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A REVIEW: QUALITY BY DESIGN

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ABSTRACT

"Quality by Design" (QbD) is the modern approach to pharmaceutical product quality. The excellent calibre of medications is guaranteed by Pharmaceutical Quality by Design, which is covered in this article along with information on it. There is discussion and mention of some of the Quality by Design components. The process variables and quality characteristics of each unit operation are identified. The benefits, options, and procedures for pharmaceutical product quality through design are described. Pharmaceutical development strives to produce a high quality product and its manufacturing process to consistently deliver the product's targeted performance. Although products cannot be quality-checked, quality should be taken into consideration when designing. Important Quality by Design elements, the Quality Target Product Profile, and critical quality attributes are all included. It also contrasts quality by design with end-product testing in terms of product quality. The cornerstone of Quality by Design is the ICH Guidelines. It is based on the ICH Guidelines for Pharmaceutical Quality Systems, Pharmaceutical Development, and Q8, Q9, and Q10, respectively. It also examines the use of Quality by Design in the manufacturing and development of pharmaceutical products.

KEYWORDS: Quality by Design, Quality target product profile, Critical quality attributes, Risk Assessment, Design of Experiments.

INTRODUCTION

Pharmaceutical development aims to create a high-quality product and its production method to deliver the products desired performance consistently. Scientific understanding is provided to support the establishment of the design space, specifications, and manufacturing controls by the information and expertise gained from pharmaceutical development research and manufacturing experience. Pharmaceutical development study data can serve as a foundation for effective risk management.[1] It is crucial to understand that products cannot be assessed for quality; rather, quality should be incorporated into the design from the beginning.[2] Changes in formulation and manufacturing procedures made during development and lifecycle management should be viewed as chances to learn more and assist the design space's formation in new ways Incorporating pertinent information learned from experiments with unexpected results might also be helpful.[3] The applicant submits a design space proposal, which is subject to regulatory review and approval change is not regarded as occurring when working within the design space. Exiting the design space is seen as a change and ordinarily starts a regulatory post-approval change process.

The product should always be created with the patient's needs and intended use in mind. Product development methods differ from company to company and from one product to another.[4] The strategy can also change, and it needs to be described in the submission. A candidate may opt for a blend of both an empirical and more methodical approach to product development. Incorporating prior knowledge, study findings using design of experiments, quality risk management, and knowledge management (ICH Q10) across the product's lifespan are a few examples of a more methodical approach to creation (also known as quality by design).[5] Such a methodical technique can improve obtaining the intended product quality and aid regulators in comprehending a company's plan. The understanding of products and processes can be updated with the information learned during the product lifecycle.[1-5]

Definition [ICH Q8 (R1)]

A methodical strategy for development that starts with predetermined goals and stresses knowledge of the product and process as well as process control, supported by reliable science and high-quality risk management.[6]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for planning, evaluating, and managing manufacturing through timely measurements of crucial quality and performance characteristics of new and in-process materials and processes, to guarantee the safety

of the finished product. The term "Quality by Design" (QbD) refers to an approach that includes improving scientific understanding of the critical processes and product qualities, developing controls and tests based on the limits of scientific knowledge during the development phase, and utilizing the knowledge gained throughout the product's life cycle to work on a continuous improvement environment. A pharmaceutical development strategy referred to as QbD focuses on formulation design and development as well as manufacturing procedures to uphold the required product quality. To guarantee the establishment and use of the subject-specific knowledge in an autonomous and integrated manner, guidelines and mathematical models are used.

