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A review on quality by design approach for pharmaceuticals

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Abstract

Quality by design (QbD) is an important part in today's pharmaceutical quality developments. Quality design (QBD) is a modern and systematic approach to product development and pharmaceutical quality. Quality by design is a concept proposed by well-known quality expert Joseph M. Juran. This paper presents Pharmaceutical Quality by Design (QbD) and how it can be used to ensure pharmaceutical quality. QbD provides a comprehensive framework that integrates quality principles, risk assessment, and knowledge management throughout the product lifecycle. This explores the key concepts and principles of QbD, including the use of Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and Critical Process Parameters (CPPs). The implementation of QbD involves the application of various tools and methodologies, such as design of experiments (DoE), risk assessment techniques, and process analytical technology (PAT). The objective of this review is to discuss the concept of quality by design and describe its application in pharmaceutical product development.

Keywords: Quality by design (QbD), quality target product profile (QTPP's), critical quality attributes (CQA's), critical material attributes (CMAs), critical process parameter (CPPs), design of experiment (DOE), process analytical technique (PAT)

Introduction

Quality: The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity^[6]

Quality by Design (QbD) is a systematic approach used in various industries, including pharmaceuticals, biotechnology, and manufacturing, to ensure the quality and reliability of products and processes

Quality by Design (QbD)^[22].

Quality by Design means—designing and developing formulations and manufacturing processes to ensure a predefined quality

Quality by Design requires – understanding how formulation and manufacturing process variables influence product quality.

Quality by Design ensures – Product quality with effective control strategy

The pharmaceutical industry is attentive to product efficacy, safety, and quality. By using a scientific instrument like QbD, product quality has been rising. The QbD technique is successfully used in the formulation development process. The implementation of ICH quality criteria Q8 to Q11 is always being proposed by regulatory authorities^[9].

From product development to manufacturing, scientific approaches can provide clear and necessary knowledge. By increasing productivity and quality, these QbD tools will minimize the risks^[9].

The goal of pharmaceutical development is to produce a high-quality product and manufacturing method that consistently delivers the expected performance of the product^[11].

This approach is known as "Quality by Design," and it is defined 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"^[11].

Definition

- **Quality:** Quality is “standard or suitability for intended use.” This term includes such attributes of identity, potency, and purity. Quality means customer satisfaction in terms of service, product, and process^[1].
- **Quality by Design:** QBD is a systematic approach to pharmaceutical development that

focus on ensuring product quality by design rather than relying on end product testing alone and that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [3, 7].

Objective of quality by design (QbD) [1]

- To promote continuous improvement and innovation throughout the product life cycle.
- To achieve meaningful clinical trial-based product quality specifications.
- To allow for regulatory flexibility in specification development and post-approval changes.
- To improve product capability while reducing variability.
- To increase product development and manufacturing efficiency.
- To improve root cause analysis and change management after approval.
- The primary goals of QbD are to ensure quality products, for which item and process attributes critical to desired execution must result from a combination of

prior learning and new estimation during advancement.

Importance of QbD in pharmaceuticals

Even though the pharmaceutical industry has focused on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity [2].

The pharmaceutical industry works hard to develop, manufacture, and bring new drugs to market while also meeting regulatory requirements to demonstrate that the drugs are safe and effective [22].

The product should be designed to meet the needs of the patients and to provide the best possible product performance. A new approach to drug development could increase efficiency, provide regulatory relief and flexibility, and provide significant business benefits throughout the product's life cycle [22].

The ICH Q8 guideline mentions the concept of QbD, which states that "quality cannot be tested into products, i.e., quality should be built in by design." [22]

Difference between current approach v/s QbD approach: [5, 9]

Current Approach	QbD Approach
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
It includes only data intensive submission which includes disjointed information without "big picture".	It includes Knowledge rich submission which shows product knowledge & process understanding.
Here, any specifications are based on batch history.	Here, any specifications based on product performance requirements.
Here there is "Frozen process," which always discourages changes.	Here there is Flexible process within design space which allows continuous improvement.
It focuses on responsibility which often avoids or ignores variation.	It focuses on robustness which understands and control variation.

