ejpmr, 2020,7(6), 331-340

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

QUALITY BY DESIGN (QBD): A MODERN APPROACH FOR DEVELOPMENT OF QUALITY PHARMACEUTICALS

***[1]Kiran Bhaskar Kudande, [2]Sachin Jalindar Fartade and [3]Ravindra Babasaheb Gawand**

[1]Department of Quality Assurance Techniques, MIT-WPU School of Pharmacy, Paud Road, Kothrud, Pune-411038, Maharashtra, India.

[2]Department of Pharmaceutics, School of pharmacy, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded-431606, Maharashtra, India.

[3]Department of Pharmaceutical Quality Assurance, Dr. Vithalrao Vikhe Patil College of Pharmacy, Viladghat, Ahmednagar-414111, Maharashtra, India.

***Corresponding Author: Kiran Bhaskar Kudande**

Department of Quality Assurance Techniques, MIT-WPU School of Pharmacy, Paud Road, Kothrud, Pune-411038, Maharashtra, India.

Article Received on 06/04/2020 **Article Revised on 27/04/2020** **Article Accepted on 18/05/2020**

ABSTRACT

Recently the concept of "Quality by Design" (QbD) gaining much attention among pharmaceutical industries for maintaining Quality. It serves as a bridge between industry and drug regulatory authorities to move towards a scientific, risk based, holistic and proactive approach for development of pharmaceutical product. It mainly covers QbD elements include defining target product quality profile, designing product, Quality Risk Management, Design of Experiment, PAT, identifying critical quality attributes, process parameters & controlling manufacturing processes to produce consistent quality over time. Also Benefits, Steps involved in Quality by Design, pillars of QbD, Analytical QbD. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals. The purpose of this review is to discuss the concept of pharmaceutical Quality by Design and describe how it can be help to ensure pharmaceutical quality & drug development.

KEYWORDS: Quality by Design, Quality Target Product Profile, Critical Quality Attributes, Critical Process Parameter, Process Analytical Techniques, Design of Experiment.

INTRODUCTION

Quality is the most important aspect of rapidly growing pharmaceutical industry while developing a new product[1] design quality product and its manufacturing process is the main aim of pharmaceutical product development for consistently deliver intended performance of the product.[2] It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design.[3] pharmaceutical product formulation can be developed based on data obtained from product development studies. Process variables that are emerged during development stages will serve as a source for QRM. QTPPs of the product must be determined before conducting development studies. Evaluation is performed to obtained desired quality of product. Design space, specifications and manufacturing controls are including in QTPP of product.[4,5]

Definition of [ICH Q8 (R1)]

"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." Designing and developing product and predefined quality characteristics with its manufacturing process involving quality by design in pharmaceuticals. QbD established to understand how product quality influenced by material and process variables.[1,6]

Quality

"Totality of features and characteristics of a product or services that bear on its ability to stated and implied needs."[7] In Quality by Design, Quality is important word. So Quality is "standard or suitability for intended use." This term includes such attributes as the identity, potency, and purity.[8,9]

Design[10,11]

The first aspects of QbD are an articulation of the design for the product

- Design a formulation to meet patients needs and performance requirements.
- Manufacturing process is designed to consistently meet product quality attributes.
- Impact of critical process parameters and input (raw) material attributes on product quality are identified.
- The process is continually monitor and update to assure consistent product quality.

