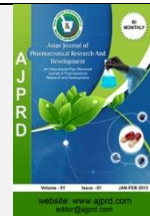


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Review Article

### Review on Pharmaceutical Quality by Design (QbD)

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#### ABSTRACT

Pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predetermined objectives and emphasizes the understanding of production and processes and process control, based on sound science and quality risk management. Quality purchasing design (QbD) is emerging to increase the promise of providing safe and effective medicines to customers and promises to improve the efficiency of product quality. Quality means eligibility for use. The quality of the medication means that the product provides therapeutic benefits to the label reproducible and free from contamination on the label. In vivo or in vitro performance test can be evaluated for drug production. Dinette by Quality guarantees the performance of the product in vitro and the performance of the in vitro product in the in vivo product. So the quality design is related to the product.

**KEYWORDS:** Quality-by-design, design space, risk management, ICH guidelines.

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#### INTRODUCTION

Quality by Design (QbD) is a concept first outlined to the designing for quality and innovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. While Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the U.S. Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs.

Quality by design is A Quality System for managing a product's lifecycle, a regulatory expectation, intended to increase process and product understanding and thereby decrease patient risk, a multifunctional exercise, Design of Experiment (DoE) and Design Space.<sup>1</sup>

The word "quality" as having two meanings: first, the presence of features that create customer satisfaction; second, the reliability of those features. Failures in features create dissatisfactions, so removing failures is the purpose of quality improvement, while creating features is the purpose of quality by design. Juran's process seeks to create features in response to understanding customer needs. These are customer-driven features. The sum of all features is the new product, service, or process.

Designing for quality and innovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. While Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the U.S. Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs.<sup>2</sup>

The Quality by Design model consists of the following steps:<sup>2</sup>

- Establish the project design targets and goals.
- Define the market and customers that will be targeted.
- Discover the market, customers, and societal needs.
- Develop the features of the new design that will meet the needs.
- Develop or redevelop the processes to produce the features.

#### Principle of QbD<sup>3</sup>

- Risk and knowledge based decisions
- Systematic approaches process development
- Continuous Improvement
- This leads to "capable" processes.

### Advantages of QbD<sup>3</sup>

- Benefits for Industry:
- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

### Understanding QbD<sup>3</sup>

- Initial Confusion
- Research and discussion
- Reaching understanding

### PRIMARY QBD DOCUMENTS<sup>4</sup>

#### Risk Assessment Report

- Performed throughout QbD Process
- Particularly important to process development

#### Quality Target Product Profile (QTPP)

- Defines the desired product characteristics and sets development goals.

#### Control Strategy Summary

- Defines the process, its inputs and outputs, and how it is controlled.

#### PPQ Report(s)

- Formal verification that the process Control Strategy has been defined appropriately and repeatedly produces the desired results.

#### Continued Process Verification (CPV) Reports

- Assuring that during routine commercial production, the process remains in a state of control (FDA); involves feedback loops into the QbD “process” where intentional process changes and/or observed variability is assessed for risk, characterized, re-validated, etc.

### QBD DEVELOPMENT PROCESS INCLUDE<sup>5</sup>

- Begin with a target product profile that describes the use, safety and efficacy of the product
- Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
- Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation

- Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.
- Design a manufacturing process to produce a final product having these critical materials attributes.
- Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
- Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
- Continually monitor and update the process to assure consistent quality.

### Quality Target Product Profile (QTPP)

#### Necessary Elements<sup>6</sup>

- Quality characteristics: sterility, purity etc. (including specific safety-related impurities where necessary)
- Pharmacokinetic characteristics: dissolution etc.
- Therapeutic effect
- Target patient population: neonate, adult etc., clinical diagnosis
- Shelf life: temperature, light conditions etc.

#### Desired Elements<sup>6</sup>

- Dosage form: liquid for injection, solid tablet etc.
- Route of administration: oral, IV, IM, SC
- Clinical setting: self or clinic administration
- Primary/secondary packaging: glass or plastic vial/syringe; blister packaging etc

### QbD and New Process Development<sup>7</sup>

- The goal of process development is creation of a process control strategy
- Definition of a QTPP, and provisional CQAs and CPPs, is essential to guide development studies
- FMEA and similar tools are very useful for initial CQA and CPP assessments.



