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A REVIEW ON VARIOUS ASPECTS OF QUALITY BY DESIGN [QbD] ON NEW DRUG APPROVAL

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Abstract

Quality by design is an essential part of the modern approach to pharmaceutical quality. Quality by design [QbD] is a relatively new idea in the pharmaceutical industry , but it has quickly become and integral aspect of current approach to quality . Quality by design was one of the design experiment approved by the FDA to maintain the quality of the drug products before reaching to the market. Quality design has been created to increase the assured of providing safe, effective medicines to customers and promised to make significant improvements in product quality performance. In vivo or invitro performance test can be evaluated for drug production . Dietite by quality guarantees the performance of the product. The understanding will facilitate better communication between those involved in risk based drug development and drug application review.

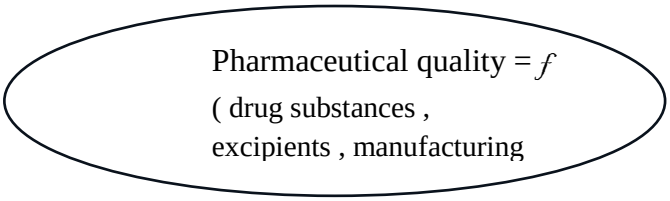
Introduction

Quality by Design (QbD) is the concept was first developed or outlined by the quality promoter Dr. Joseph M juran. He believed that quality should be planned into product.QbD is unfolded the increase the assurance of safely and effectively supply a drug to the patient. And also gives promise to significantly improve manufacturing quality performance. Quality means “standard or suitability for the intended use”. It contains such attributes as the potency, quality and purity. In 2002 FDA notify new invents for risk management to modernize the FDAs regulation for maintain good pharmaceutical quality as well as build up new regulatory framework focusing on QbD, quality maintaining system, risk management [1]. The QbD concept is considered by FDA. The QbD concept generated by International Conference on Harmonization (ICH), to guide the quality i.e. ICH Q8 and ICH Q9.

The aim of pharmaceutical development is to design a quality product and manufacturing process. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of design space, specifications, and manufacturing control .Pharmaceutical industries always rely on continuous improvement in safety, quality, and efficacy of the products. The main priority of the QbD is to enhance therapeutic benefits and absence of impurities .The product quality and performance are regulated by finished product testing with understanding of the process and critical process parameters .The pharmaceutical products formulation can be developed based on the data obtained from product development studies. The product variables that are emerged during development stages has a source for QRM .For simple to complex drug development ,QbD considers all possible sources of variability during product development exercise followed by analysing the associated risk optimum of the variability to reach target objectives.

The QBD describes the pharmaceutical development. A system for designing, methodology that prescribes formulation design and development and production processes to maintain prescribed drug quality Guidelines and mathematical models are used to ensure the establishment and usage of knowledge on the subject in an independent and integrated manner. To launch a successful QbD program, the first step is to identify the process components required for production quality and

to develop good authenticated analytical methods to test those parameters. The purpose of this review article is to provide a comprehensive understanding of the various QBD, with related problems regarding its implementation [2]. The food and drug administration office of generic drugs as developed aquestion based review for its chemistry, manufacturing and controls evaluation of abbreviated new drug applications ICH Q8 defines quality as the suitability of either a drug substances or drug product for its intended use. This term includes such attributes as the identity, strength and purity. ICH Q8 guidelines states that quality by design is a systemic approach to development that begins with pre defined objectives and emphasizes product and process understanding and process control , based on sound science and quality risk management.



Product testing is alone is not satisfied to assure that a process consistently produce a product with predetermined specifications. Adequate process design knowledge and control of factors that produce process variability and successful validations studies in conjunction with product testing provide assurance that the process will produce a product with the required quality characteristics. The quality of the pharmaceutical product can be evaluated by both in vivo or in vitro performance test .The quality by design assurance in vitro product performance and in vitro product performance provides assurance of in vivo product performance. Hence quality by design relate to product performance.