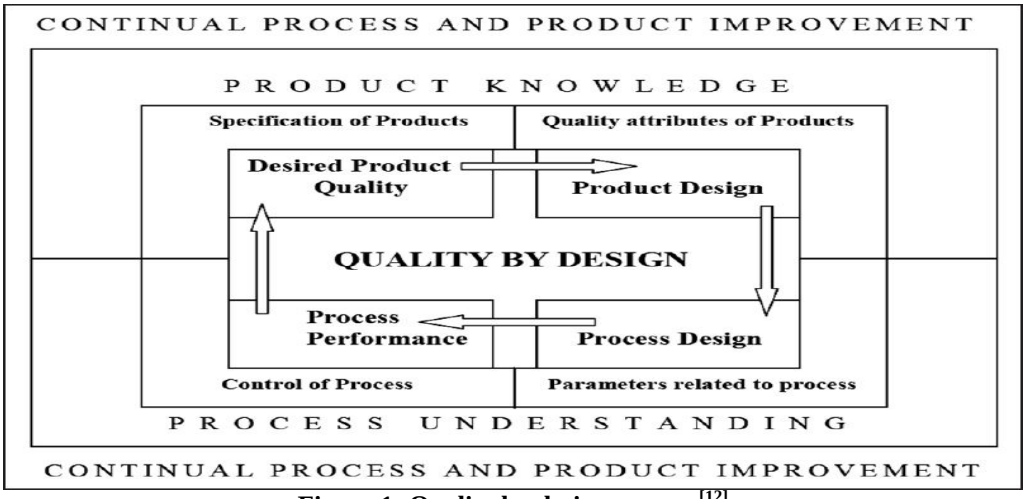

Figure 1: Quality by design system.[12]

Quality by Design

Quality by Design (QbD), a concept introduced by Dr. Joseph M. Juran, emphasizes the design of quality into product.[8]

"Quality by design means designing and developing manufacturing processes during the product development stage to consistently ensure a predefined quality at the end of the manufacturing process…"[13]

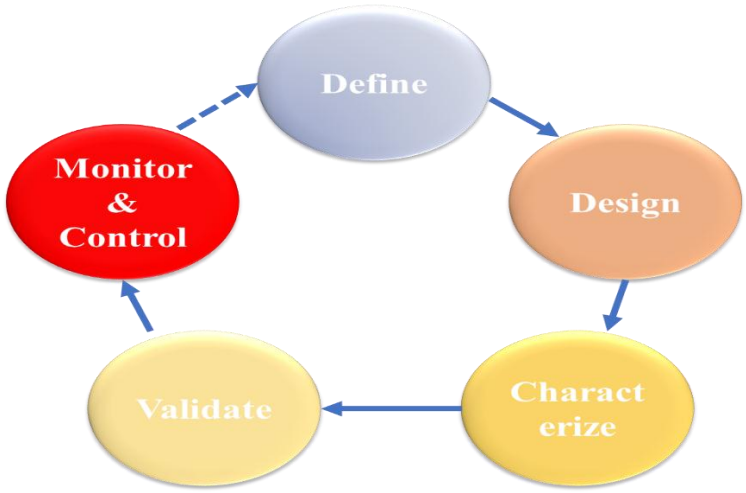

Figure 2: Quality by Design.[13]

QbD is a systematic approach to pharmaceutical product development and requires a thorough understanding of the critical factors affecting product's quality. It demands an understanding of product and process controls. Information included in International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8[13], Pharmaceutical Development, along with ICH Q9[14], Quality Risk Management, and ICH Q10[15], Pharmaceutical Quality Systems demonstrates how implementing quality by design establish the quality of product. Some of the advantages of QbD include improved product design, reduced manufacturing issues, assessment and lowering of risk, and improved post-approval change management.

A Critical Process Parameter (CPP) is a factor which has an impact on a critical quality attribute and, hence, should be monitored to ensure that the process produces the product with desired quality. Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit to ensure the desired product quality.[16]

Design of Experiments (DoE) and Process Analytical Technology (PAT) are the tools used in Quality by Design. ICH guidance Q8 defines design space as "the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality". A design space is determined at a lab scale and is scale and equipment dependent. This needs to be appropriately justified when using at a commercial scale.[17]

Quality by Design is an approach to reduce product variability and failures which helps in achieving high quality pharmaceutical products.