Figure 1: Quality by Design model

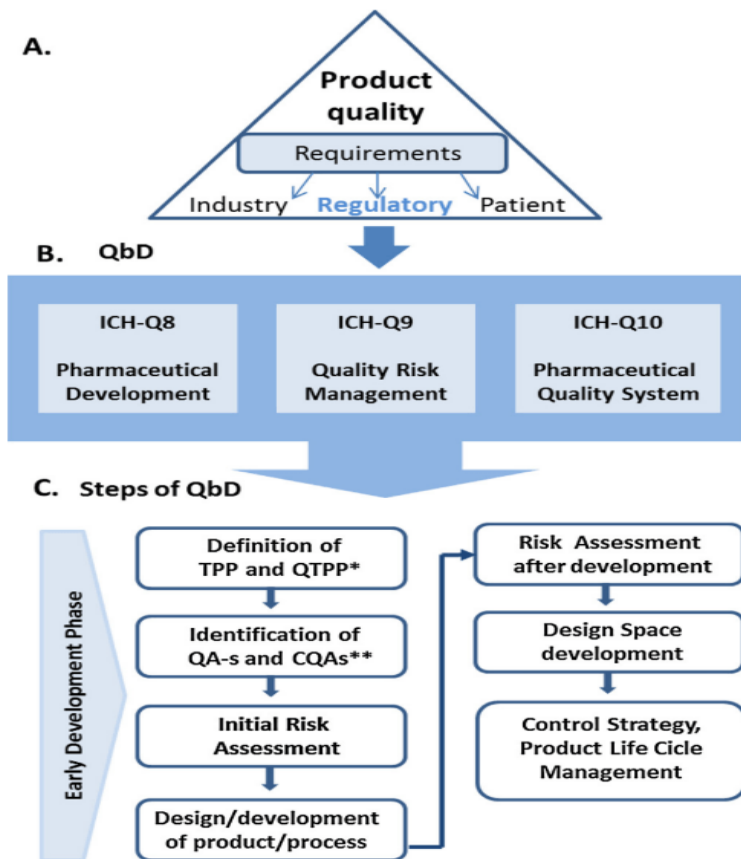


Table 1: Traditional approach & Enhanced QbD approach<sup>8</sup>

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, focus optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality system
Process Control	Some in process testing	PAT utilized, Process operation tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desire product performance
Control Strategy	By testing and inspection	Risk-based control strategy, real-time release possible

**Applying QbD to Legacy Products<sup>9</sup>**

The minimal requirement for legacy include an established control strategy and process validation which are necessary to create a CPV program.

Risk assessment is used in developing the CPV program

**From Global Policy:<sup>9</sup>**

For legacy products, most of the information required to perform such a risk assessment already exists and just requires compilation. It is recognized that integration of all legacy products may take substantial time. Each site should prioritize legacy product based on patient impact and create a timeline for evaluation of these products in the QbD program

**Manufacturing changes within the approved design space without further regulatory review.<sup>10</sup>**

- Reduction of post-approval submissions.
- More efficient technology transfer to manufacturing.

- Greater regulator confidence of robust products.
- Risk-based approach and identification.
- Innovative process validation approaches.
- Less intense regulatory oversight and less post-approval submissions.
- For the consumer, greater drug consistency.
- More drug availability and less recall.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Time to market reductions: from 12 to 6 years realized by amongst others.
- First time right: lean assets management.
- Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Absence of design freeze (no variation issues).
- Less validation burden.
- Real time controls (less batch controls).
- Realistic risk perceptions.



- Contributes substantially to realize the better, cheaper and safer mandate.

### QBD ACTIVITY WITH FDA<sup>11</sup>

- Specifically, the following activities are guiding the overall implementation of QbD:
- In FDA's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.
- Implementation of a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application demonstrating use of QbD principles, product knowledge, and process understanding.
- Implementation of a Question-based Review (QbR) Process has occurred in CDER's Office of Generic Drugs.
- CDER's Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval inspectional processes to evaluate commercial process feasibility and determining if a state of process control is maintained throughout the lifecycle, in accord with the ICH Q10 lifecycle Quality System.
- Implementation of QbD for a Biologic License Application (BLA) is progressing.
- While QbD will provide better design predictions, there is also a strong recognition that industrial scale-up and commercial manufacturing experience provides new and very important knowledge about the process and the raw materials used therein. FDA is aware that knowledge is not static and builds throughout the manufacturing lifecycle. FDA's release of the Process Validation guidance in January 2011 notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected. This vigilant and nimble approach is explained by FDA to be essential to best protect the consumer (patient).