It refers Understanding a significant transformation to streamline their R and D process, provide greater manufacturing flexibility and control, and to reduce regulatory burden, however, there is limited understanding and some major concerns regarding the implementation of QbD principles in the pharmaceutical arena. in traditional, the product quality and performance and predominantly ensured by end product testing , with limited understanding of the process and critical process parameters .The pharmaceutical quality system applicable across the life cycle of the product emphasizing and integrated approach to risk management and science .

Quality by Design encompasses all major aspects of pharmaceutical production. In drug development, a methodical, multivariate approach is used to construct an effective process design based on assessing the risk associated with various steps. In the manufacturing process, a QbD strategy permits process flexibility within the defined design space. Process control effectively uses process analytical technology to track process trends and quality assurance is a necessity of risk-based control processes, which ensures less likelihood of batch failure [3].

- Quality built into product and process by design, based on scientific understanding
- Knowledge-rich submission – showing product knowledge and process understanding
- Specifications based on product performance requirements
- Flexible process within design space – allowing continuous improvement
- Focus on robustness – understanding and controlling variations

In terms of yielding a quality product, having deep knowledge about the product and processes from the developmental phase results in better performance than traditional end-of-the-line testing. It also reduces the need for post-production interventions, which are riskier, more costly, and labor-intensive. The underpinnings of this methodology are listed below:5In terms of yielding a quality product, having deep knowledge about the product and processes from the developmental phase results in better performance than traditional end-of-the-line testing. It also reduces the need for post-production interventions, which are riskier, more costly, and labor-intensive [4].

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question basedreview (QbR) for its chemistry, manufacturing and controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs). QbR is a new quality attributes. It is a practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty first century and quality by design (QbD) initiatives, which illustrate the different phases during the life cycle of a pharmaceutical process: define, design, characterize, validate, and monitor and control. The final link between "monitor and control" and "define" represents process changes that are initiated based on process improvement opportunities identified during process monitoring or introduced otherwise to improve process performance or robustness . Changes originating in this manner would again go through the cycle illustrate.

Definition

Quality by Design (QbD) is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing. A concept introduced in International Guidelines for the Pharmaceutical Industry since 2009 (ICH) guidelines.

Objectives

The main objectives of QbD are as follow

1. Increasing manufacturing efficiency.
2. Increasing the efficiency in product development.
3. Enhancement of product quality and performances to meet patients needs.
4. Increase in process capability.
5. Avoidance of regulatory compliances.
6. Incorporation of risk management.
7. Reduction in production costs and waste.
8. Reduction in product variability, defects and rejections.

The main outcomes of QbD are as follows

1. Maintenance of product quality to meet expected clinical performances.
2. Maintenance of product quality by efficient manufacturing and formulation process.

Principle

Quality by design aims to optimize the development, manufacturing, and control processes of drugs to improve their safety and overall quality. It requires a deep manufacturing of the product critical quality attributes , which are the measurable characteristics that determine its performance , and the critical process parameters which are the variables effecting the manufacturing process . The core principle of quality by design is to identify and understand the relationship between the products CQAs and the CPPs that influence them. Quality by design seeks to enhance the development, manufacturing, and control processes of drugs. This knowledge is acquired through a combination of scientific experimentation, risk assessment, and statistical analysis. By thoroughly examining these relationships, manufacturers can establish a design space where the product consistently meets the desired quality standards [5].

The design space defines the range of CPPs that ensure the product's CQAs are within acceptable limits. It provides flexibility for process optimisation while maintaining the required quality attributes within the design space, manufactures can establish appropriate process controls, monitoring techniques, and quality assurance systems can ensure consistency and predictability in product performance.

Advantages

1. Better understanding of the process.
2. Less batch failure.
3. More efficient and effective control of change.
4. Return on investment.
5. Reduction of post approval submission.
6. Less intense regulatory oversight and less post approval submissions.
7. More drug availability and less recall and improved yields, lower cost, less investigations, reduced testing, etc.
8. Continuous improvement over the total product life cycle.