HISTORICAL BACKGROUND

In 2007, the FDA obtained a total of 5000 proposals for new drug applications (NDAs) and biological license applications and abbreviated new drug applications (ANDAs).Pharma- ceutical cGMPs for the 21st Century: A Risk-Based Approach" was introduced by the FDA in August 2002. A further guidance on process analytical technology (PAT) was released as part of the, cGMPs for the 21st Century" initiative, which hoped to encourage the adoption of more modern and flexible manufacturing technology in the pharmaceutical industry.[18, 13]

In March 2004, the FDA launched The Critical Path Initiative (CPI) to address the steep decrease in the number of innovative pharmaceutical products submitted for approval. The national strategy was to modernize the pharmaceutical sciences through which FDA-regulated products are developed, evaluated, manufactured and used.[14]

This prompted to the publishing of a guideline to aid manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current thinking for cGMP regulations. The impetus is to have quality in-built. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.[15]

Good manufacturing practices for the 21st century have been regularly developing as the ICH quality initiatives have been adopted. The move from empirical assessment based on performance to the concept of "building quality in" based on critical attributes has obtained traction as new guidance documents have been published.

Table 1: Traditional Approach and Enhanced QbD approach.[19,20]

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy, real-time release possible

Pillars of QbD

The QbD framework is supported on four pillars[21], which are as follows.

1. Product design goal

The quality target product profile (QTPP) needs to be outlined followed by identifying the various critical quality attributes (CQA) that should be present in the product. Factors that define the product are included in the QTPP and these factors include, among many others, dosage form, dosage strength, delivery system, route of administration, and the intended use of the product. Physical, chemical, biological, or microbiological properties of a product which are required to be within some specified limit, distribution, or range in order to ensure that the product has the desired quality are termed as CQA. Both QTPP and CQA provide a framework for the designing of the product and its understanding, which is achieved by characterizing the solubility, stability, compatibility etc of a substance through experiments on different formulations like gels, ointments, and sprays.[21,22]

2. Process design space

In the pharmaceutical industry intra and inter batch variations are very common. These variations can be minimized with the help of the design space robustness. As per the ICH Q8, design space is an "established multidimensional combination and interaction of material attributes and/or process parameters exhibited to provide assurance of quality".[18] The determination of the extent to which a variation in the process may affect the product quality aids in recognition of critical process parameters (CPPs). The anticipation of issues and achievement of a better process control is possible when the design space is defined. The limits of the sets of the parameter that is to be refined can be described with the help of the product experience, actual experimental data, or literature guidance.[21]

3. Control space

A control space can be defined on the basis of the process design space. It allows us to understand the processes in such a way that the quality of the product can be ensured from the variability of the known production process, which permits a better control over multifaceted production processes. This concept can be illustrated by thinking of dataset of a reference product having tightly clustered data points representing the output of a tightly controlled process. When the output of this process is plotted and compared with a reference then it will indicate whether the process is in control or not. If a study of DoE is conducted for a product right at the developmental stage, then several deviations can be

avoided along with the added advantages, which will lead to the elimination of various wasted efforts as well as the early determination of the root causes of unexpected adverse outcomes.[21]

4. Operating space

The best combination of statistically determined parameters, which can easily accommodate any variability occurring naturally in both CPPs and CQAs, is termed as operating space. In case of generics, the operating space should lie within the boundaries of the control space allowing the testing of a reference product having a combination of same parameters, while in case of new products, the operating space should lie within the boundaries of the design space complying with regulatory guidelines. A competitive advantage can be gained by the innovators through a comprehensive exploration of the design space carrying out tests on several formulation batches with the objective of refining their product.[21]

