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REVIEW ARTICLE

Quality by Design Approach: An over view on Design Development and Evaluation of Pharmaceutical Products

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ABSTRACT

Quality by Design is a novel approach to ensuring the quality of pharmaceutical products. It goes over how to use Quality by Design to ensure pharmaceutical quality. This review defines Quality by Design and highlights some of its features. Each unit operation's quality attributes and process parameters are identified. Pharmaceutical Quality by Design is discussed along with its benefits, potential, and steps. It is based on ICH Guidelines Q8, Q9, and Q10 for Pharmaceutical Quality Systems and Pharmaceutical Development, respectively. Pharmaceutical development aims to create a high-quality product and manufacturing process that consistently produces the product's desired results. Things must be designed with quality; it cannot be tested into them. The Quality target product profile, important quality traits, and major components of Quality by Design are all included. It also compares product quality based on end-of-life testing to product quality based on Quality by Design.

Keywords: Quality by Design (QbD), Critical quality attributes, Design space, PAT (Process Analytical Technology).

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INTRODUCTION

The pharmaceutical market has long been regarded as one of the most strictly regulated industries, consistently producing high-quality drug products for human consumption with the desired pharmacotherapeutic effects for the treatment of a wide range of ailments [1]. The major problems with drug product quality can be attributed to a variety of factors, including variable starting materials, a lack of manufacturing process automation and control, and a lack of understanding of the product and process parameters [2]. Figure 1 depicts the key sources of variability associated with the development of pharmaceutical products, which are largely responsible for product recall.

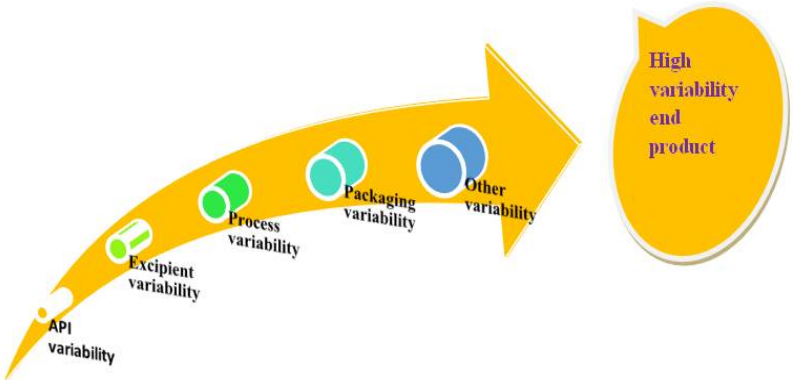

Fig.1. Sources of Variability in drug product quality

The United States Food and Drug Administration (USFDA) took the first step toward instilling quality paradigms into pharmaceutical development and regulatory practise as a result of poor pharmaceutical product quality [3]. In this regard, a concept paper titled "Pharmaceutical cGMP for the Twenty-First Century" was published in 2004, highlighting the agency's vision for revolutionising the quality [4]. 2 Following this initiative, the ICH established various regulatory guidance's (Q8, Q9, and Q10) and established the concept of quality by design (QbD) as a holistic approach that results in high-quality, robust drug products [5].

QbD is based on the principle that "Quality cannot be tested into a product, rather it should be built into it". The "design space" of a product includes all of its equipment, materials, and operators. The design area should be well specified and defined prior to obtaining regulatory clearance. Variables affecting the quality of the produced goods are tracked when production occurs outside the design space. [6]. All of these factors have been examined for QbD purposes, and conclusions have been reached. The regulatory submission dossier contains all of this information. The process variables discovered during the development stages will be used to generate QRM [7]. Before beginning development studies, the product's QTPPs must be defined with the ultimate product quality in mind, and assessments are performed to achieve the target product quality. Product QTPP includes design space, specifications, and production controls.

Design [8].

1. The product is created to satisfy the demands of the patient as well as the performance criteria.
2. The process is meant to ensure that product quality criteria are routinely met.
3. On product quality, the impact of initial raw materials and process variables has been identified.
4. Process variability's critical causes are recognised and managed.
5. The process is constantly reviewed and modified to ensure that quality is maintained throughout time.