The Foundation of QbD: ICH Guidelines: [3, 4, 11]

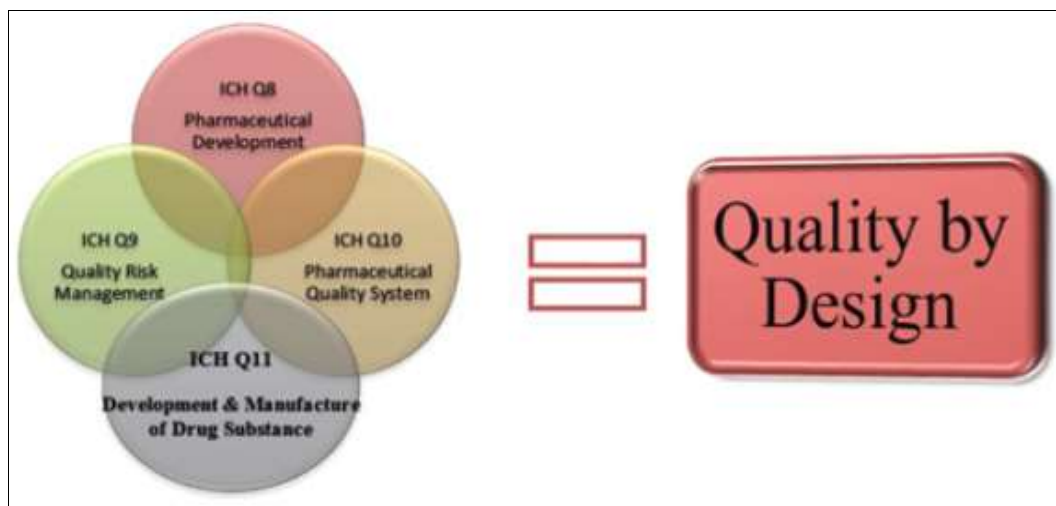


Fig 1: Content of Quality by Design

ICH Guidelines

- Q8 = Pharmaceutical Development
- Q9 = Quality risk management
- Q10 = Pharmaceutical Quality System
- Q11 = Development and Manufacture of Drug Substance

ICH Q8 pharmaceutical development

ICH Q8 gives pharmaceutical development guidance and highlights the importance of a systematic approach to product development. It supports QbD by encouraging a

deep understanding of the product and the identification of critical quality attributes (CQAs) that are vital for ensuring product quality.

ICH Q9 quality risk management

The ICH Q9 standard gives guidelines on quality risk management, which is an essential component of QbD. It promotes a systematic and proactive approach to risk identification, assessment, control, and communication throughout the product lifetime.

ICH Q10 Pharmaceutical quality system

ICH Q10 is concerned with the establishment and maintenance of a pharmaceutical quality system (PQS) that ensures the consistent manufacture of high-quality products. It provides a framework for putting in place an efficient quality management system and incorporating QbD principles into daily operations.

ICH Q11 Development and manufacture of drug substance

ICH Q11 focuses on establishing a commercial manufacturing process capable of consistently producing drug substances of the intended quality.

Role of QBD: [14, 25]

QbD ensures that a product is designed in such a way that it meets the needs of the patients as well as the needs for better action. Also, with QbD implementation, the process is designed in such a way that the important quality attributes of the product are met on a consistent basis.

- With the use of QbD, it is possible to gain a better knowledge of the impact of process parameters and starting raw materials on product quality. Control techniques are used to control and identify critical sources of process variability.
- QbD ensures continuous process monitoring and must be regularly updated in order to maintain consistent quality throughout time.
- QbD ensures that a product is designed in such a way that it meets the needs of the patient as well as the requirements for improved performance.
- Also, with QbD implementation, the process is designed in such a way that the important quality attributes of the product are regularly met.

