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Critical evaluation of quality by design software

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Abstract

Quality by design (QbD) represents the modern approach to ensuring pharmaceutical quality. This concept has significantly influenced the progress of pharmaceutical sciences, having been established and applied globally in accordance with the International Conference on Harmonization (ICH) Guidelines. The proposed ICH guidelines—Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems—provide a foundation for integrating quality into products.

In the QbD framework, it is crucial to define the desired product performance profile, known as the Target Product Profile (TPP), and the Target Product Quality Profile (TPQP), as well as to identify Critical Quality Attributes (CQA). Based on this, we can design both the product formulation and the process to meet these attributes. This leads to recognizing the impact of raw material Critical Material Attributes (CMA) and Critical Process Parameters (CPP) on the CQAs, and identifying sources of variability

Keywords: Quality By Design; Design of Experiments; Target Product Profile (TPP); Target Product Quality Profile (TPQP); Critical Process Parameter (CPP)

1. Introduction

The goal of pharmaceutical manufacturing is to consistently create a high-quality product and process. In this rapidly expanding industry, ensuring consistency is crucial when developing new products. The primary objective of a pharmaceutical product is its procedure. Its effectiveness ensures the desired outcome is reliably achieved. Quality should be built in from the beginning, not just checked afterward. Based on gathered information, product development studies and method variables form the basis for Quality Risk Management (QRM). Prior to development, the Quality Target Product Profiles (QTPPs) must be determined. The goal of evaluation is to achieve the highest consistency possible. The QTPP includes the plan, specifications, and production controls. Quality by Design (QbD) in pharmaceutical sciences, proposed by the FDA and ICH, emphasizes that quality should be built into the product, not tested into it.

1.1. Definition of Quality by Design

According to ICH Q8 (R1) guidelines, Quality by Design (QbD) is a systematic approach to development that starts with predefined objectives and focuses on product and process understanding and control, grounded in sound science and quality risk management. As per FDA PAT guidelines, QbD involves designing, analysing, and controlling manufacturing through timely measurements of critical quality and performance attributes during processing, impacting product quality and safety.

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1.2. Quality by Design

Quality by Design (QbD) involves creating and producing high-quality products. Manufacturing techniques ensure that a consistent standard of quality is maintained throughout the development process until production is complete.

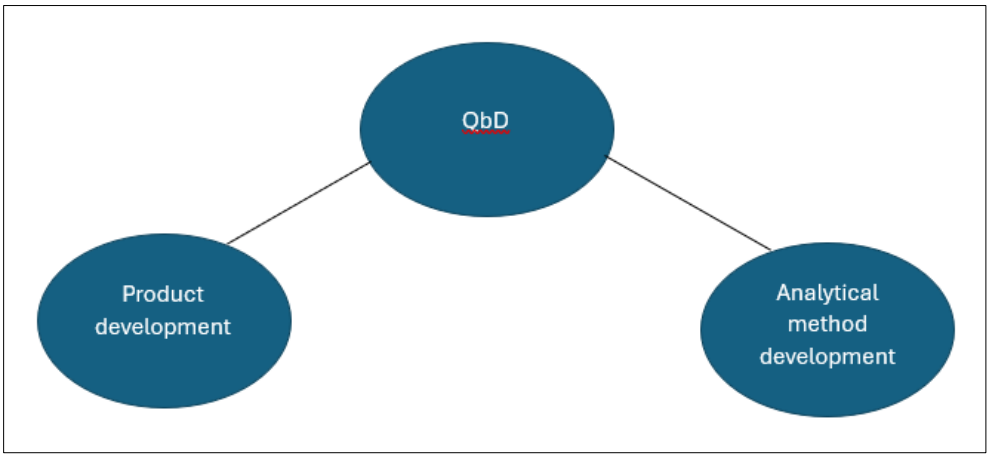

Figure 1 Quality by Design

1.3. Concepts & Backgrounds of QbD

- Concept first outlined by Joseph M. Juran
- In 1970, Toyota pioneered many QbD CONCEPTS
- In 1990, Medical devices began to incorporate Quality by Design aspects
- In mid-2002 FDA published a concept paper on cGMP for 21st century

1.4. QbD's 3 goals

- Getting high-quality products is the primary goal of QbD.
- Positive performance testing is one of the other goals.
- To guarantee the integration of process and product expertise acquired throughout development.