Disadvantage

1. Internal unwillingness in company.
2. Lack of technology to implement.
3. Alignment with third parties.
4. Lack of concrete guidance for industry.
5. New concepts hard to adapt.
6. Just starting to be recognised by authorities.
7. Required time to understand process and product.

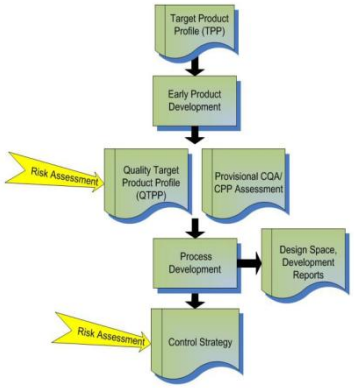
Benefits

- Eliminate batch failures.
- Minimize deviations and costly investigations.
- QbD is good science.
- Better development decisions.
- Incorporate risk management.
- Empowerment of technical staff.
- Avoid regulatory problems.

QBD Key Elements

In a pharmaceutical QbD approach to product development, the applicant identifies characteristics that are crucial to quality from the patient's perspective, converts them into the drug product's critical quality attributes (CQAs), and defines the relationship between formulation and manufacturing variables and CQAs to consistently deliver a drug product with the desired CQAs to the patient.QbD consists of the following elements:

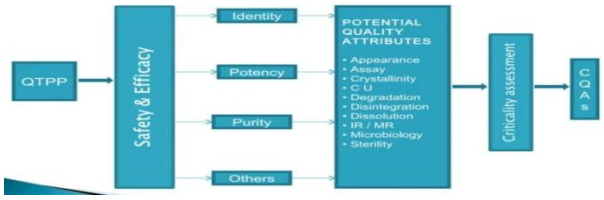
1 . Quality target product profile [QTPP]
2. Identification of critical quality attributes [CQA
3. identification of critical material attributes [CMA]
4. Critical process parameters
5. Design space
6. Control strategy



1. Quality Target Product Profile [QTPP]

Quality Target Product Profile (QTPP) is a key component of the Quality by Design (QbD) approach in pharmaceutical development. It serves as a strategic tool for ensuring that a drug product meets the intended therapeutic outcomes while maintaining quality, safety, and efficacy. The QTPP defines the critical attributes of a drug product that are necessary to achieve its desired performance from the perspective of both the patient and regulatory authorities [6]. This framework helps guide the formulation, process development, and scale-up activities

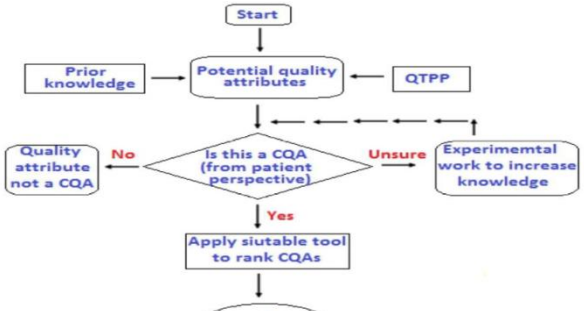
to ensure the final product meets predefined quality standards.



2 . Identification of Critical Quality Arrtibutes [CQA]

Identification of Critical Quality Attributes (CQAs) is a fundamental step in the Quality by Design (QbD) approach, crucial for ensuring that a pharmaceutical product consistently meets its predefined quality, safety, and efficacy standards. CQAs are the physical, chemical, biological, or microbiological properties or characteristics of a drug product or process that need to be controlled within specified limits to ensure the desired product quality [7]. The identification of CQAs plays a central role in guiding the formulation, development, and manufacturing of pharmaceutical products.

Drug product CQAs normally studied includes physical attribute, assay, content uniformity, drug release/dissolution, degradation products, redispersibility, microbiological limits, isotonicity, impurities etc.