6. Steps involved in quality by design products: [2, 3, 10]**1. Development of new molecular entity**

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

2. Manufacturing

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

3. Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance




Seven Steps of Quality by Design Start Up Plan: [9]


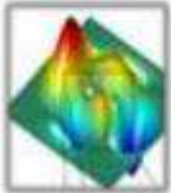


1. Hire an independent Quality by design skilled Person
2. Audit your organization and process with the expert conducting a gap analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

7. Element of quality by design

1. Quality Target Product Profile (QTPP)
2. Critical Quality Attributes (CQA's)
3. Quality Risk Management
4. Design Space Development
5. Control Strategy
6. Product Lifecycle Management & Continual Improvement

Table 1: Quality By Design [22]

Quality Target Product Profile		Define QTPP (Quality Target Product Profile) Based on THERAPEUTIC EQUIVALENCE for Generic Drug Product= PHARMACEUTICAL EQUIVALENCE (same dosage form, route of administration, strength & same quality) + BIO-EQUIVALENCE (same pharmacokinetics in terms of Cmax, AUC to reference product.
Critical Quality Attributes		Determine CQAs (Critical Quality Attributes) Considering QUALITY [Assay, Uniformity of Dosage units,], SAFETY [Impurities (Related substances), Residual Solvents, Microbiological limits], EFFICACY [Dissolution & Absorption] & MULTIDISCIPLINARY [Patient Acceptance & Compliance.
Risk Assessment Of Cmas & Cpps		Quality Risk Assessment of CMAs & CPPs by 1.RISK IDENTIFICATION: by Ishikawa Fishbone 2.RISK ANALYSIS by Relative Risk based Matrix Analysis 3.RISK EVALUATION by Failure Mode Effective Analysis

Design Of Experiments		DoE & Generation of Design Space For SCREENING & OPTIMIZATION of CMAs & CPPs with respect to CQAs by superimposing contour plot to generate OVERLAY PLOT (Proven acceptable Ranges & Edges of failure) based upon desired ranges of Responses
Process Analytical Technology		Development of PAT System For continuous automatic analyzing & controlling critical processing through timely measurements of CMA & CPAS by INLINE ANALYZERS WITH AUTO SENSORS with the ultimate goal of consistently ensuring finished product quality with respect to desired CQAs
Control Strategy		Implementation of Control Strategy For CONTROLS OF CMAs, CPPs within Specifications, by Real Time Release Testing, Online Monitoring System * Inline PAT Analyzers [based upon previous results on development, Scale Up. Exhibit/ Validation batches]
Continual Improvement		Continual Improvement Based upon CONTINUAL RISK REVIEW & RISK COMMUNICATION BETWEEN PLANT, QA, QC, RA, R&D, AR&D during routine commercial manufacturing experience

1. Quality Target Product Profile (QTPP):

Quality Target Product Profile (QTPP) is an important concept in Quality by Design (QbD) that helps define the desired characteristics and quality attributes of a pharmaceutical product [1].

QTPP is defined as "Prospective summary of the quality characteristics of a drug product that will ideally be achieved to ensure the desired quality, taking into account the drug product's safety and efficacy" by ICH Q8 (R2) [14]. Basically, it is a tool for setting strategy for drug development. Recently, QTPP has become widely employed in development planning, clinical and business decision-making, contacts with regulatory agencies, and risk management [14].

A pharmaceutical product that will fulfill the required standards for quality, safety, and effectiveness. The QTPP will assist in identifying important quality characteristics such potency, purity, pharmacokinetic profile, shelf-life, and sensory qualities [2]. QTPP helps formulation scientists set up strategies for formulation and maintain well-organized formulation.

2. Critical Quality Attributes (CQA's)

After identifying the QTPP, the next step is to determine the

applicable CQAs [3].

QbD is a systematic approach to pharmaceutical development that focuses on comprehending and controlling a product's essential quality attributes (CQAs) throughout its lifecycle.

According to ICH Q8, critical quality attributes (CQA) are physical, chemical, biological, or microbiological characteristics or qualities that must exist within the proper limit, range, or distribution to provide the intended product quality [8, 21].

CQAs typically involve those elements that have an impact on the stability and purity of a product. CQAs for drug products can be determined using the Target Product Profile [25].

Quality risk management and experimentation are used to identify CQAs and determine the effect of variation on product quality [3].

- Physical attributes (e.g., appearance, shape, size, etc.).
- Chemical attributes (e.g., purity, stability, impurities, etc.).
- Biological attributes (e.g., potency, activity, etc.).
- Performance attributes (e.g., dissolution, disintegration, etc.)