### INTEGRATED PLANNING<sup>12</sup>

- Integrated planning requires a team with a leader whose sole accountability is for the total success of the new product from defining the opportunity through customer purchase, use, service, and recommendation to others. This team leader reports directly to a senior executive, or the team leader can be a senior executive. Each team member's job is to ensure the success of the new product.
- In addition to organizational integration, a successful team must begin with clearly articulated common goals for the product that are measurable and authorized by the enterprise. These goals must, at a minimum, cover such elements as:
  - The customers or customer segments to be served by the new product
  - The relative and absolute quality goals
  - The volume of sales or revenue to be generated in an initial time period and for the long run

- Market share, penetration, or sales relative to key competitors
- the release date
- The team will follow a structured process. The structure is the common framework for all participants in launching the new product and helps ensure success.

### Customer-focused optimization

Quality by Design starts and ends with the customer. Every new product introduction has some amount of trade-off involved. If there are multiple customers, they may have conflicting needs. Even the same customer may have needs that compete with each other. Capacity and speed compete with cost of operation. Capacity can compete with speed. Flexibility and feature-rich offerings may have reduced ease of use, and so on. Quality by design offers a range of tools and methods intended to make these tradeoffs explicit and optimal for the customer. Some tools are highly mathematical, and others relate more to customer behavior. Quality by Design sets strong expectations for creative approaches to functional design, product features and goals, and production design<sup>12</sup>

### Control over variation and transfer to operations

Quality by design incorporates modern tools to preemptively control variation. These tools and methods begin by measuring and understanding the variation that exists by using historical data, testing, and modeling to help forecast, analyze, and eliminate the deleterious effects of variation using standard statistical techniques. Process control consists of three basic activities:<sup>12</sup>

- Evaluate the actual performance of the process
- Compare actual performance with goals
- Take action on the difference. The final activity of the quality by design process is to implement the plan and validate that the transfer has occurred.

### PHARMACEUTICAL QUALITY BY DESIGN

The FDA imperative is outlined in its report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach." (Pharmaceutical Quality for the 21st Century, 2007) In the past few years, the agency has implemented the concepts of QbD into its pre-market processes. The focus of this concept is that quality should be built into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. This is a successor to the "quality by QC" (or "quality after design") approach that the companies have taken up until the 1990s (Process Validation: General Principles and Practices. The QbD initiative, which originated from the Office of Biotechnology Products (OBP), attempts to provide guidance on pharmaceutical development to facilitate design of products and processes that, maximizes the product's efficacy and safety profile while enhancing product manufacturability<sup>13</sup>

### ICH ACTIVITIES

ICH guidelines Q8 (on Pharmaceutical Development), Q9 (on Quality Risk Management), and Q10 (on Pharmaceutical Quality System) provide some assistance

for manufacturers to implement Quality by Design into their own operations (ICH Quality Guidelines), (CMC), (International Conference on Harmonisation).<sup>14</sup>

The ICH Steering Committee meets twice a year to discuss the progress of its efforts. This practical input should help ensure that quality risk management and knowledge management are used to make lifecycle adaptations that maintain process control and product quality.<sup>14</sup>

## CONCLUSION

Quality by Design is intended to enhance process knowledge and is based on existing guidance and reference documents. QbD is a quality system that builds on past and sets future regulatory expectations; the QbD can be viewed as a process defined by series of document

requirements. These documents organize and demonstrate process knowledge and understanding. QbD can be applied to legacy and new products, but the supporting document package may differ. The QbD suite of documents is "alive". They can and should be revised as the knowledge base changes. It ensures robust commercial manufacturing methods for consistent production of quality drugs. It ensures the consumers that therapeutic equivalent generics are manufactured every single time. QbD methodology helps in identifying and justifying target product profiles, product and process understanding. There is a need for vigorous and well funded research programs to develop new pharmaceutical manufacturing platforms.

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