1.5. QbD's Benefits

- Batch failures must be prevented at all costs.
- Reduce deviations and costly investigations to prevent regulatory compliance issues.
- Empower skilled personnel with an effective, agile, and scalable system.
- Establishing a scientific knowledge base for all services can boost production efficiency, reduce costs, and minimize project rejections and waste.
- Scientific collaboration with business enterprises has enhanced.
- Maintain consistency in the information provided.
- Integrate risk management into the policy.
- Reduce the time spent testing the final product, enabling quicker release decisions.

2. Steps Involved in Quality by Design Products

2.1. Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval.

2.2. Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

2.3. Control Strategy

- Risk based decision
- Continuous Improvement

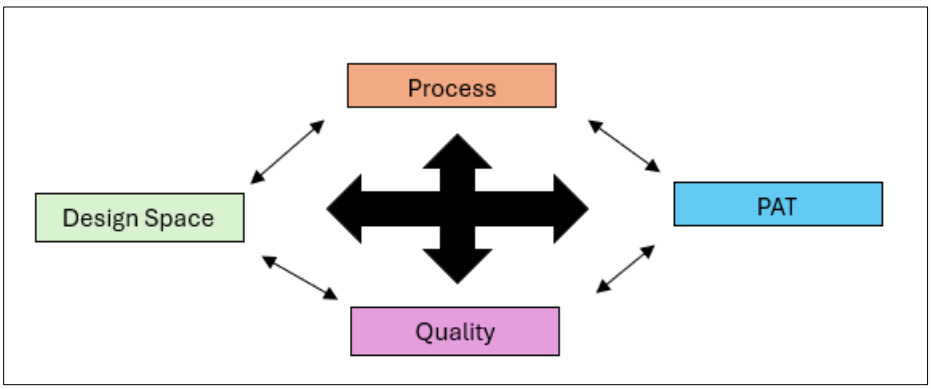

Figure 2 Steps Involved in QbD

2.4. Characteristics of QbD

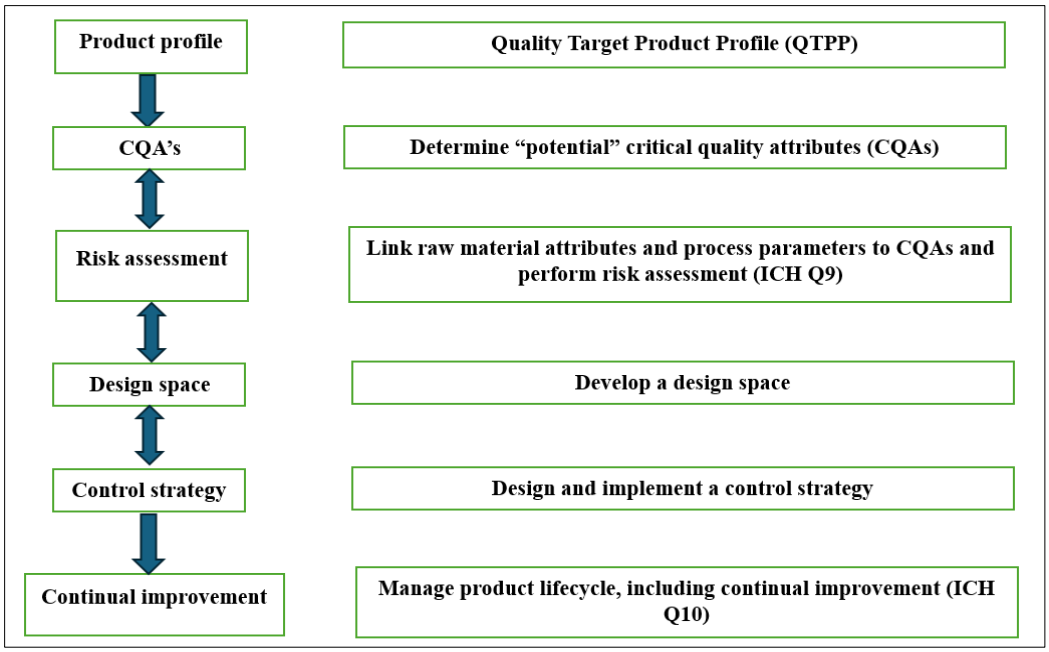

Figure 3 Characteristics of QbD

It involves the following key elements during pharmaceutical development.

3. Quality Target Product Profile (QTTP)

- **Definition**: A prospective summary of the quality characteristics of a drug product intended to ensure the desired quality, safety, and efficacy.
- **Purpose:**
  - Guides drug production strategy.