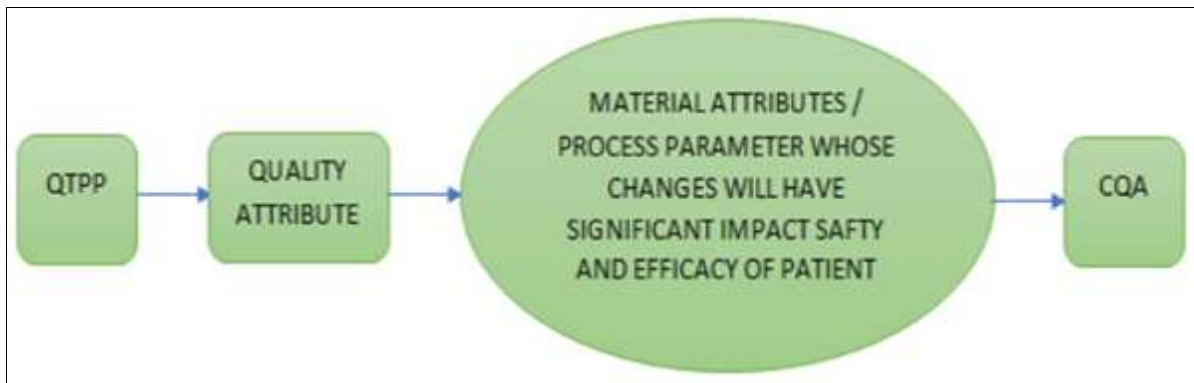


Fig 2: Impact of CQAs [8]

Critical Quality Attribute (CQA) related to materials is referred to as Critical Materials Attribute (CMA) and Critical Process Parameter (CPP) related to process [19].

- **Critical Materials Attribute (CMA's):** Critical material attributes (CMA) are related with materials used in the manufacturing of pharmaceutical products, such as drugs and excipients.
- **Critical Process parameter (CPP's):** Critical process parameters (CPPS) are process inputs that, when changed within their normal operating range, have a direct and significant impact on CQA.

3. Quality Risk Management

Risk management is an ongoing component of QbD throughout the product lifecycle. It involves setting up control measures, monitoring processes, and changing as needed to maintain product quality within the desired parameters [15].

Risk management is considered as an essential component of QbD design. Throughout the product's lifetime it is a key component of the overall quality control and assurance process. Continuous risk management solutions are used to manage and reduce hazards as they emerge [15].

- Principles of quality risk management are [15].
- Scientific knowledge-based evaluation of the risk to quality which eventually links to the protection of the patient.
 - Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved

ICH guideline Q9 gives description of risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, Risk Assessment, Risk Communication, Risk Control, Risk Evaluation, Risk Identification, and Risk Management [15].