3. IDENTIFICATION OF CRITICAL MATERIAL ATTRIBUTES [CMA]

Identification of Critical Material Attributes (CMAs) is an essential step in the Quality by Design (QbD) approach to pharmaceutical product development [8]. CMAs are the physical, chemical, biological, or microbiological properties of raw materials, excipients, or active pharmaceutical ingredients (APIs) that significantly affect the quality of the final drug product. By identifying these attributes, manufacturers can ensure that the materials used in production will consistently lead to a high-quality, safe, and effective product. Critical quality features are also influenced by the choice of salt, solid forms, particle size, and morphology. In most circumstances, material qualities can be quantified and fixed, but they can also change throughout processing. Examples include impurity profile, porosity, specific volume, and sterility [9].

4. CRITICAL PROCESS PARAMETERS

Critical Process Parameters (CPPs) are essential variables in the Quality by Design (QbD) framework for pharmaceutical development. CPPs are the key parameters in the manufacturing process that have a significant impact on the Critical Quality Attributes (CQAs) of the final drug product. By identifying, monitoring, and controlling these parameters, manufacturers can ensure that the drug product consistently meets the desired quality standards, ensuring safety, efficacy, and regulatory compliance. The selection of CPPs, which are responsible for ensuring CQAs, is done through a list of potential CPPs that has been made based on risk analysis [10].

Parameters

There are three parameters they are

A. Unclassified parameters

Unclassified Parameters in Critical Process Parameters (CPPs) refer to process variables or conditions that, while potentially influencing the Critical Quality Attributes (CQAs) of a pharmaceutical product, have not yet been fully identified, characterized, or formally classified as critical during the product development process [11]. These parameters may affect the final product's quality or performance but are not initially considered critical or may not have a direct or fully understood relationship with CQAs at the time of analysis. More research or data are required to determine whether an unclassified parameter is critical or non-critical. Manufacturers may use tools such as Design of Experiment (DOE) or Process Analytical Technology (PAT) to investigate the impact of unclassified parameters on product quality and determine if they need to be controlled or monitored. Unclassified data are crucial because they may eventually be found to be critical or non-critical.

B . Critical parameters

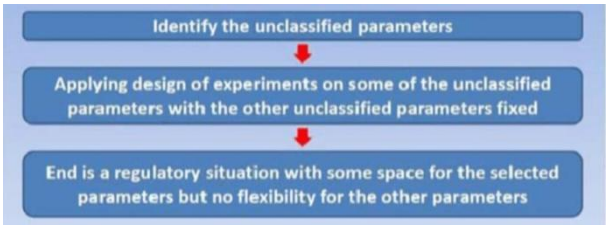
Critical Process Parameters (CPPs) are process variables in pharmaceutical manufacturing that, if not properly controlled, can significantly impact the Critical Quality Attributes (CQAs) of a drug product. CPPs are essential for ensuring the product's safety, efficacy, and consistency, and are key components of the Quality by Design (QbD) framework. By identifying and controlling CPPs, pharmaceutical manufacturers can optimize the development and production processes to consistently meet regulatory standards and deliver high-quality products [12]. Examples of critical parameters can include things such as temperature, pressure, pH, humidity, mixing time, stirring speed, and composition. These parameters can directly affect the quality of the final product, such as its purity, potency, and stability Manufacturers can monitor and control critical parameters in real-time using Process Analytical Technology (PAT) and other tools to ensure that the process is operating within the design space and that the product meets the required quality standards [13].

C. Non critical parameters

Non-Critical Parameters in the context of Critical Process Parameters (CPPs) refer to process variables or conditions that do not have a significant impact on the Critical Quality Attributes (CQAs) of the final drug product [14]. Non-critical parameters are typically controlled within a broader range or monitored less rigorously compared to Critical Process Parameters (CPPs). Non-critical parameters can include equipment settings or environmental conditions that have no direct impact on product quality but must be controlled for other reasons such as safety, regulatory compliance, or process efficiency. The temperature in the manufacturing room is an example of a non-critical parameter; it can affect the process, but as long as it is controlled within a certain range, it will not have a significant impact on the final product. Non-critical parameters are important to consider in QbD because they can still affect the process and may require control, but they are not as important as critical parameters[15]. While these parameters are still important for maintaining a stable and efficient manufacturing process, variations in these parameters are not expected to affect the product's quality in a way that would cause safety or efficacy concerns.

