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Quality by Design Explained: Modern Approach to Product Development

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ABSTRACT

Regulatory bodies have given quality an important value for pharmaceutical product. The pharmaceutical industry is always looking for methods to improve and guarantee the product's quality, safety & efficacy. Quality by Design (QbD) is a modern approach for quality of pharmaceuticals. The ICH quality guidelines serve as its foundation, and its primary components are Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System), and Q11 (Development and Manufacturing of Drug Substances). It serves as a bridge between industry and drug regulatory agencies as they work toward a scientific, risk-based, holistic, and proactive approach to pharmaceutical product development. This study focuses on creating and developing formulations as well as manufacturing procedures to assure product quality within established parameters. This review article's goal is to explain how to ensure pharmaceutical quality and medication development while also discussing the idea of pharmaceutical quality by design.

INTRODUCTION

Quality: For pharmaceutical products, quality has been assigned by all regulatory agencies. The term quality is commonly used by every person but there is no precise definition of it. There are totally different definitions of quality supported specific circumstances. This term includes that the purity, identity, & strength of the substances meets the quality standards. Quality means consumer satisfaction with products, services, and processes. The customer demands perfection in quality, dependability, cost effectiveness, and timely delivery. Customer satisfaction may be achieved in two ways: by providing features and ensuring that the items are defect-free. The product must include features such as performance, trustworthiness, robustness, zero error status, ease of use, and serviceability, as well as be devoid of flaws. Quality activities must discover quality issues early enough to enable for appropriate response without compromising cost, time, or quality. The emphasis should be on preventative measures rather than simply correcting quality issues. Quality may be the driving factor that propels leads to many characteristics. Thus, quality must be integrated into products and services through appropriate planning in order to avoid future failures [1-3].

Quality by design: The pharmaceutical industry emphasizes product purity, quality, safety, and efficacy. The application of scientific techniques like QbD (Quality by Design) and PAT (Process Analytical Techniques) has led to higher product quality. Scientific tools can provide clear and adequate information throughout the product development and manufacturing processes. These scientific QbD technologies can lower the risk of loss by improving the overall output and quality of the process and product. Nowadays, the QbD technique is widely used and successfully used in regular formulation development and manufacture. The ICH guidelines specify all of the primary objectives for quality issues. The ICH guidelines explain the Quality by Design. Q8 (pharmaceutical development), Q9 (pharmaceutical risk management), and Q10 (pharmaceutical quality systems) are three of the ICH recommendations that emphasize quality by design and associated features. The ICH guideline Q8 (pharmaceutical development) is broken into two sections: part 1 addresses pharmaceutical development, and part 2 is an appendix to the guideline that describes the concepts of QbD. The ICH Q8 criteria described Quality by Design, which states that "quality can't be tested in products, i.e. quality should be inbuilt by design" [4-6].

The Quality by Design was outlined by ICH Q8 (Pharmaceutical development) 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. It involves designing,

developing formulas, and manufacturing procedures to guarantee that predetermined product standards and specifications are met" [7-8].

2. Background and concept

Quality by Design is an idea initial given by Joseph M. Juran. He is known as "father of quality". He stated that it is possible to plan or design the quality. He thinks by improving the quality of the products and procedures to boost business results [9]. The QbD was mentioned in ICH Q8, which defines that, "To determine quality it can't be tested in products, i.e. Quality should be built into product by design". In 1970, Toyota created a number of QbD concepts to improve their early-stage cars. Since then, other industries, such as technology and telecommunication, have adopted these concepts and created QbD. Medical device designers started taking product quality into consideration in 1990. A report on 21st-century Good Manufacturing Practices was released by the FDA in the middle of 2002. According to these documents and publications, industries should develop the safety, quality, efficacy, and purity of their new product as soon as possible [10-13].

3. Key characteristics of QbD

- ✓ A method for efficient and cost-effective drug development
- ✓ A systematic and effective procedure
- ✓ Quality will be integrated over time.
- ✓ Used in the development of drug goods and chemicals
- ✓ Applicable to analytical strategies.
- ✓ Can be enforced in single step or in full process.
- ✓ It can be used throughout the drug's life cycle.
- ✓ Always influenced by regulators [14-16].

4. Opportunities of QbD

- ✓ Efficient, adaptable and versatile system.
- ✓ Optimize production potential while lowering costs, project rejections, and waste.
- ✓ Develop scientific knowledge of all products and processes.
- ✓ Higher interaction with industry on scientific problems.
- ✓ Maintain consistent data.
- ✓ Implement risk management [17-19].

Fig: 1 Steps in quality by design approach **[20-23]**

In short, Quality by design is a systematic and knowledge-based scientific approach that maintains Critical Quality Attributes through well-described control strategy and design space by combining and relating of Critical Material Attributes and Critical Process Parameters to produce the predefined Quality Target Product Profile as described in fig. 1 [20-25].