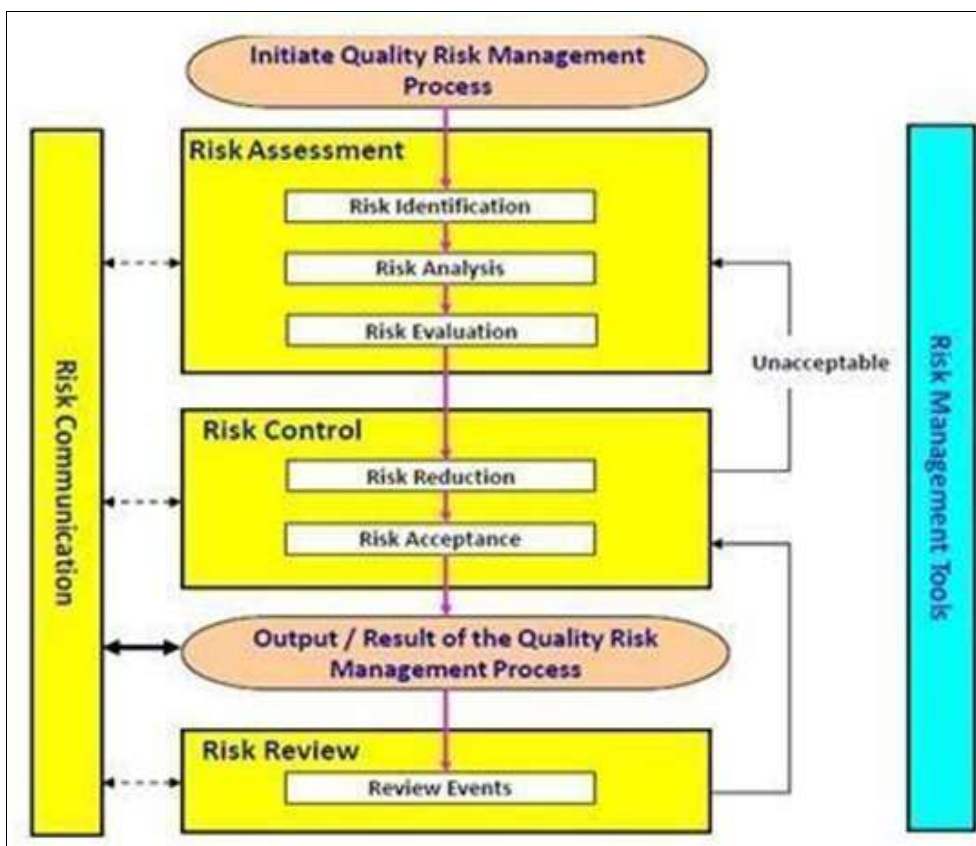


Fig 3: Overview of Quality Risk Management Process (as per Q9=Quality Risk Management) [14]

The first stage in risk management is to identify and prioritize potential risks. These risks include instrument operation methods, reagent properties, and cycle time.

Risk Analysis and Evaluation: During the Risk Analysis step of the QRM process, the possible harm(s) associated with each potential risk are estimated. The analysis could be qualitative, quantitative, or a combination of the two.

4. Design Space Development

A "multidimensional combination and interaction of input factors (e.g. material qualities and process parameters) that have been proved to offer assurance of quality" is how a design space is described ^[11].

A design space can be created for a single operation, several operations, or the complete process. Creating a design environment is optional, according to FDA standards, because product and process understanding can be built without one ^[11].

Working in the design space is not considered a change. Movement out of the design space is considered a change and would generally initiate a regulatory post-approval change process ^[12].

The applicant proposes design space, which is subject to regulatory assessment and approval ^[12,9].

Design Space refers to the product processes that ensure product quality, safety, and efficacy. Risk assessment can assist in understanding the relationship and influence of process parameters and material qualities on product and range of variables with which consistent quality can be obtained ^[9].

5. Control Strategy

Control strategy is defined as "A planned set of controls, derived from current product and process understanding that assures process performance and product quality" ^[15].

Quality Control Strategy encompasses process controls, specifications and design space ^[13].

ICH Q10 characterizes a control technique as "an arranged arrangement of controls got from current item and procedure understanding that guarantees procedure execution and item quality.

▪ Elements of a Control Strategy ^[12]

1. Procedural controls
2. In-process controls
3. batch release testing
4. Process monitoring
5. Characterization testing

6. Product Lifecycle Management & Continual Improvement:^[1]

Throughout the product life cycle, product quality can be improved. Companies can assess modern approaches to improving product quality. Process performance can be tracked to ensure quality consistency. Maintenance can be performed on a regular basis using the company's own internal quality system. Product quality is frequently upgraded throughout the product lifetime; businesses can adopt inventive techniques to increase quality.

Continuous improvement is an essential element of any

modern quality system. QBD focuses on product quality as well as continual process improvement to reduce variability. Pharmaceutical Quality System (PQS) is the foundation for continual improvement. It aids in the "identification and implementation of appropriate product quality improvements, process improvements, and variability improvements, thereby increasing the ability to meet quality standards."

Tools of QBD

1. Design of Experiment (DOE)
2. Process Analytical Technology (PAT)
3. Risk Assessment

1. Design of Experiment (DOE): ^[4, 14]

Design of experiments (DOE) is a procedure for efficiently organizing experiments so that the resulting data may be examined to provide meaningful and objective findings.

The term "design of experiment" refers to a systematic, organized strategy for determining the relationship between elements affecting a process and the outcome of that process.

In experiments, we purposely change one or more process variables (or factors) to see how the change affects one or more response variables.