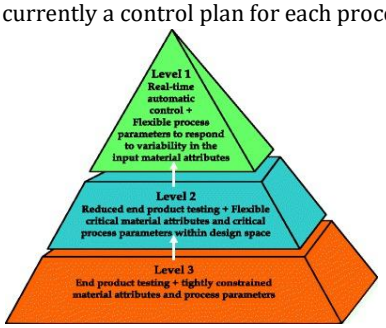
5. Design Space

The term "design space" refers to the set of operating conditions under which a process or product is expected to perform as intended and meet the required quality standards in the field of Quality by Design (QbD). Design space is the set of all process and material attributes (e.g., temperature, pressure, concentration) that, when maintained within a specified range, guarantee that the drug product will consistently meet its desired quality characteristics (CQAs) [16]. Design space is created by combining process understanding, experimentation, and risk assessment. Key Process Parameters (KPPs) and Critical Quality Attributes (CQAs) can be identified by understanding the underlying processes and their interactions, as well as through experimentation and risk assessment. The relationship between KPPs and CQAs can then be used to define the design space, which is the set of operating conditions under which the process or product is expected to function as intended. It refers to the multidimensional combination of input parameters (such as raw materials, process parameters, equipment settings) and their respective ranges that have been demonstrated to ensure that the product meets its desired Critical Quality Attributes (CQAs) consistently and reliably [17].



6. Control strategy

A control strategy is a comprehensive plan that encompasses both proactive and reactive controls to maintain the desired product quality, safeguard patient safety, and ensure regulatory compliance [18]. All of these components of the control strategy are included in Process Analytical Technology (PAT). This system includes testing for raw materials, in-process materials, and finished products. A control strategy is a critical component of the Quality by Design (QbD) approach in pharmaceutical product development and manufacturing. It defines the system of controls (e.g., materials, equipment, and process parameters) and their interactions that are implemented to ensure that the product consistently meets its predefined Critical Quality Attributes (CQAs) throughout its lifecycle. The control strategy is designed to monitor, manage, and control variability in both the formulation and the manufacturing process, ensuring consistent product quality and regulatory compliance. There is currently a control plan for each process.



The following components of a control strategy include:

- Materials input characteristics (e.g., drug substances, excipients)
- The state of the equipment
- In-process checks.
- The final product's specifications [19].

TOOLS OF QbD

1. Risk assessment

In the area of Quality by Design (QbD), risk assessment is a crucial tool because it enables the systematic identification and assessment of potential risks related to a given product or procedure. Risk assessment in the tools of Quality by Design (QbD) is a critical component in ensuring that the pharmaceutical product development process is both effective and reliable [20]. Identifying potential risks associated with the product or process, such as chemical or physical risks, is known as hazard identification. Risk characterization entails assessing the likelihood and seriousness of these hazards as well as figuring out the overall risk connected to the process or

product. QbD emphasizes designing quality into the product from the beginning, and risk assessment plays a central role in identifying, evaluating, and mitigating potential risks that could affect product quality.

2. Mechanistic Models (RM)

Mechanistic Models (RM) in the context of Quality by Design (QbD) are mathematical and computational models that are used to understand, predict, and control the behavior of the pharmaceutical manufacturing process These models are based on fundamental scientific principles that describe how different variables affect the process and, consequently, the product quality. In QbD, mechanistic models are essential tools to enhance the understanding of the processes, which helps in the design of robust products and processes.. Mechanistic models can be used to identify important process parameters and their relationships, as well as to simulate the behavior of a product or process [21].