- Aids in strategy planning, clinical and commercial decision-making, and R&D.
- Ensures the drug product consistently achieves the therapeutic benefit mentioned on the label.
- QTPP Connection:
- Identity
- Assay (measurement of drug substance)
- Purity/Impurity
- Stability
- Example of a typical QTPP for an immediate release solid oral dosage form:
- Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability
- Dissolution

- **Important Note:** QTPP focuses on product performance elements applicable to patients. Process control specifications, such as tablet density or hardness, are not included in QTPP.

4. Critical Quality Attributes (CQAs)

- Definition: Assessments of quality for products/services, influenced by physical, chemical, biological, or microbiological factors.
- Scope: Includes properties of raw materials (e.g., drug content, excipients), intermediates, and drug products.
- Relation to QTPP: CQAs are subsets of QTPP, focusing on product consistency, protection, and effectiveness. While strength and dosage type are QTPP attributes, they are not CQAs since they remain constant during drug production.
- Identification: Done through risk evaluation as per ICH guidance Q9, using prior product knowledge, lab, nonclinical, and clinical data, and literature references.
- Examples of CQAs: Assay, content uniformity, and dissolution, which are critical due to potential variability from formulation or process changes.

5. Quality Risk Management (QRM)

- Definition: A mechanism for assessing, controlling, communicating, and reviewing risks to the quality of a drug product, using scientific expertise and experience.
- Documentation: The level of formality and documentation needed is proportional to the risk and efficiency of the management process.
- Relation to Quality by Design (QbD): QRM is crucial for developing and implementing QbD throughout the product lifecycle, supporting decision-making based on risk assessments from development to full-scale manufacturing.
- Purpose: Ensures drug product quality by proactively identifying and monitoring potential quality issues during development and production.
- ICH Q9 Quality Risk Management Methods:
  - Failure Mode Effects Analysis (FMEA)
  - Failure Mode, Effects and Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk ranking and filtering
  - Supporting statistical tools

6. Design Space

- Definition: A multidimensional combination of input variables and their interactions that ensures quality assurance. It can be used for a single unit operation, a series of unit operations, or the entire process.
- FDA Guidelines: Defining design space is optional for product and process comprehension but helps in better understanding and overall control.
- Uses of Design Space:
  - Connects process inputs (input variables, process parameters) and Critical Quality Attributes (CQAs).

- Applicable to multiple unit operations or the entire process.
- Usable before or after Market Authorization (MA).
- Supports candidate presentations.
- Facilitates interaction with design firms.
- Necessary for regulatory approval and evaluation.

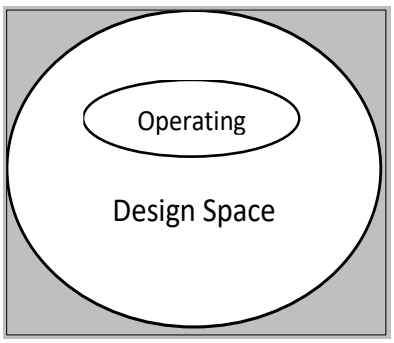

Figure 4 Design Space

7. Control Strategy

- Definition: Techniques include input material sensors, process controls and monitoring, design spaces, and final controls to ensure product specifications.
- Current System: Every process has a control strategy to ensure the consistency of finished drug products through a series of tests.
- In-process Checks: Comprehensive checks, like blend uniformity or tablet hardness, are required.
- Regulatory Requirements: Manufacturers cannot adjust batch records, operating criteria, or methods without FDA supplements due to the system's rigidity.
- Purpose: The rigidity is necessary because manufacturers must understand how drug materials, excipients, and process parameters affect product quality.

8. Critical Material Attributes (CMA) and Critical Process Parameters (CPP):

- CMA: When a material attribute's change significantly affects production consistency, it is critical.
- CPP: Parameters ensuring CQAs, selected using risk evaluation from potential CPPs.
- Critical Process Parameter: A parameter critical when it has a significant impact on CQAs.
- Types of Parameters/Attributes:
  - Critical Parameters: Changes result in failure to obtain QTPP.
  - Non-Critical Parameters: No QTPP failures within operating range; no interactions within acceptable range.
  - Unclassified Parameters: Criticality uncertain; more information needed for classification.
- Risk Assessment Methods for Process Variables and CQA:
  - Failure Mode Effect Analysis (FMEA)
  - Ishikawa (Fishbone) Diagram
  - Pareto Analysis
- Application of Methods:
  - FMEA: Ranks variables by risk, selects high-risk parameters for further study.
  - Ishikawa Diagram: Identifies all possible variables affecting CQAs.
  - Pareto Analysis: Quantifies the impact of problems on selected CQAs.