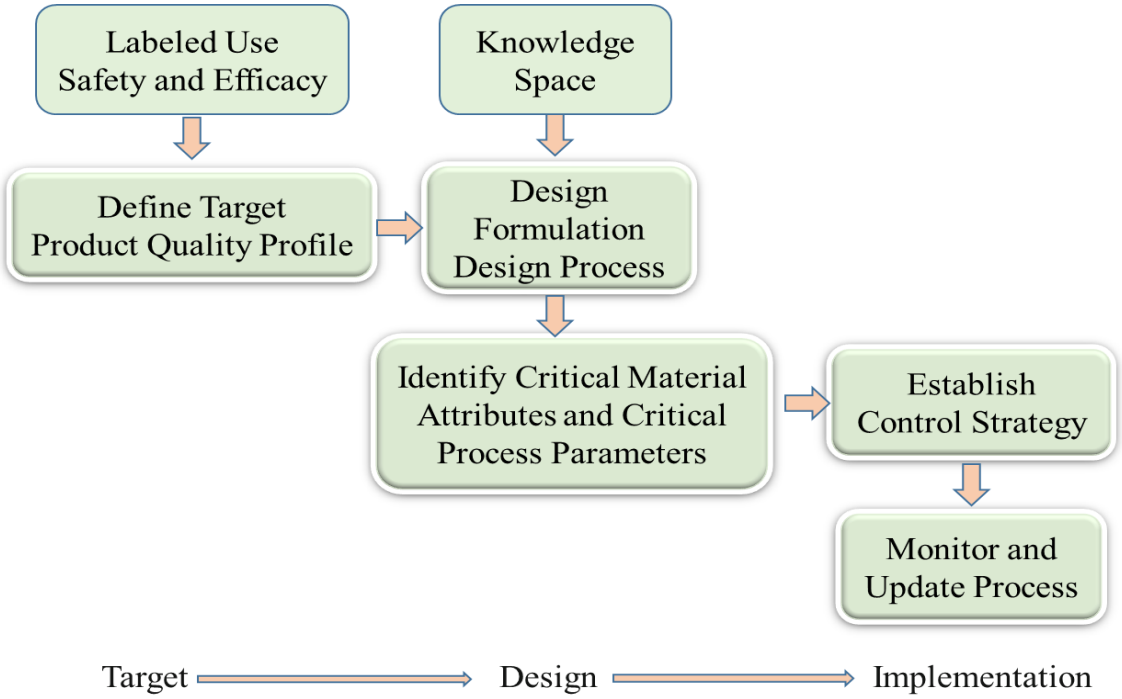

Figure 3: Overview of QbD.

Steps involved in quality by design products[23-25]

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

Key Charactristics of QbD[13-14]
- A tool for focused & efficient drug development
- Dynamic and systematic process
- It is applicable to analytical methods
- Can implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Always encouraged by Regulators.

Benefits of QbD[8,15,16,21,26-28]
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing capability, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information Incorporate risk management
- Reduce end-product testing
- Speed-up release decision.

Steps for Pharmaceutical QbD implementation

The practical implementation of QbD in the development of new pharmaceutical products can go through the following steps[8,29,30]

1. Hire an independent quality by design expert

2. Your organization audit and process by expert and conducting gap analysis.
3. Hold a basic quality by design workshop.
4. Review an expert report and recommendations.
5. Draft an implementation plan timelines and estimated cost.
6. Assign the resources.
7. Retain the independent expert as your "Project Assurance" advisor

Key Elements of QbD

It involves the following key elements during pharmaceutical development.

1. Quality Target Product Profile (QTPP)

According to ICH Q8 (R2), QTTP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to establish the desired quality, taking into account safety and efficacy of the drug product". Basically, it is a tool for setting the tactics for drug development. QTTP is used in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management.

It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic effect promised in the label. The QTTP guides formulation scientists to developed formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label.

For example, a typical QTPP of a solid oral dosage form would include

– Tablet Characteristics
– Identity
– Assay and Uniformity
– Purity/Impurity
– Stability, and
– Dissolution

It is necessary to acknowledge that QTPP should only include patient relevant product performance elements. For example, tablet density or hardness may be considered as a specification for process monitoring but may not be included in QTPP. Also, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size.[22,29]

2. Critical Quality Attributes (CQA's)

It establishes a link between CPP & CQAs: Identification of attribute or parameters that can be used as a surrogate for clinical safety & efficacy.[21,22,29] CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in process materials), and drug product. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy.