Well-understood products and processes and quality by design (QbD) [9]

The term "quality by design" describes the process of creating manufacturing processes during the product development stage in order to consistently guarantee a specific quality at the conclusion of the manufacturing process. Simple schematic representation of QbD shown in **Fig.2.**

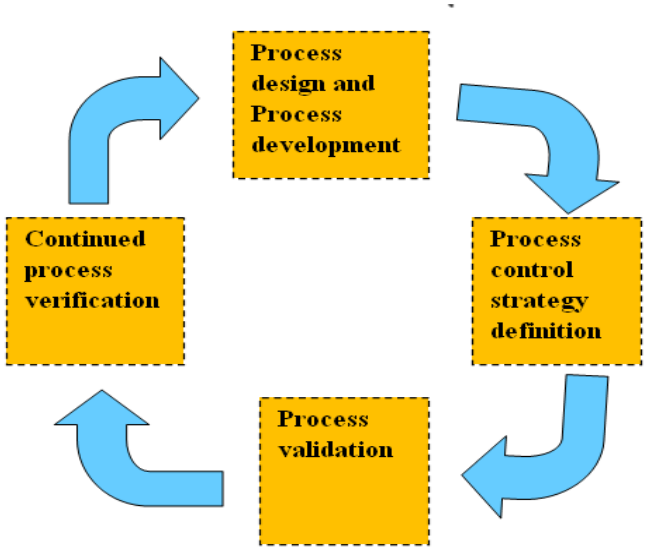

Fig.2: Quality by Design

QbD BY PHARMACEUTICAL PRODUCTS [10]

Despite its emphasis on quality, the pharmaceutical industry has fallen behind other industries in terms of manufacturing efficiency and productivity. Current Pharmaceutical Industry Situation: Revalidation costs money. Offline analysis for ongoing needs Specifications for the products are the main means of control. Unforeseen scaling-up problems inability to comprehend mistakes A methodical approach to development: This begins with clearly defined goals. Focuses on understanding of the product and process Managing processes understanding in (Figure 3).

Fig.3. Process Control

QUALITY TARGET PRODUCT PROFILE [11]

A summary of the drug development programme in terms of labelling concepts, with a primary focus on safety and efficacy. Description Pharmacology in Clinical Practice Indications and Applications Contraindications Warnings Precautions Adverse Effects Drug Addiction and Abuse Excessive dosing Animal Pharmacology and/or Animal Toxicology Dosage and Administration Clinical Research A natural extension of the Target Product Profile for product quality - The drug product must possess certain qualities (attributes) in order to establish formulation strategy and maintain the formulation's efficacy and to provide the therapeutic benefit stated on the label guide. It aids in identifying what is required/critical for the patient/consumer in the Quality Target Product Profile (such as Critical Quality Attributes, CQAs) Identifies risks and the best ways to manage them. Optimizes the use of tools/enablers Creates and facilitates knowledge sharing [12]. An iterative, learning, life-cycle process for improving decision-making and therapeutic outcomes for the benefit of the patient [13].

CRITICAL QUALITY ATTRIBUTES

It is necessary to identify the critical quality attributes, such as those defining purity, potency, and surrogate for Bioavailability Criticality, among others. It is based on the impact of a quality attribute/parameter on the product's safety, efficacy, and quality (manufacturability). Create a link between CPP and CQAs by identifying attributes or parameters that can be used as a surrogate for clinical efficacy and safety (important to the patient) (Figure 4)[14].

Manufacturability is another important business attribute that is critical to quality. The level of criticality for an API manufacturing process may differ from that of a drug product manufacturing process. API is one component of a drug product and one step away from the patient's Criticality continuum. Multiple levels of criticality can be used to describe various levels of risk. [15].

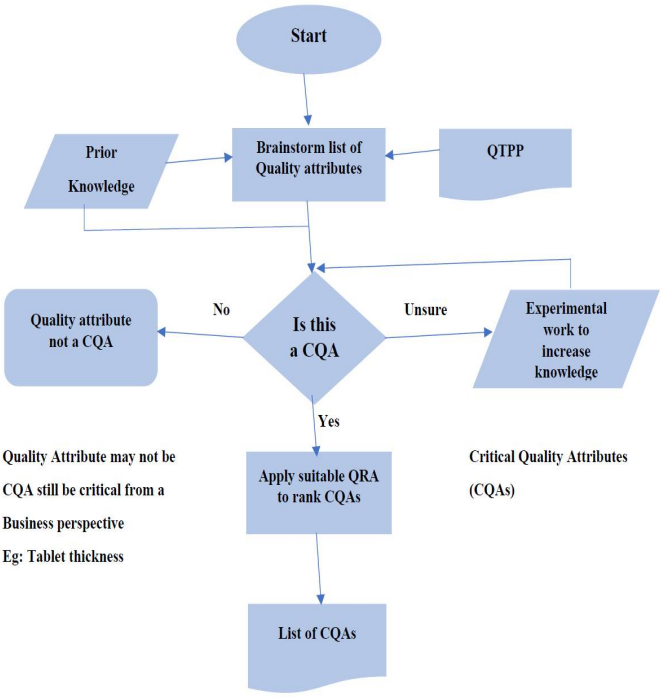

Fig.4. Decision tree to decide Critical Quality Attributes

Certain Basic elements of QBD [16]