5. Target Product Profile

Target Product Profile is defined as a "prospective and dynamic summary of the quality characteristics of a drug product that are going to be achieved to confirm that the required quality, and so the efficacy and safety, of a drug product is realized". It links the drug development activities with specifications. The concept focuses on patient care and labelling, including:

- Mechanism of action: The way in which the product affects a biological organism.
- Indication for use: The population, along with the target sickness or symptom of a disease or ailment.
- Clinical pharmacology: Pharmacokinetics, distribution, and transformation mechanisms.
- Primary efficacy outcomes: The primary clinical result measure.
- Secondary efficacy outcomes: Other conditions that might be fulfilled during a clinical trial but don't appear to be necessary for a successful, positive study outcome [26-28].

6. Quality Target Product Profile (QTPP)

QTPP is a logical extension of the Target Product Profile for product quality. Based on ICH Q8 (R2), QTTP is "prospective summary of the quality characteristics of a drug product that are going to be achieved to ensure the desired quality, taking into consideration safety and efficacy of the drug product". It is a drug development tool. It is the quality attributes that a pharmaceutical product must have in order to fulfil the requirements for therapeutic benefit.

QTTP has recently become widely employed in development planning or design, clinical and commercial decision making, contacts with regulatory agencies, and risk management. The QTTP helps formulation scientists design formulation strategies and maintain targeted, efficient, and cost-effective formulation efforts. QTPP refers to identity, purity, assay, dose form, and label stability. A drug product created, produced, and manufactured in line with QTPP specifications, including dissolution/release acceptability requirements. It sets measurable goals for:

- Indications and routes of administration
- Strength and dosage form
- Properties that influence pharmacokinetic characteristics, such as mechanical performance and dissolution
- Drug product standards, such as quality, purity, stability, sterility and drug release [29-31]

7. Critical Quality Attributes

Identifying the relevant CQA comes next after determining the QTPP and it outlines as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate and acceptable limit, range, or distribution to substantiate the desired product quality" [32-33]. As a result, CQAs are subsets of QTPP that may alter if formulation or process parameters change [34]. For example, QTPP may include extra pharma product quality elements such as strength and dose form that CQA does not address because they will not change during the drug development process. However, CQA will contain QTTP features such as content uniformity, assay, dissolution, and permeation flow [35]. Determination of Critical

Quality Attribute (CQA) from the targets outlined in QTPP, CQA based on the following factors:

1. Analysis of effects of changing formulation and/or process variables.
2. Severity of a patient's harm when a product doesn't meet the permitted range or specification for that feature [36-37].

- **Critical process attributes**

In order to ensure that the process achieves the intended quality result, it should be monitored or regulated because it includes independent process aspects that are likely to have an impact on the CQAs of an intermediate or final medicinal product.

- **Critical material attributes**

To achieve the intended quality of the output material, an input material's (active pharmaceutical component or excipients) chemical, physical, biological, or microbiological characteristic or feature must lie within a specified range [38]. The relationship between all the parameters are shown in fig. 2.

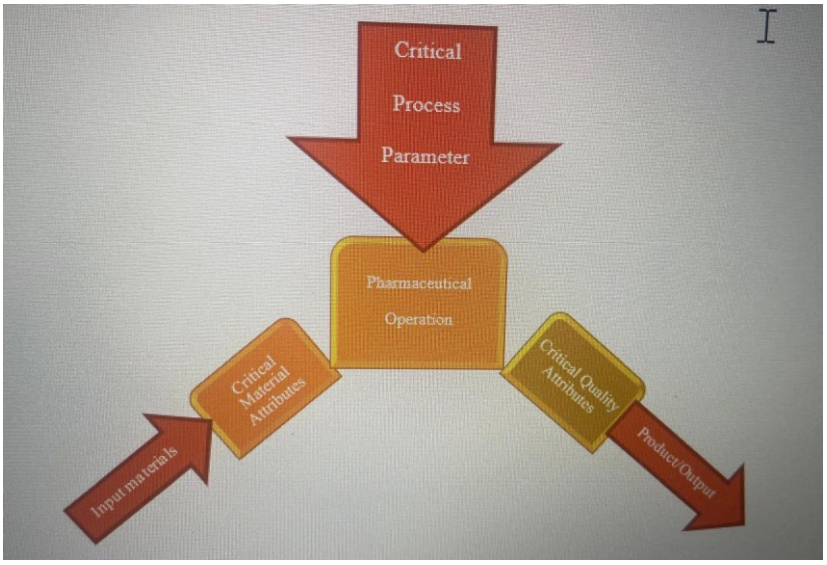

Fig: 2 Relationship between CMAs, CPPs and CQAs **[38-39]**

8. Risk Assessment

Hazards are identified through risk assessment, which also analyses and evaluates the risks of being exposed to certain hazards. The initial step in any quality risk assessment is to develop a specific risk question or describe the disadvantage. If the hazard or risk in issue is adequately defined, it will be easier to determine the types of information required to answer the risk question and the appropriate risk management instrument. Three basic questions are usually helpful in accurately defining the risk for assessment purposes:

1. What may go wrong?
2. What is the likelihood that something will go wrong?
3. How severe are the consequences?

Risk management tools & methods:

- ✓ **Failure Mode Effects Analysis (FMEA)**
  - Simplify complicated, large-scale operations to manageable steps. (The efficacy of risk management initiatives may be tracked and risks can be prioritized using FMEA)
- ✓ **Failure Mode, Effects and Criticality Analysis (FMECA)**
  - The pharmaceutical business should primarily use FMECA for manufacturing process failures and hazards since it connects criticality to severity, probability, and detectability.
- ✓ **Fault Tree Analysis (FTA)**
  - Combinations of the tree of failure modes and logical operators (FTA) can be utilized to determine the failure's primary cause. To fully understand the underlying cause of complaints or deviations, FTA may choose to look into them.
- ✓ **Hazard Analysis and Critical Control Points (HACCP)**
  - A systematic approach to criticality that is proactive, preventive, and structured (HACCP can be used to identify and manage risks related to physical, biological, and chemical hazards).
- ✓ **Hazard Operability Analysis (HAZOP)**
  - The Hazard Outsourcing Process (HAZOP) is a brainstorming technique that may be used for manufacturing processes, as well as for outsourced production, formulation, upstream suppliers, instruments & facilities for drug substances and drug products.
- ✓ **Preliminary Hazard Analysis (PHA)**
  - The probability of the risk occurrence occurring Early in a project's development, when there is minimal data or information on operational procedures or design elements, PHA is most frequently utilized.
- ✓ **Risk ranking and filtering**
  - Assessing and classifying risks based on the factors that contribute to each risk (risk filtering and classification can be used to choose production locations for regulatory or industry inspections) [40-42].

9. Design Space

A Design space is described as, "multidimensional combination and interaction of input variables (e.g. material attributes and process parameters) which are incontrovertible for quality assurance". The FDA guidelines suggest that developing a design space is optional because understanding of the product and process can be established without an appropriate design space. But a higher approach can help you better understand and manage a system as a whole. It is possible for a single unit operation, many unit operations, or the entire process to have its own design space [43-44].

Uses of Design Space

1. Connection between the process input (process parameters & input variables) required quality.
2. Used for one or more-unit operations or until the process is finished.
3. Projected by applier.
4. Operating between the design space: not considered as an associate modification.
5. Subject to regulatory approval and assessment [45-46].

Control Strategy

ICH Q10 (Pharmaceutical Quality systems) define a control strategy as "a planned set of controls, derived from current

product and process for understanding that ensures process performance and product quality". It includes parameters and their attributes associated to with drug-product materials or compounds, instrumentally operational conditions, facilities, finished-product specifications, in-process controls, associated observation, management methods and frequency. It ensures that the procedure stays inside the parameters established by the design space.

Specifically, the control strategies may even be included.

- ✓ Managing the properties of input materials (such medication components, excipients, and primary packaging materials) by understanding how they impact the end product's quality.
- ✓ It covers the product's specifications.
- ✓ It deals with procedure controls.
- ✓ It covers facilities controls, including utilities, environmental systems, and operational conditions.
- ✓ The unit activities that affect the quality of the downstream process or end product, including drying on degradation and particle size distribution in granulate on dissolving, are controlled.
- ✓ The program will be monitored (e.g., through regular product testing) to confirm variable prediction models.

Throughout the entire product lifecycle, from product and process design to the final product, as well as the active pharmaceutical ingredient (API) and drug product manufacture, packaging, and distribution, control strategies will be implemented to define the necessary controls—supported patient requirements [47-50].

10. Continuous Improvement throughout Product Life Cycle

The quality approach to method development is not the same as the life cycle approach. Businesses have the chance to assess novel strategies to improve product quality at every stage of the product lifecycle. A major component of the present quality system is continuous improvement, which increases productivity by streamlining processes and getting rid of unnecessary production efforts.

This includes good integration of process knowledge into the management of deviations, change control, etc. According to Morefield, "this includes continuous improvement of process performance and therefore the design allows flexibility for continuous improvement in analytical technique can without prior regulatory approval due to previously made design space". Throughout the product's lifecycle, changes are also needed to enhance the operational performance or the control strategy. Changes might include, but are not limited to, the inclusion of an additional controls, the introduction of a new technique or technology, the alleged purpose of incorporating a new impurity or tightening specifications, or the alignment with a procedure in a very compendial updated. The nature of the modification dictates the action to be taken and a risk assessment should be carried out to identify what action is needed and, therefore, the change or modification should be documented [51-52].

CONCLUSION

Quality by Design (QbD) marks a transformative approach in pharmaceutical development, shifting away from conventional quality control toward a more proactive, science-driven, and risk-based methodology. By incorporating quality considerations from the earliest stages of development, QbD improves product consistency, enhances manufacturing efficiency, and ensures better alignment with regulatory standards across the product lifecycle. Anchored in the ICH guidelines—Q8, Q9, Q10, and Q11—this framework fosters a comprehensive understanding of critical process and product parameters, enabling manufacturers to predict potential risks and maintain control over variability. In the face of evolving regulatory demands, implementing QbD is not just beneficial but essential for developing reliable, high-quality pharmaceutical products. Ultimately, QbD advances the mutual objective of both industry and regulators: providing patients with safe, effective, and high-quality medicines.

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