9. Tools Of Quality by Design

9.1. Design of Experiments (DOE)

The Design of Experiments (DOE) is a standardized method to determine relationships between variables and their impact on a process's outputs. DOE claims to produce results four to eight times the cost of setting up the experiment in a fraction of the time. In Quality by Design (QbD), DOE derives maximum information from minimal experiments. For pharmaceutical processes, parameters include raw material attributes (e.g., particle size) and process parameters (e.g.,

speed, temperature). Critical quality attributes (CQAs) for inputs might be time, and for outputs, uniformity, tablet stiffness, and thickness. While it's impossible to experimentally analyse all input/output variables and process parameters in each unit operation, DOE helps identify ideal conditions and key factors impacting CQAs.

9.2. PAT (Process Analytical Technology)

Many people are interested in scientific, risk-managed pharmaceutical production, manufacturing, and quality assurance. The Process Analytical Technology (PAT) system includes various methods, which can be categorized into four classes according to PAT guidelines.

- Multivariate tools for design, data acquisition, and analysis.
- Process analysers
- Process control tools

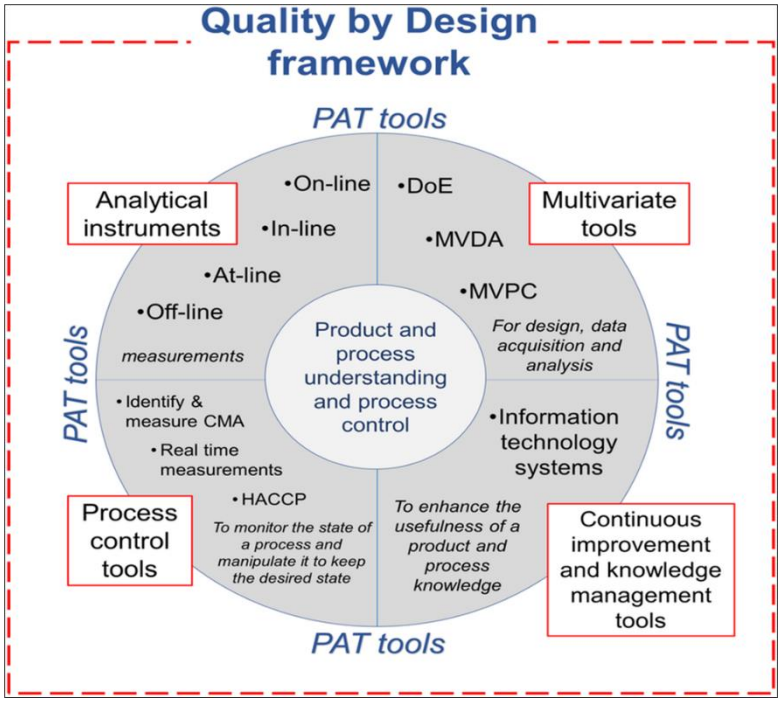

Figure 5 PAT tools

10. Analytical QbD Method Validation

Validating an analytical process over different API batches is a QbD method validation approach. Designed using DoE and MODR knowledge, it ensures API manufacturing adjustments are validated without revalidation. It covers experiences, measurement complexity, control strategy, quality assurance, and all required ICH validation elements. This method uses fewer resources than conventional validation while maintaining high quality.

QbD is versatile and can be applied to numerous analytical methods, including:

Chromatographic techniques like HPLC can significantly enhance forced degradation studies, system creation, and impurity determination in pharmaceuticals.

- Karl Fischer titration is used for determining moisture content.
- Vibrational spectroscopy, including the UV process, is employed to classify and quantify compounds.
- HPLC is a chromatographic technique utilized in pharmaceuticals for stability testing, process development, and impurity elimination.
- Processes in the biopharmaceutical industry encompass a wide range of activities essential for the development and production of biopharmaceutical products.
- Dissolution studies.

- Hyphenated technique like LC-MS.
- Advanced techniques include mass spectrometry, ultra-high-performance liquid chromatography, and capillary electrophoresis.
- Analysis of genotoxic impurity.