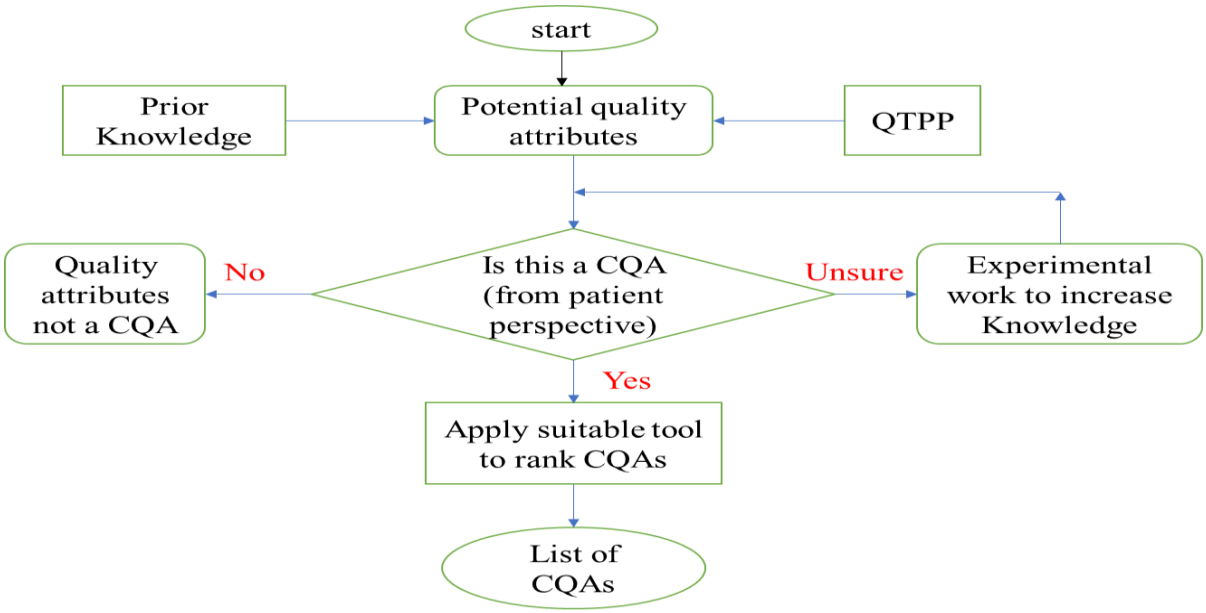

Figure 4: Decision Tree to Decide CQAs[31]

Once QTPP has been identified, then next step is to identify the relevant CQAs. A Critical Quality Attributes (CQA) is defined as "a physical, chemical, biological, or microbiological property or characteristic that must be within an appropriate limit, range, or distribution to produce the desired product quality.[18,32] For example, QTPP may include additional quality attributes of the drug product like strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTPP attributes such as assay, content uniformity, and dissolution, will also be a part of CQA as they may be altered by formulation or process variables.[29,30]

Table 1: Typical CQAs for drug substance and drug products.

For Drug Substance (chemical)	For Drug Product (Tablet)
Appearance	Appearance
Particle size	Identification
Morphic form	Hardness
Water Content	Uniformity of Dosage
Residual solvents	Physical Form
Organic Impurities	Dissolution
Inorganic impurities	Degradation products
Heavy metals	Water content
Residue on ignition	Assay
Assay	Microbiological limits