Design of experiments (DOE) is a structured and prepared approach to determining the relationship between elements that influence the outputs of a method. When DOE is used in the pharmaceutical industry, the factors are the raw material attributes (e.g. particle length) and system parameters (e.g. speed and time), while the outputs are the critical satisfying attributes such as combination homogeneity, tablet hardness, thickness, and friability.

Advantages of Design of Experiment

1. Exhaustive information from a minimum number of experiments
2. Study effects individually by simultaneously varying all operating parameters
3. Can account for variability in experiments, process, materials, or operators
4. Able to provide understanding about the interaction between various variables
5. Determine acceptable ranges of critical process parameters contributing to identification of a design space.

Basic steps involved in DoE approach are as follows:

1. Defining input and output variables and range
2. Select appropriate experiment design and perform the run
3. Model diagnostic
4. Illustration of design space
 - The design space can be tabulated or graphically displayed using various methods. Graphically the design space can be illustration by the following:
 - A. Contour plots
 - B. Three-dimensional plots
 - C. Overlay Plots

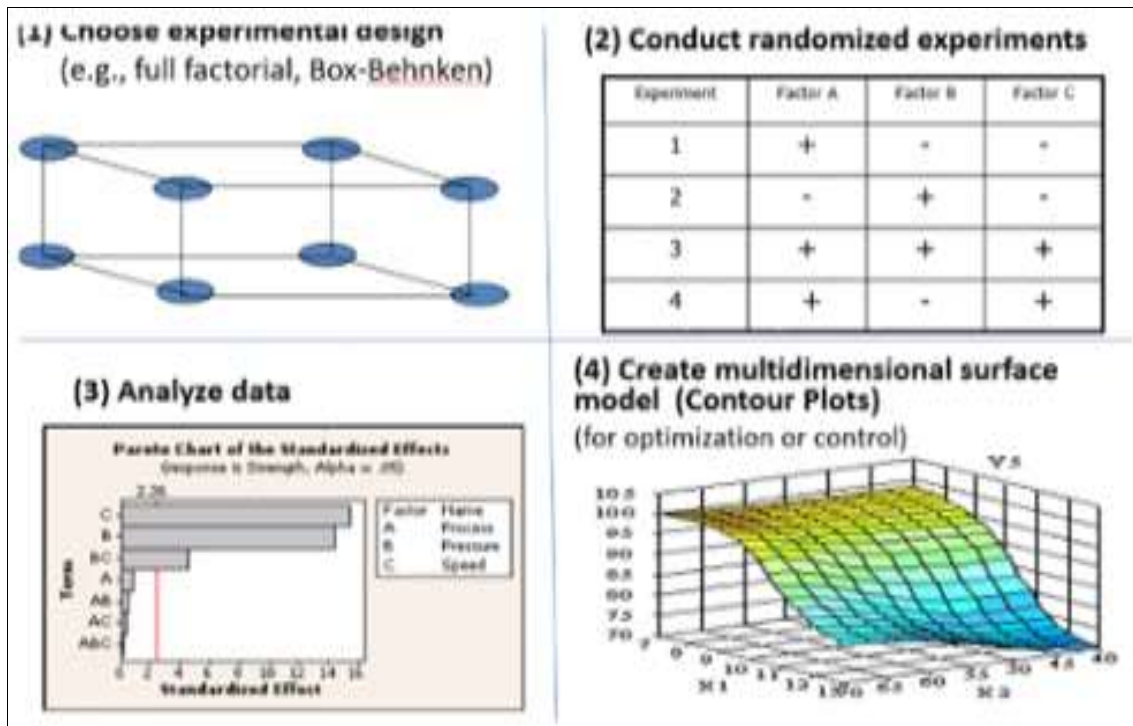


Fig 4: Design of Experiments [22]

Types Of Quality by Design Commonly Used

1. Screening Design (S.D).
2. Response Screening Design.
3. Fractional Factorial Design.
4. Placket – Burman Design.
5. Box- Behnken Design.

2. Process Analytical Technology (PAT): [4, 22]

PAT has been defined as “A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality”.

The goal of PAT is to “enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design.”

The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges.