In the context of Quality by Design (QbD), an analytical method can be established through the following five steps

- **Analytical Target Profile (ATP):** The first step involves defining the ATP, which outlines process requirements and performance parameters. A suitable instrument technique is then chosen based on these requirements, allowing the method to achieve its primary objectives.
- **Systematic Method Establishment:** After selecting an appropriate analytical method, a systematic approach is developed. This involves preparing and studying the technique through various experiments to gain a preliminary understanding of robustness and method performance.
- **Risk Assessment:** Information gathered during method development is subsequently applied to risk assessment. This evaluation identifies risk factors that should be further investigated in a Design of Experiments (DOE) study.
- **Control Strategy and Method Operable Design Region (MODR):** DOEs help in developing a control strategy and establishing the MODR. The method's Normal Operating Condition (NOC) is considered at each stage within the MODR, and both the MODR and NOC are evaluated and validated.
- **Knowledge Management:** Finally, knowledge management is an ongoing phase in QbD. This means that knowledge gained from process optimization, development, verification, and implementation should be collected, utilized, and transferred throughout the method's lifecycle.
- **Method Operable Design Region (MODR):** MODR (Method Operable Design Region) is akin to the "design space" in analytical QbD. It outlines the range for critical input variables to achieve the ATP (Analytical Target Profile).

11. Essential elements of QbD:

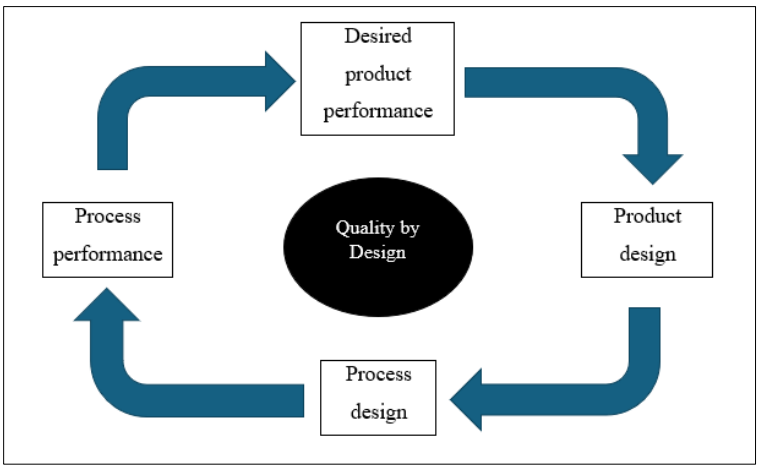

Figure 6 Essential elements of Qbd

This method necessitates a thorough understanding of how the formulation, development, and manufacturing process of a product may affect its quality (Fig. 2). QbD entails identifying the sources of variability, assessing how they affect the end result, and then managing that variability. The product's performance is what determines its quality. Carefully adhering to QbD can minimise or even eliminate the requirement for final product testing.

The following five steps to establish an analytical method in a QbD (Quality by Design) context:

- **Analytical Target Profile (ATP):** Identify the process requirements and performance parameters. Choose a suitable instrument technique to meet these requirements.
- **Develop Systematic Method:** Establish a systematic method for the chosen technique, including test preparation and experiments to gauge robustness and method state.

- **Perform Risk Assessment:** Apply the information from method creation to perform risk assessment, identifying risk factors to be studied further in a Design of Experiments (DOE).
- **Create Control Strategy and MODR:** Use DOEs to develop a control strategy and establish a Method Operable Design Region (MODR). Evaluate and validate the Normal Operating Condition (NOC) within the MODR.
- **Implement Continuous Knowledge Management:** Continuously gather, use, and transfer knowledge gained from process optimization, creation, verification, and use throughout the method's life cycle.

12. Current vs. QBD approach to pharmaceutical development

Table 1 Current vs. QbD Approach

Current Approach	QbD Approach
Quality is ensured through thorough testing and meticulous inspection. Data-intensive submission containing fragmented information without a cohesive overview. Specifications derived from batch history. A rigid process that discourages any modifications. Emphasis on reproducibility, often at the expense of acknowledging variation.	Quality is integrated into the product and process by design, grounded in scientific understanding. Submission enriched with comprehensive product knowledge and process understanding. Specifications are determined by product performance requirements. Adaptable process within the design space, enabling continuous improvement. Prioritize robustness by understanding and controlling variation.

13. Quality by Design (QbD) can be applied to various analytical methods, including

- Chromatographic techniques like HPLC for forced degradation studies, system creation, and impurity determination in pharmaceuticals.
- Karl Fischer titration for moisture content determination.
- Vibrational spectroscopy, such as UV process, for classifying and quantifying compounds.
- HPLC for stability tests, process development, and impurity determination in pharmaceuticals.
- Processes in the biopharmaceutical industry.
- Dissolution studies.
- Hyphenated techniques like LC-MS.
- Advanced techniques such as mass spectroscopy, ultra-high-performance liquid chromatography, and capillary electrophoresis.
- Analysis of genotoxic impurities.

