Quality by Design: An Overview

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Abstract- A new method for developing products called quality by design (QbD) has significant business advantages across the course of the product life cycle. In the modern pharmaceutical quality control procedure, QbD has taken on a crucial role. The corner stone's of QbD are Q8 (pharmaceutical development), Q9 (quality risk management), and Q10 (quality systems) of the ICH standards. To design and develop the formulation and process, QbD defines the risk assessment, life cycle management, critical quality characteristics (CQA), and quality target product profile (QTPP). In order to guarantee the seamless production and high calibre of pharmaceuticals, this study aims to explain how QbD can be applied.

Keywords: QbD, ICH guidelines, Pharmaceutical, Quality control, Manufacturing, Design space, QTPP, CQAs.

INTRODUCTION

The Latin term "Qualitus," which denotes overall excellence or a distinguishing characteristic, is where the word quality first appeared. The ability to function as intended is the most basic definition of quality. Quality is the ability of a drug substance or drug product to be used as intended. Some qualities like individuality, strength, and purity are included in this word. High-quality pharmaceutical products are free from impurities and contaminants and offer the therapeutic, pharmacokinetic, and reproducible benefits that are indicated on the label. The three aspects of quality are durability, performance, and dependability. The product's planned quality is known as quality by design (QbD). Dr. Joseph M. Juran coined the phrase "quality by design" (QbD), and the automobile sector was the first to use it. Quality by design (QbD) in pharmaceutical sciences was proposed by Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH). The basic concept of quality by design is that 'the quality is not to be tested into the product, but it should be built into it[1].

Definition of Quality by Design (QbD):

Based on good science and quality risk management, QbD is a systematic approach to development that starts with predetermined objectives and emphasizes product and process understanding and control. This is in accordance with the ICH Q8 (R1) guideline[1, 2].

In accordance with FDA PAT guidelines, quality by design (QbD) is a method for planning, evaluating, and managing manufacturing through timely measurements (i.e., during processing) of essential quality and performance attributes of new and in-process materials and processes that would affect the product's safety requirements.

History of Quality by Design (QbD):

Joseph M. Juran, a well-known authority on quality, established the idea of QbD. In 1986, W. Edwards Deming, who was not in a crisis at the time, also provided an intriguing explanation of quality by design using the example of illness. The FDA unveiled a brand-new program called cGMP for the 21st Century: A Risk-Based Approach in 2002. With this project, the FDA aimed to update its regulations regarding pharmaceutical quality and create a new framework that was centered on quality by design, risk management, and quality systems. Understanding how process and product variables affect product quality is necessary for Quality-by-Design (QbD). Apart from the FDA's consideration of this novel idea in its cGMP project, two significant guidelines-Q8 pharmaceutical development and Q9 Quality Risk Management were released as part of the International Conference on Harmonization (ICH) guidelines[3].

Objectives of Quality by Design (QbD)[3]:

The main objective of QbD is to achieve the quality products. Other objectives are:

- To achieve positive performance testing.
- To ensure combination of product and process knowledge gained during development.

Foundation of Quality by Design (QbD):
ICH guideline Q8 for pharmaceutical development, Q9 for Quality Risk Management and Q10 for Quality systems are foundation of QbD (Fig. 1)

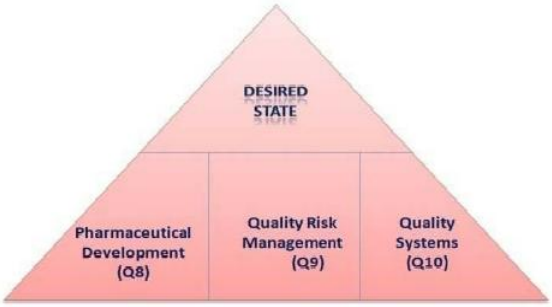


Fig.1. Foundation of Qbd

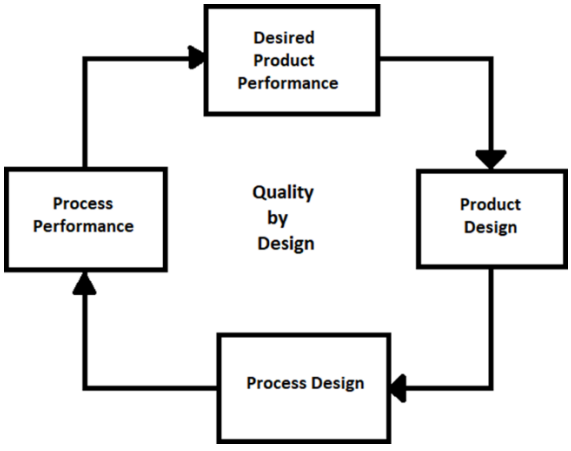
Advantages of Quality by Design (QbD) [1, 2, 3]:
There are many advantages of QbD as enlisted below:

- It gives higher level of assurance of the quality of the product.
- It is cost saving and efficient for industry.
- It minimizes or eliminates the potential compliance actions.
- It provides opportunities for continual improvement.
- It facilitates innovation.
- It enhances opportunities for first cycle approval.
- It increases process capability and reduce product variability and defects.
- It eliminates batch failures.
- It empowers technical staff.
- It provides better understanding of the process.
- It ensures better design of product with fewer problems.

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 systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

Table no .1 Traditional approach & Enhanced QbD approach

Fundamental aspects of Quality by Design (QbD) [4]:
With this technique, it is necessary to fully understand how the development and process of a product's formulation will affect the product's quality (Fig. 2). Understanding the causes of variability, their effects on the finished product and reducing this variability are all part of QbD. The performance of the product determines its quality. Final product testing is either less necessary or not necessary at all if QbD is properly implemented.



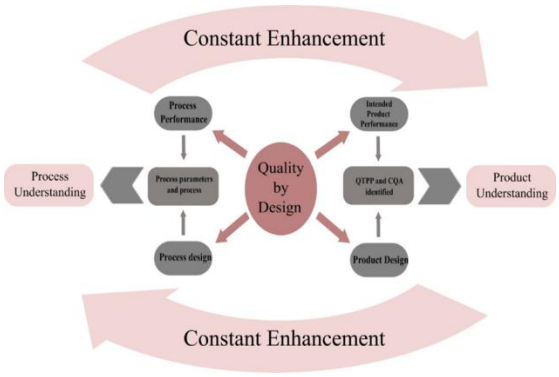


Fig.2. Fundamental Aspects of QbD

Steps involved in QbD / Elements of QbD[5]:

1. Clinical development
   - Preclinical study
   - Nonclinical study
   - Clinical study
   - Scale up
   - Submission for market approval
2. Manufacturing
   - Design Space
   - Process Analytical Technology
   - Real Time Quality Control
3. Control Strategy
   - Risk based decision
   - Continuous improvement
   - Product performance

Seven steps of quality by design start up plan:

- Hire an independent Quality by design expert.
- Audit your organization and process with the expert conducting a gape analysis.
- Hold a basic quality by design workshop with all your personal.
- Review the expert's report and recommendation.
- Draft an implementation plan, timelines and estimated costs.
- Assign the resources (or contract out).
- Retain the independent expert as your "Project Assurance" advisor.

Quality by design (QbD) and well understood product and processes:

- All critical sources of variability are identified and explained.
- Variability is controlled by the process.
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.
- To gain enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters considering appropriate use of quality risk management principles.

QBD in pharmaceutical companies:

Despite its emphasis on quality, the pharmaceutical industry cannot keep up with other industries in terms of production efficiency and productivity. Current scenario in pharmaceutical industry:

• Re-inspection cost
• Autonomous analysis of process requirements based on:
• Product specifications as the main means of control.
• Unpredictable scaling issues

Important attributes about QBD[6]:

1. Quality Target Product Profile (QTPP): The quality target product profile forms the basis of design for the development of the product. It mainly focuses on the safety and efficacy.

Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage forms, livery systems.
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetics characteristics (Dissolution, Disintegration)
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

Benefits of QTPP are as follows:

- Identifies risks and best approaches to manage.
- Generates and enables knowledge sharing.
- An integrative learning, life-cycle process for optimizing decision making and therapeutic outcomes for the patients benefit.
- A drug product designed, developed and manufactured according to quality target product profile with specification (Such as

Dissolution/Release Acceptance Criteria) consistent with the desired in vivo performance of the product.

2. Critical Quality Attributes (CQAs):

A Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting:

- Product purity, strength,
- Drug release and stability.

CQAs for other delivery systems can additionally include more product specific aspects such as:

- Aerodynamic properties for inhalational products,
- Sterility for parentrals,
- Adhesion properties for transdermal patches.

