, and Ierapetritou), reviews the tools and methods that have been developed in the process systems engineering literature to address issues of process feasibility and flexibility under uncertainty. It is shown that process design under uncertainty can be posed as a stochastic optimization problem. Moreover, the review notes that in general the design of the process and its automatic control system need to be treated in an integrated fashion since the automatic control system generally can serve to increase the design space. The concepts are illustrated with two single-unit examples: a powder blender and a roller compactor.
Chapter 7, Using Quality by Design Principles as a Guide for Designing a Process Control Strategy (Burcham and coworkers), reports a comprehensive process engineering study involving the implementation of an impurity control strategy for a new drug substance. The study makes extensive use of predictive models to determine optimal processing conditions and to map the design space around those conditions. The mechanistic models developed include complex reaction kinetics and mass transfer processes, which were developed through intensive experimentation using appropriate PAT and traditional analytical methods. The process models were used as an integral part of an in silico approach to identify the boundaries of the design space requiring experimental confirmation.

Chapter 8, A Strategy for Tablet Active Film Coating Formulation Development Using a Content Uniformity Model and Quality by Design Principles (Chen and coworkers), presents in detail the development of a mechanistic model to predict the relative standard deviation of table content uniformity of an active film coating unit operation. Systematic studies to identify the most important operating variables, develop model parameters, and validate model prediction across scales are reported. The model is shown to be an effective tool for developing the design space for this unit operation, including establishing the effects of scale-up.

Chapter 9, Quality by Design: Process Trajectory Development for a Dynamic Pharmaceutical Coprecipitation Process Based on an Integrated Real-Time Process Monitoring Strategy (Wu and Khan), describes the features, strengths, and limitations of principal component analysis of real-time process measurements as a means for process trajectory monitoring, identification of singular points of the trajectory, and development of understanding of important phenomena occurring during the dynamic process. A case study of a coprecipitation process monitored using near-infrared (NIR) and turbidity measurements is detailed. Implications for design space development are discussed.

Chapter 10, Application of Advanced Simulation Tools for Establishing Process Design Spaces Within the Quality by Design Framework (Khinaast and coworkers), reports on the value added by advanced simulation tools in building fundamental process understanding, especially of the impact of critical sources of process variability. The use of discrete element modeling (DEM) is described to investigate a powder blending operation with the goal of screening and prioritizing potentially critical input variables and mapping out a blending experimental space. Similarly, computational fluid dynamics (CFD) is used to construct a detailed three-zone model of film formation on a tablet surface and then to characterize the critical process parameters of the coating operation. In each case, Design of Experiment (DOE) on the most important parameters are utilized to develop a design space.

Chapter 11, Design Space Definition: A Case Study—Small-Molecule Lyophilized Parenteral (Mockus and coworkers), builds on Chapter 4 and
proposes a novel Bayesian treatment to enable the establishment of the reliability limit of a design space and describes the application of the approach to a lyophilized parenteral product. The proposed approach also provides quantitative estimates of the risk of failure of key product attributes.

Chapter 12, *Enhanced Process Design and Control of a Multiple-Input Multiple-Output Granulation Process* (Ramachandran), demonstrates the use of a previously validated mechanistic three-dimensional population balance model of a continuous wet granulation process to investigate controllability and identify the most effective input–output variable pairings for designing a feedback control system. The results are then used to suggest possible alternative process designs.

Chapter 13, *A Perspective on the Implementation of QbD on Manufacturing Through Control System: The Fluidized Bed Dryer Control with MPC and NIR Spectroscopy Case* (Velazquez and coworkers), builds on Chapter 3 and illustrates the use of automatic process control coupled with real-time NIR particle moisture content measurement to control a fluid bed dryer. Model-predictive controller design with design space constraints imposed on air velocity and inlet temperature is demonstrated for both batch and continuous operations of a pilot plant dryer.

Chapter 14, *Knowledge Management in Support of QbD* (Joglekar and coworkers), discusses the potential role of knowledge management systems in providing the structured framework for recording, using, and learning from the data that are generated in product development and manufacture. The relevant literature is reviewed, and the features of a specific workflow-based system are described. Applications to an active pharmaceutical ingredient (API) development and a drug product design space development are outlined.

The coeditors hope that these chapters serve to stimulate continued developments in tools, methods, and applications that will further solidify the role of QbD concepts and thought processes in pharmaceutical development and manufacture. In addition, we hope that the technology vendor community may be stimulated to develop software implementations that will make process model building, physical property estimation, process and control system design, and probabilistically based design space development efficient and reliable for the scientists and engineers of pharmaceutical industry.

**References**