- **The Target Product Quality Profile (TPQP)**

The TPQP is a tool for laying the strategic groundwork for drug development, or "planning with the end goal in mind."

Drug Substance and Excipient Properties

To achieve the labelled drug-product quality, the drug substance must be thoroughly characterised in terms of physical, chemical, biological, and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties.

- **Manufacturing Process Design and Development**

Process design is the first stage of process development, in which an outline of commercial manufacturing processes, including intended manufacturing scales, is documented.

Testing of the final product versus quality by design [17]

A comparison is made between product qualities determined by end product testing and quality determined by design. These activites shown in Figure 5, 6.

Fig.5: Flow Chart for Product Quality by End Product Testing

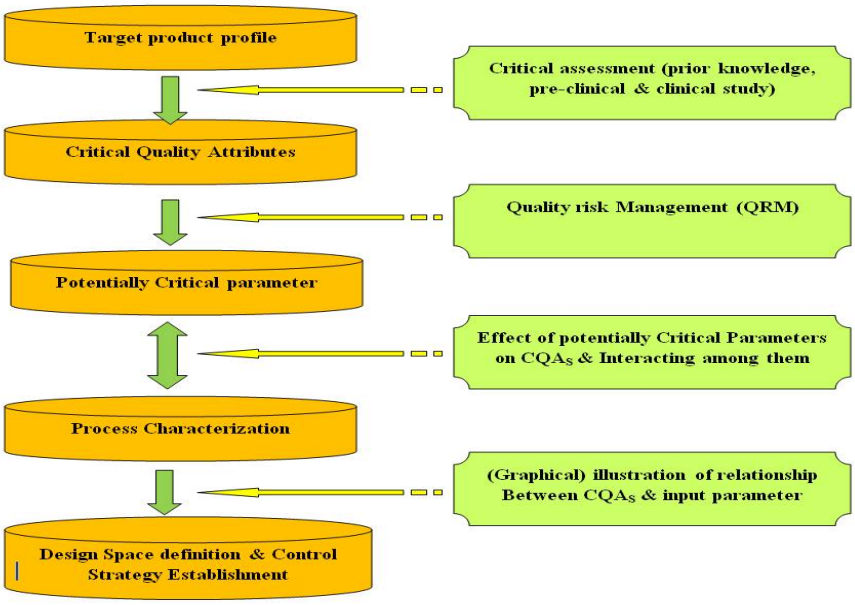

Fig.6. Simplified flow chart for QBD Process

ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QbD

ICH Guidelines Q8 for Pharmaceutical Development [18,19]

The US FDA announced Quality by design (QbD), a recent innovation in pharmaceutical regulation, pushed the pharmaceutical sector to design the final product's quality rather than simply test it. A systematic approach to development, QbD is "based on sound science and quality risk management, emphasises product and process understanding, and starts with predefined objectives," according to ICH guideline Q8.

1. Components of Drug Product Given by ICH Q8:

- Drug Substances:[20]

The drug substances' compatibility with excipients should be assessed. The compatibility of the drug substances with each other should also be evaluated for products that contain more than one drug substance [21].

- Formulation Development:[22]

The development of the formulation includes identifying the attributes that are critical to the quality of the drug product and highlighting the evolution of the formulation design from the initial concept to the final design. Comparative in-vitro studies, such as Dissolution (or) in-vivo studies, such as BE, connect clinical formulations to proposed commercial formulations [23].

Design of experiments or other tools are then used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy. Given below, is a fish-bone diagram for depicting the cause and efect relationship among the formulation and process variables shown in **Figure 7[24]**.