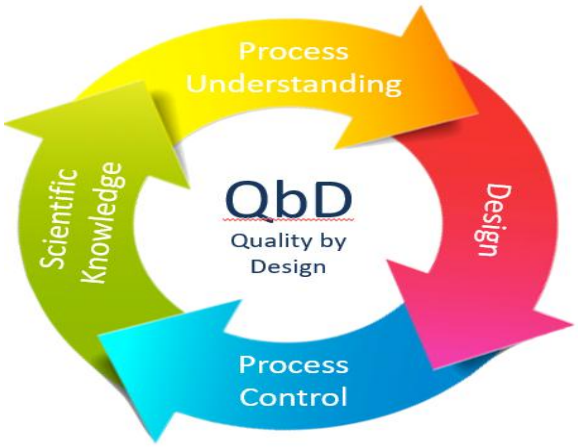

Fig. 1: content of quality by design.

Design

- The product is made to satisfy both patient needs and performance standards.
- The process is created to consistently meet the requirements for product quality.
- It is known how process parameters and initial raw materials affect product quality.
- The most important sources of process variability are found and managed.
- To ensure consistent quality throughout time, the procedure is constantly reviewed and modified.

Role of QbD[7-9]

1. Quality by Design ensures that a product is designed to meet patient needs and specifications for improved performance.
2. Another benefit of using QbD is that the process is designed to consistently achieve the important product quality requirements.
3. With the application of QbD, it is simple to comprehend the impact of process variables and initial raw materials on the quality of the result.
4. By using appropriate control procedures, it is possible to identify and control important causes of process variability.
5. QbD guarantees ongoing process monitoring, and it must also be updated frequently to maintain constant quality over time.

Steps involved in quality by design products[10-12]

1. Development of new molecular entity
a. Preclinical study
b. Nonclinical study
c. Clinical Study
d. Scale up
e. Submission for market Approval
2. Manufacturing
a. Design Space
b. Process Analytical Technology
c. Real-time Quality Control
3. Control Strategy
a. Risk-based decision
b. Continuous Improvement
c. Product performance

Seven quality by design steps start-up strategy

1. Engage a Quality by Design expert who is independent.
2. Have a gap analysis performed on your organization and process by the expert.
3. Host an introduction to quality by design workshop for all of your friends.
4. Examine the expert's report and advice.
5. Create a schedule for implementation, along with estimated costs.
6. Distribute the assets (or contract out).
7. Continue to work with the impartial specialist as your "Project Assurance" advisor.

A Process of QbD

A methodical methodology called pharmaceutical quality by design identifies important characteristics, the manufacturing process,[13] and the product specification.

Pharmaceutical quality by testing (QbT), a conventional strategy for ensuring product quality and performance, includes raw material testing, a set manufacturing process for drug products, in-process material testing,

and end-product testing. This approach differs significantly from QbD.

The manufacturing technique used by QbD is customizable, reliable, and produces repeatable results. The development and application of QbD heavily rely on knowledge management and quality risk management.[14]