3. Process Analytical Technology (PAT)

Process Analytical Technology (PAT) is a critical tool in Quality by Design (QbD) that focuses on using advanced analytical techniques and real-time monitoring to ensure that manufacturing processes consistently produce products of the desired quality. Analytical techniques such as spectroscopy, chromatography, and mass spectrometry, as well as process control techniques such as multivariate data analysis and modeling, are examples of PAT tools. PAT enables a deeper understanding of the process, helps identify critical process parameters (CPPs), and allows for continuous control of product quality throughout the manufacturing cycle [22]. PAT also enables the identification of Key Process Parameters (KPPs) and their relationships, which can then be used to optimize the design of the process or product, resulting in higher quality and lower variability

4. Prior Knowledge (PK)

Prior knowledge is an important tool in the field of Quality by Design (QbD) because it allows for the incorporation of existing knowledge about the process or product into the design process. It includes existing data, prior experiences, literature, historical data, scientific principles, and knowledge from previous projects or products that inform decision-making during the design and optimization of pharmaceutical formulations and processes. QbD practitioners can find potential sources of variability and create controls to reduce them by utilizing prior knowledge. The use of Prior Knowledge (PK) in QbD is crucial for improving the efficiency of the development process, reducing risks, and ensuring that quality is built into the product from the start.

5. Design of Experiments (DOE)

Design of Experiments (DOE) is a powerful and essential tool in Quality by Design (QbD) that enables systematic investigation and optimization of the relationships between various process variables (factors) and product quality attributes (responses). It enables the systematic varying of various inputs to ascertain their influence on the output [23]. The Design of Experiments (DOE) method involves methodically organizing, carrying out, analyzing, and deriving conclusions from controlled tests to assess the variables that affect the value of a parameter or set of parameters. DOE allows for a structured approach to experimentation, enabling the identification of Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) while providing insights into the design space for pharmaceutical product and process development.

Disputes of the QbD Approach

The primary and main barrier to QbD implementation is a lack of knowledge about the pharmaceutical process. The QbD approach is intended to ensure that quality is built into products from the beginning of the development process rather than being tested in at the end of production.

- Reaching agreement on how to address QbD through collaboration and cooperation between field inspectors and the FDA review and compliance sectors continues to be a difficulty [24].
- These disputes generally revolve around the complexity, resource demands, regulatory hurdles, and the need for new skill sets.
- For the effective application of QbD, there is a need for more collaboration across numerous disciplines inside the organization, including process development, production, and quality control.

Applications of QbD

1. Pharmaceuticals

- In modified release products.
- In solid oral dosage forms.
- Impact of genotoxic impurities on process development.
- Nano-suspension preparations.
- In analysis of excipients and APIs.

2. Biopharmaceutics

- In manufacturing of proteins.
- In production and characterisation of monoclonal antibody.
- For chromatographic technique used for purification.
- PAT and QbD for bio pharmaceutical.
- In nano medicine.

Conclusion

Now a day's researcher utilizes QbD as an important tool for getting the quality, QbD has eliminated the burden of exhaustive and time consuming conventional approach without compromising with quality of the product. Hence QbD is an integral part of modern research in pharmaceutical industry. Although the adoption of QbD requires an investment in resources, time, and expertise, its long-term benefits in terms of consistent quality, reduced variability, and regulatory acceptance make it an essential approach for modern pharmaceutical

development. QbD focus over all aspects desired in an quality product like ascertaining drug product quality profile, priorizing input variables for optimization, monetization & validation of QbD methodology and in the last QbD validation, scale up and production .The fast growth of interest in QbD and its tools indicates that the approaches are not fashionable phenomena but responses to the demands of modern manufacturing process25. QbD is a cost and time efficient approach in design and manufacturing, with DoE, risk assessment, and PAT as its tools to achieve a better understanding on the materials and processes, which make the QbD available and feasible to the pharmaceutical field.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest.

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