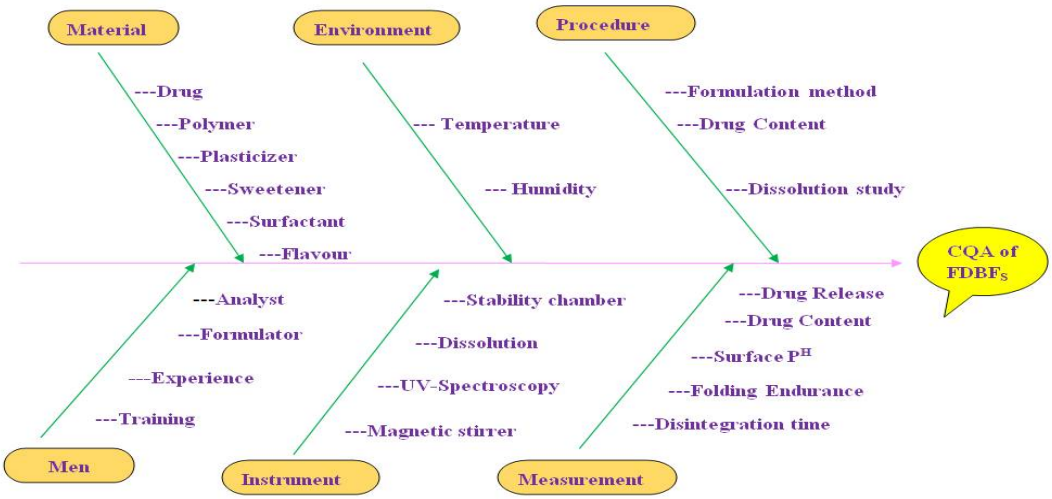

Figure 7: Ishikawa fish-bone diagram depicting the cause and effect relationship among the formulation and process variables

- Container and Closure System
- The materials used for primary and secondary packaging should be justified.
- An interaction between the product and the container or label should be considered[31].

ICH Guidelines Q9 for Quality Risk Management: [25]

Provides general guidelines and references for some of the most important risk assessment tools [26]. It offers the following non-exhaustive list of common risk management tools. Basic risk management facilitation methods (Ishikawa fishbone diagram, flowchart, check sheets, etc. Fault tree analysis [27].

ICH Guidelines Q10 for Quality systems: [29,30]

Pharmaceutical Quality Systems describe how Quality by Design works to ensure drug product quality on a high level. These guidelines apply throughout the product's lifecycle to the processes that aid in the design, development, and preparation of drug substances such as API and drug products such as biotechnology and biological products. Foundation of QBD Representation shown in Figure 8[31].

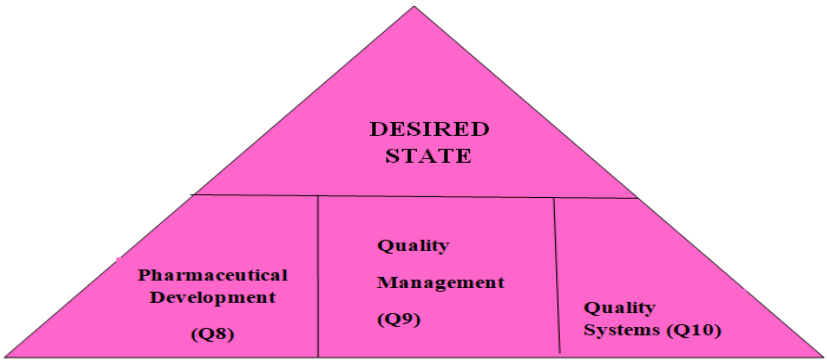

Figure 8: The Foundation of QBD

Critical Concept: Design Space

Combination on multiple dimensions with interactions Variables (e.g., raw material attributes) and process parameters are put through multidimensional interactions[32,33].

- ✓ Quality assurance has been demonstrated.
- ✓ Defined by applicant and reviewed by regulator
- ✓ Defined regulator
- ✓ Once the design space has been approved, the regulatory post-approval change requirements will be reduced.
- ✓ approval Design space inside vs. outside Inside space - Regulatory manoeuvrability within the design space Regulatory domain[34].

APPLICATIONS OF QUALITY BY DESIGN

Qbd's advancement in pharmaceutical development and manufacturing can be explained in comparison to the traditional approach [35].

- **In Pharmaceutical Development**

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

- **In life cycle management**

Continual improvement enabled within design space.