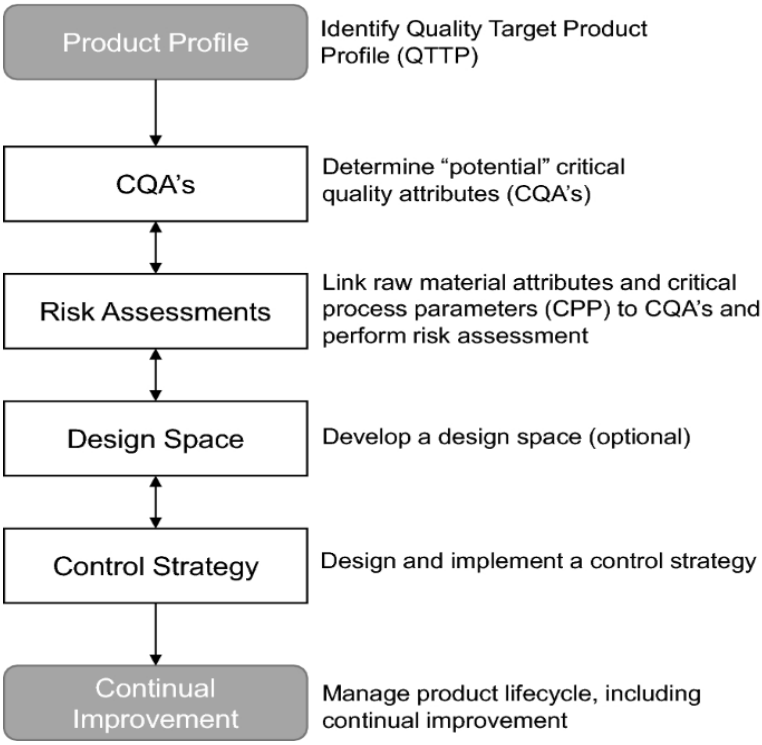

Fig. 2: Flow chart of a Process of QbD.

Elements of quantity by design

Identification of attributes that are crucial to quality from the patient's perspective occurs in a QbD approach to product development.[15] The components of QbD are as follows:

1. Establishing the quality, safety, and efficacy targets for the product.
2. Identifying potential drug product critical quality attributes (CQA) for research and management of those product features that affect product quality.
3. Determining critical material attributes (CMA)[16] and critical process parameters (CPP) and connecting them to critical quality attributes.
4. Establishing a control strategy with guidelines and measures for every stage of the manufacturing process.
5. Management of the product lifecycle and ongoing development.
6. These components offer a more organised method of pharmaceutical development, which promotes innovation.

Quality target product profile

Quality Target Product Profile (QTPP) is defined by ICH Q8 as "A prospective summary of the quality characteristics of a drug product, taking into account safety and efficacy of the drug product, that will ideally be reached to ensure the required quality.[17] It contains:

1. Therapeutic use
2. Dosage form
3. Route of administration
4. Dosage strength
5. Pharmacokinetics
6. The container closure system

Risk assessment

The CQAs for drug products are linked to risk assessment by material characteristics (such as density, particle size distribution, moisture content, etc.) and process parameters (such as temperature, drying rate, mixing speed, etc.).[18] The scientific process of risk assessment, which is a component of quality risk management, makes it possible to pinpoint the material characteristics and production-process variables that might have an impact on product CQA. Once the parameters have been determined, mathematical methods are used to increase the level of process comprehension.[19]

The foundation of QbD on ICH Guidelines Q8, Q9, Q10

ICH Guideline Q8 is for Pharmaceutical Development,
ICH Guideline Q9 is for Quality Risk Management,
ICH Guideline Q10 is for Quality Systems.

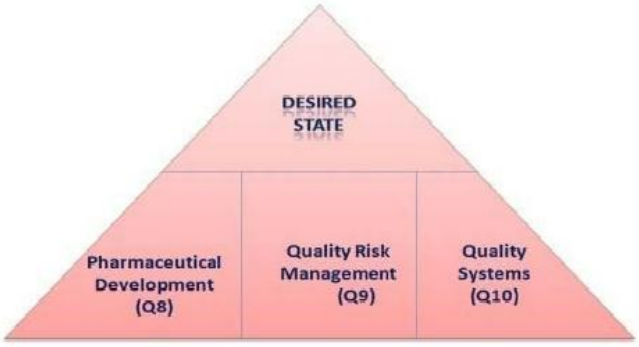

Fig. 3: Foundation of QbD.

Design space

The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes is described by the design space, which is a essential component of quality by design.[20]

- One of two ways to characterize a design space is by employing elegance mathematical relationships or by describing it in terms of different material qualities and processing factors.
- A design space is a more accurate representation of the established understanding process.
- Operations carried out within the design space produce goods with the appropriate quality traits.