FDA defined PAT as “a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.”

PAT tools

To implement a successful PAT project, a combination of three main PAT tools is essential:

- Multivariate data acquisition and data analysis tools: they are usually advanced software packages that aid in the design or carrying out experiments, the collection of raw data, and the statistical analysis of this data in order to discover which parameters are CPP.
- Process analytical chemistry (PAC) tools: in-line and on-line analytical devices used to measure the CPP parameters. These mostly comprise near infrared spectroscopy (NIRS), but also biosensors, Raman

spectroscopy, and others.

3. Risk Assessment: [9, 23]

QbD involves a systematic risk assessment to identify critical quality attributes and critical process parameters that have a significant impact on product quality.

The relationship between material qualities and process parameters is represented by risk assessment.

It is carried out throughout the product's lifecycle to identify critical material qualities and critical process parameters.

Risk assessment can have an impact on product quality and preliminary experimental findings. The qualities of a drug substance's relative risk were assessed as high, medium, or low.

According to ICH Q9 Quality Risk Management, “the production and use of a drug product, along with its constituents, necessitates some degree of risk.” Quality risk assessment should be founded on scientific information and ultimately linked to patient safety, with documentation of effort formality and quality risk management processes appropriate with level of risk. ICH Q9 provides a systematic method to quality risk management but excludes risk assessment, particularly in product development. However, the risk assessment methodologies specified in ICH Q9 also apply to product development risk assessment. The purpose of risk assessment prior to development studies is to identify potential high risk and identify process variables that may affect the quality of the drug product. This helps prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainties. The results of the study determine which variables are important and which are not, which facilitates the establishment of a control strategy

Risk Assessment Method mentioned in ICH Q9 guideline are as follows.

1. Failure Mode Effects Analysis (FMEA).
2. Failure Mode, Effects and Criticality Analysis (FMECA).

3. Fault Tree Analysis (FTA).
4. Hazard Analysis and Critical Control Points (HACCP).
5. Hazard Operability Analysis (HAZOP).
6. Preliminary Hazard Analysis (PHA).

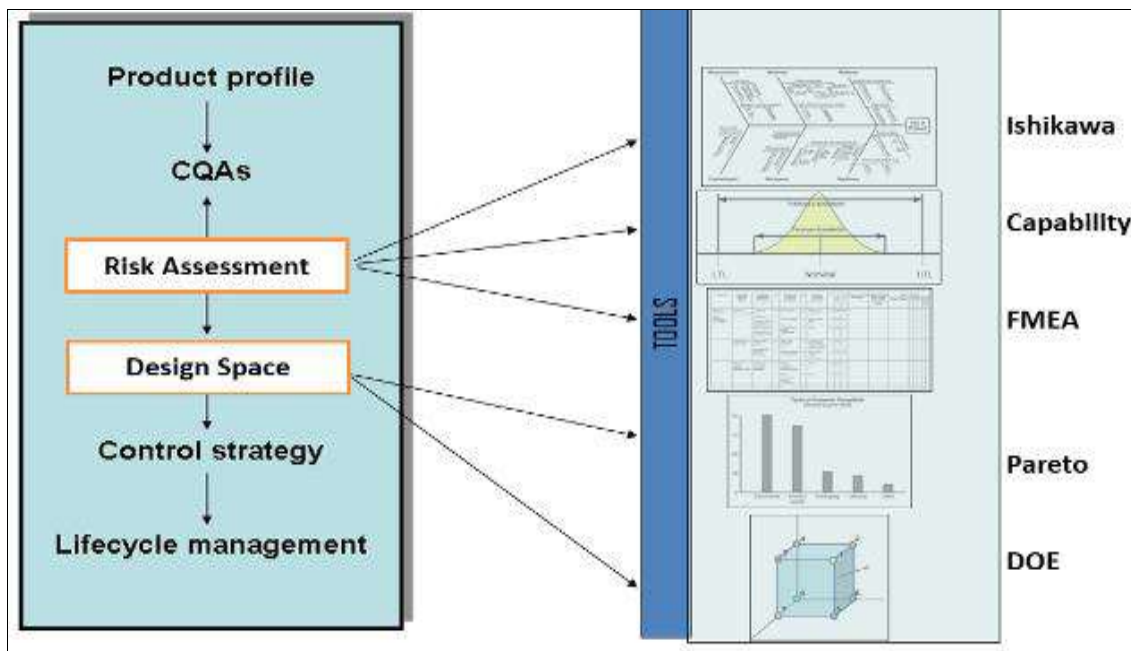


Fig 5: Quality Risk Management [22]