CQAs for drug substances, raw materials and intermediates include:

- Particle size distribution
- Bulk density

3. Risk Assessment:

Risk Assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and it repeated as more information becomes available and greater knowledge is obtained. They can overcome by once the significant parameters are identified they can be further studied to achieve a higher level of process understanding. e.g., through a combination of design of experiments, mathematical models or studies that leads to mechanistic understanding.

Risk Assessment Tools are:

- Failure Mode Effect Analysis (FMEA)
- Failure Mode Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operate ability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)

4. Design Space:

The relationship between the process inputs (material attributes and process parameters) and Critical Quality Attributes can be described in the Design Space (Fig.3). Working within a design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

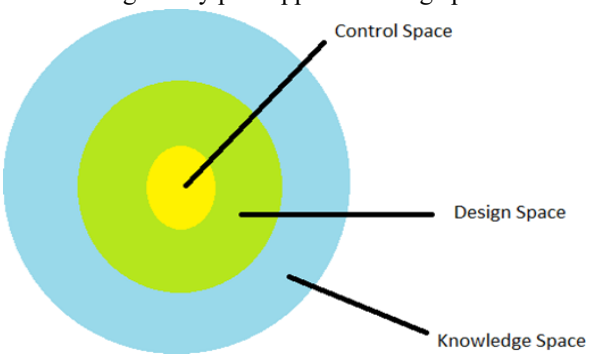


Fig.3: Design Space

5. Control Strategy:

A control strategy can include:

- Control of input material attributes based on an understanding of their impact on process ability or product quality. E.g., drug substance, excipients, primary packaging materials etc.
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or product quality. e.g., the impact of drying on degradation, particle size distribution of the granulate on the dissolution
- In-process or real-time release testing instead of end-product testing. E.g., measurement and control of CQAs during processing
- A monitoring program. e.g., full product testing at regular intervals for verifying multi variant prediction models.

6. Life cycle management:

In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product life cycle with regard to process consistency and throughput could take place with fewer post approval submissions.

Barriers to QbD[7]:

1. Culture challenges:
- Move from prescriptive approach
- More sharing of scientific information
2. Business challenges:
- Business justification
- Management support
- Budgeting across business units
3. Implementation challenges:
- Collaboration between functions
- Experience with new concepts
- Work load and resource limitations

Applications of QbD[8]:

1. Pharmaceutical Development:

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product

2. QbD in CMC Review Process:
- Science-based assessment
- Restructured organization and reorganized staff – pre market staff and post-market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP
3. Office of New Drug Quality Assessment (ONDQA):
- Science-based assessment
- Restructured organization and reorganized staff premarket staff and post market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP
4. Office of Generic Drugs(OGD):
- QbD contains the important scientific and regulatory review questions
- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product
- 416 applications received using QbD by June 2007
- Successful in ensuring that questions address issues regarding QbD
5. Office of Biotechnology Products:
- Have more complex products
- Already doing some aspects of QbD
- In process of preparing to accept applications using QbD
- Beginning a pilot for biotech products for QbD– using mainly comparability protocols
- Also implementing Q8,Q9and Q10

Benefits of implementing QbD in FDA[9, 10, 11]:

- Enhances scientific foundation for review
- Provides for better coordination across review, compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review(establishing a QMS for CMC)
- Provides for more flexibility in decision making
- Ensures decisions made on science and not on empirical information
- Involves various disciplines in decision making
- Uses resources to address higher risks

QbD for industry and regulatory bodies[12, 13]:

QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline. The following roles are described for Pharmaceutical industry and regulatory bodies are listed in Table 2.

Industry	Regulatory Agency
Development of scientific understanding of Critical process and product attributes.	Scientifically based assessment of product and Manufacturing process design and development.
Controls and testing are designed and based on limits of scientific understanding at development stage.	Evaluation and approval of product quality specifications in light of established standards. For example: purity, stability, content uniformity etc.
Utilization of knowledge gained over the Product's life cycle for continuous improvement.	Evaluation of post-approval changes based on risk and science.

Table2: Role of QbD for industry and regulatory bodies

CONCLUSION

Based on current guidelines and reference materials, Quality by Design (QbD) is a proposal to enhance process understanding. Quality by Design (QbD) is a system that builds upon previous work and establishes future legal requirements. In the realm of pharmaceutical processes, such as formulations, drug development, analytical techniques, and biopharmaceuticals, QbD assumes significance. Adoption of QbD is mostly driven by regulatory requirements. In order to officially promote their product, the pharmaceutical sector must comply with regulations.

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