Control strategy

The control strategy's job is to make sure that consistently high-quality products are produced.[21] It includes:

- Material input controls (Drug substance, excipients, packaging material, etc.)
- Maintenance of the predetermined product parameters
- Controlling important process variables.
- Testing the release in real-time.
- A general program of monitoring

Critical quality attributes

- Finding the essential quality characteristics, such as those defining purity, potency, and a substitute for bioavailability is crucial, critiquing, etc.[22] is predicated on how a quality trait or parameter affects the product's safety, effectiveness, and quality.
- Establish a connection between CPP and CQAs by identifying a parameter or attribute that can serve as a stand-in for clinical safety and efficacy.[23]
- Manufacturability is another trait that is essential to quality and is crucial to a business.
- A manufacturing process for an API may be more crucial than a manufacturing process for a medicinal product.
- The API is one part of a pharmacological product, moving the patient further along the continuum of criticality.[24] Several criticality levels can be used to describe different danger levels.
- The level of criticality rose as attribute or parameter boundaries approached the borders of failure.[22-24]

Certain Key Aspects of QBD

- A technique for "planning with the aim in mind," or developing the tactical framework for drug development, is the Target Product Quality Profile (TPQP). Recently, there has been an increase in the usage of the TPP for risk management, clinical and business decision-making, and development planning.[25]
- Excipient and Drug Substance Properties The drug material must be extensively characterized by its physical, chemical, biological, and mechanical qualities, such as solubility, polymorphism, stability, particle size, and flow properties,[26] to consistently attain the drug-product quality indicated on the label.
- Design and development of formulas since not all prototype formulations can be tested on humans, sensitive in vitro dissolving techniques must be created for a development program to be successful.
- Process Design and Development for Manufacturing It is impossible to separate process development from formulation design since a formulation cannot become a finished product without following a specified process. Process design is the first phase of process development, during which an overview of the desired manufacturing scales and commercial manufacturing procedures are documented.[27] All the elements that must be taken into account while designing the process, such as the facility, the tools, the material transfer, and the manufacturing variables, should be included in the outline. The QTPP and CQAs are additional aspects to take into account while developing processes.[25-27]

Advantages of QbD[28-31]

The QbD has a lot of benefits. Research has highlighted several difficulties that could arise in the application of QbD. These highlighted challenges outline numerous areas that FDA may take into account to hasten the adoption of QbD. When the FDA's activities are applied to the subdivisions, such as drug kind and adoption level, they become much more obvious. The advantages range from

1. In addition to economic savings.
2. It provides a high level of assurance regarding the quality of the drug product.

3. With QbD, sponsors' transparency can be improved, leading to a better comprehension of the control measures for the drug product to obtain approval and eventually commercialization.
4. With the deployment of QbD, the scale-up, validation, and commercialization can become logical, transparent, and predictable.
5. It improves the effectiveness of the methods used to make pharmaceuticals.
6. It reduces harsh punishments and drug recall.
7. It makes regulatory oversight more effective.
8. It updates manufacturing modifications made after approval and regulatory procedures.
9. Opportunities for first cycle approval are improved.
10. It reduces the computer supplement and aids in ongoing improvement.
11. It shortens the time required for CMC review while improving the quality of Chemistry, Manufacturing, and Control (CMC).
12. Information in regulatory submissions is improved flexibility in regulations.
13. Reduces variation in the product.

Limitation of the scope of QbD

1. QbD increases inquiries, scrutiny, and approval delays.
2. Causes pre-approval inspection, which causes delays in approval.
3. Design space and Design of Experiments (DoE) are the same.
4. "Criticality and Risk" denote that when a parameter is constrained, its criticality is controlled. [32]

CONCLUSION

Quality by design strategy contributes to the development of efficient and cost-effective products and their production process in a shorter period. Through QbD, reproducible goods with the necessary quality. Although QbD is still in its infancy and has to be standardized globally. Due to its many advantages, the pharmaceutical sector is adopting QbD concepts and using this method in the product development process. Complying with new technological developments and impending regulatory needs is also essential. Therefore, QbD has a bright future in the creation of high-calibre medications.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

QbD: Quality by Design; QbT; Quality by Testing; CQA: Critical Quality Attributes; CMA: Critical Material Attributes; CPP: Critical Process Parameter; QTPP: Quality Target Product Profile; CMC: Chemistry, Manufacturing, and Control; DoE: Design of Experiments.

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