14. Applications of Quality by Design

14.1.1. For the Chromatographic methods

- In impurity determination
- In chromatographic column screening
- Use HPLC to develop the material of a drug product
- In stability studies and In UHPLC

14.1.2. For hyphenated technique like LC-MS

- In bioanalytical method development with precision and accuracy
- In dissolution studies for testing release of drug
- For spectroscopic measurement
- In mass spectroscopy and IR spectroscopy
- In handling complex spectroscopic data
- In modified release products
- In ablating process

- In compatibility study analysis of API and Excipients
- In Biopharmaceuticals
- For Biotechnological Products
- In formulation and processing of protein liposomes
- Screening of variables, and establishment of design space on liposomes containing hydrophilic API.
- Identifying critical quality attributes (CQA):
- Software facilitates the analysis of product attributes that have a major influence on performance and quality, enabling targeted quality control procedures.

14.2. Critical material attributes (CMAs) identification

Examining raw materials to identify important characteristics that may affect the quality of the finished product.

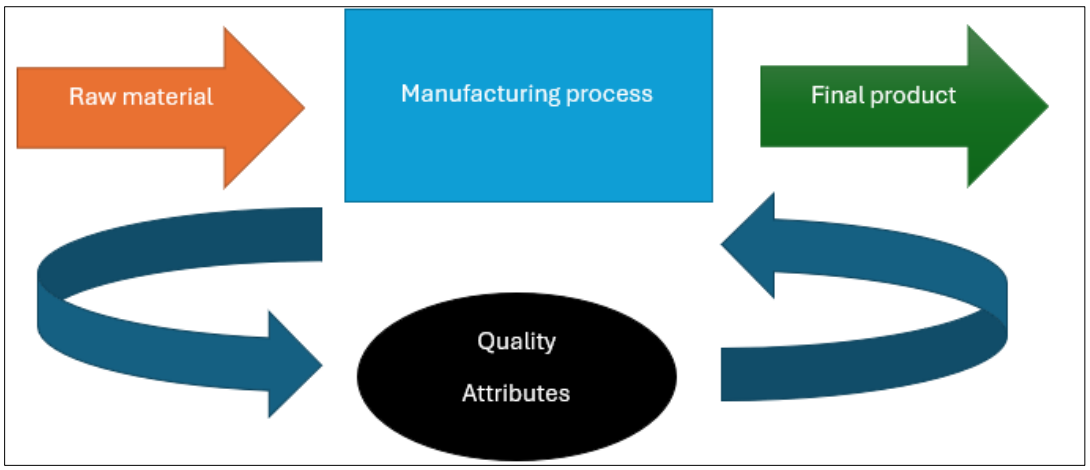

Figure 7 Overview of Quality by Design

15. Conclusion

Quality by Design (QbD) is proposed to enhance process knowledge based on existing guidance and reference documents. QbD is a quality system that builds on past experiences and sets potential regulatory expectations. It becomes crucial in pharmaceutical processes such as drug development, formulations, analytical methods, and biopharmaceuticals. The primary reason for adopting QbD is to meet regulatory requirements, as the pharmaceutical industry requires regulatory compliance for product approval and marketing.

Quality by Design (QbD) is an essential aspect of the modern approach to pharmaceutical quality. This paper clarifies the utilization of QbD, including:

- Emphasizing the importance of the Target Product Quality Profile (TPQP) in articulating a quantitative performance target for QbD.
- Identifying critical material attributes that provide a mechanistic link between finished product quality and the manufacturing process.
- Explaining that critical process parameters are working parameters and should be integrated with critical material attributes to define the relationship between unit operation outputs and inputs.
- A classification system defines method parameters and in-process material attributes as non-critical, unclassified, or critical. This classification helps in determining the significance and necessary control measures for each parameter and attribute.
- The management strategy serves as a framework for the gradual implementation of QbD elements into operation.
- A cost-effective approach to streamline a field involves identifying non-interacting process variables and excluding them from formal experimental designs.

A potential scientific tool for quality assurance in the pharmaceutical sector is QbD. It reduces the time-consuming process of scale-up most-approval adjustments and offers a safe operating range that guarantees or provides confidence

for batch-to-batch consistency, quality, safety, and efficacy. Qbd successfully provides a layout or the path from the initial defining objective and finally successfully commercializes the product.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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