9. ADVANTAGES OF QBD: [13, s18]

- It is concerned with both patient safety and product efficacy.
- It is simple to gain a scientific grasp of the production process for a product.
- It includes both product design and process development.
- The science-based risk assessment can be carried out by this approach.
- It is a robust process.
- It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight.
- Better understanding of the Process

Applications: [11]

1. For Chromatographic technique

- In determination of impurity
- In screening of column used for chromatography
- In development of HPLC method for drug products substance
- In capillary electrophoresis
- In stability studies

2. For hyphenated technique

- In LC-MS method development
3. In bioanalytical method development
 4. In dissolution studies
 5. For spectroscopic measurement
 - In mass spectroscopy
 - In IR spectroscopy
 - In handling complex spectroscopic data
 6. In modified release products
 7. In tableting process
 8. Nanosuspension preparation
 9. In analysis of API and Excipients

10. In Biopharmaceuticals

Challenges and future perspective quality by design: [16, 20]

Challenges

Though Quality by Design is an essential part of the modern approach to pharmaceutical quality, but lack of understanding regarding the pharmaceutical process is the cause and also the major limitation for QbD implementation.

The majority of pharmaceutical companies feel that easier guidance on how to actually implement QbD is required.

Companies wanted FDA clarification on QbD terminology, authorized methods, criteria for selecting and deselecting essential quality attributes, standards for judging control sufficiency, and criteria for analytical method substitution.

Ten key challenges are the foremost problematic for QbD adoption. These challenges are evaluated by their relevancy against different drug type as well as different levels of adoption.

- The first four challenges occur within companies:
 1. Internal misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
 2. Lack of belief in business case i.e., there is a lot of uncertainty over timing of and investment for QbD implementation.
 3. Lack of technology to execute (e.g., Difficulty managing data, limited understanding of CQA'S Implementation.
 4. Alignment with third parties (i.e., How to implement QbD with increasing reliance on suppliers and contract manufacturers?)
- The next six challenges are directly related to the regulatory authority:
 1. Inconsistency of treatment of QbD across regulatory authority

2. Lack of tangible steering for business
3. Regulators not prepared to handle QbD applications
4. The way promised regulatory benefits are currently being shared does not inspire confidence
5. Misalignment of international regulatory bodies
6. Current interaction with companies is not conducive to QbD

Future Perspective

"Quality by Design" does not necessarily mean "less analytical testing," but it does imply "the right analysis at the right time" and is based on science and risk assessment. Implementing quality by design helps to establish rough and robust methods that help to comply with ICH guidelines, which is why pharmaceutical firms are implementing this QbD idea.

- It suggests that procedures such as target profile, CQA, design space, and risk assessment are equally applicable to analytical methods.
- In the future, quality by design is going to be customary to a far bigger extent. Together it will be additionally applied within the production space, as a result of currently, its often used within the development space, wherever we tend to use the event approach within the method.

Conclusion

In the pharmaceutical industry, Quality by Design (QbD) has emerged as a powerful framework for ensuring the quality, safety, and efficacy of drug products. QbD principles provide a systematic and science-based approach to pharmaceutical development and manufacturing, enabling companies to design quality products from the beginning. Here is an overall conclusion for QbD in the pharmaceutical industry. Implementation of quality by design at materials and processing method will provide a quality based effective and robust product. Production improvements to Manufacturers with significantly reduced batch failures and regulatory bodies will have greater confidence in the robust quality of products. QbD offers the opportunity for much greater regulatory flexibility. It focuses on building quality into the product and manufacturing processes as well as continuous process improvement, thus leading to reduction of variability. Quality by Design (QbD) elements and tools play an important role in facilitating a higher level of process understanding and create opportunities for investigation and developing control strategies in formulation and process development.

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