BENEFITS OF QbD IMPLEMENTATION FOR THE FDA [36]

- It improves the scientific basis for review and allows for better coordination between review, compliance, and inspection.
- Enhances the information provided in regulatory submissions.
- Ensures greater consistency
- Improves quality of review (establishing a QMS for CMC).
- Allows for greater decision-making flexibility.
- Ensures that decisions are based on science rather than empirical data.
- involves many disciplines in the decision-making process.
- Utilizes resources to deal with greater risks

BENEFITS TO INDUSTRY [37,38]

- ✓ Ensures more successfully designed products with fewer manufacturing issues Reduces the amount of manufacturing supplements needed for changes made after a product has been released; relies on process and risk understanding and risk mitigation.
- ✓ Permits the use of new technology without regulatory oversight to enhance manufacturing.
- ✓ Enables potential manufacturing cost reductions overall –less waste
- ✓ Ensures less hassle during review –reduced deficiencies–quicker approvals
- ✓ Enhances FDA interactions by dealing on a scientific rather than a procedural level.
- ✓ Allows for ongoing product and production process improvements.

Pharmaceutical Development

Widely used in pharmaceutical development and manufacturing basic schematic representation shown in **Figure 9**.

Fig. 9. Pharmaceutical developments

Utilizing QBD in Process Analytical Technology[39, 40]

a method for planning, assessing, and managing production through the timely measurement of critical quality performance characteristics of raw materials, processes, and materials used in production, with the aim of ensuring the quality of the finished product. It has been proven that a multidimensional combination and interaction of process parameters and input variables can provide quality assurance.

- Linkage between process inputs and critical quality attributes
- Proposed by Applicant
- Subject to regulatory assessment and approval
- Implementation before or after MA
- Established for one or more unit operation(s) or up to complete process
- Working within the design space: not considered as a change.

Quality by design methodology used in the coating process [41]

Quality should be ingrained in products rather than tested into them. The following are variables that have an impact on the coating process is shown in Figure: 10.

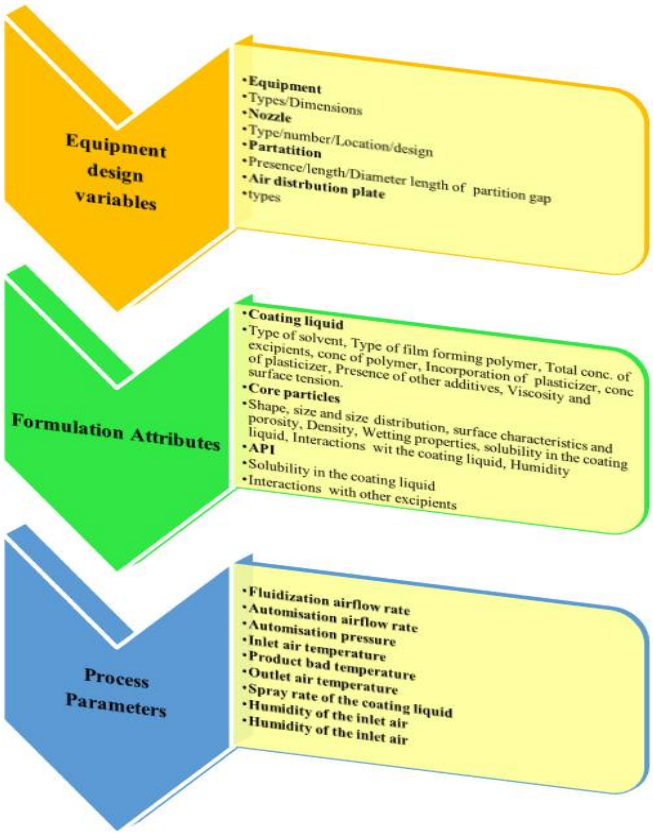

Figure 10: Parameters of the coating process

CONCLUSION

An effort to develop a reliable method that can be demonstrated with a high degree of assurance that it will consistently produce data that meets predetermined criteria when used within predetermined boundaries is the aim of a well-characterized method development effort. All potential factors (the inputs) and all crucial analytical results (the outputs) are examined to ascertain the relationships during method development. A technique similar to that described in ICH Q8 and Q9 is used to identify critical analytical factors. A QbD strategy based on a risk-assessed change control procedure should be used instead of continuing with analytical technology transfer exercises and ICH validation. Every time a method is changed, a risk analysis should be done. To make sure the method performance criteria are still met, a method evaluation and, if necessary, an equivalency exercise should be carried out if the change has the potential to move the method outside of its known design space. QbD is the future of product and process improvement, and as such leads to continuous improvement and innovation in products and processes.

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