3. Quality Risk Management

Quality risk management is a process for the assessment, control, communication and review of risks to the quality of the drug product .The quality risk management system should confirm that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately connects to the protection of the patients health. The level of formality and documentation of the quality risk management process is commensurate with the level of risk.[21] Quality risk management (QRM) is a key helper for the development and application of QbD.[16] ICH Q9 Quality Risk Management indicates that, the manufacturing and use of a drug product necessarily entail some degree of risk.[22,29] central in Quality by design in product lifespan is relying upon risk management techniques to make decision. Good risk management decision depend upon the knowledge you obtain through the product development phase into full scale manufacturing[13] Risk assessments study results determine which variables are critical and which are not critical, which then guide the development of the control strategy for in process, raw material and final testing.[22] It is one of the tools gives a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. Previous knowledge consists of prior experience and understanding of what has been successful or unsuccessful, and recognition of issues, problems, or risks. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality problems during development and manufacturing.[28]

Method mentioned in ICH Q9 guideline are as follows[9,14,17]

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);
7. Risk ranking and filtering;
8. Supporting statistical tools .

4. Critical Material Attributes (CMA) And Critical Process Parameters (CPP)[13,17,22]

1. A material attributes is critical when a practical change in that attribute can remarkably impact the quality of the output material .
2. CPPs are responsible for ensuring the CQAs & it is identified from a list of potential CPPs with the help of risk assessment.
3. A process parameters is critical when it has a excessive impact on a critical quality attributes.

Three categories for parameters or attributes

a. Critical parameters: - A realistic change in parameter can cause the product to fail to get QTPP is critical parameter.

b. Non-critical parameter: - No failure in QTPP determined the within the potential operating space & no interactions with other parameters in the established suitable range.

c. Unclassified parameters: - The criticality of unclassified parameters is undetermined or unknown. The additional data are required to classify an unclassified parameter as critical or non-critical.

Risk assessment is linkage between input process variable and CQA. Following tools are come under risk assessment they are as follows:

1. Failure mode effect analysis (FMEA)
2. Ishikawa or fishbone diagram,
3. Pareto analysis.

A FMEA can then be implemented to rank the variables based on risk and to select the process parameters with higher risks for further studies to gain greater understanding of their effects on Critical Quality Attributes. An Ishikawa or fishbone diagram is employed to spot all potential variables; they are as follows raw materials, instrumental factors, and environmental factors, which can have an impact on a particular CQA. Pareto charts were used for quantitatively distinguish the impact of every issue on the chosen CAAs. Main goal of chromatographic method development is determination and separation of compound. In QbD approach the emphasis is given on rugged and robust method through risk assessment.

5. Design Space

A Design space is defined as, "Multidimensional combination and interaction of input variables that have been demonstrated to give assurance of quality".[33,34] A design space may construct for a single unit operation, multiple unit operations, or for the entire process. According to FDA guideline, defining design space is optional since the product and process understanding can be developed without a formal design space, nevertheless, above approach can assist to better understanding and attain overall control of a system.[30]

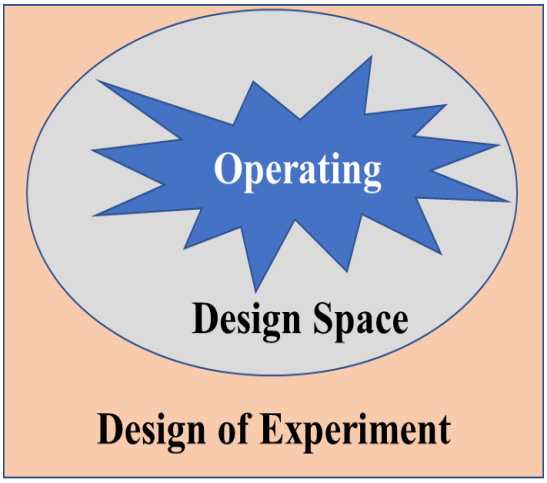

Figure 5: Design Space & Design of Experiment.[35]

Used of Design Space[27]

1. Linkage between process inputs such as inputs variables and process parameters and critical quality attributes (CQAs).
2. Used for more than one-unit operation(s) or up to complete process.
3. Can be implemented prior or after MA.
4. Presented by Applicant.
5. Working between the design space.
6. Subject to regulatory approval and evaluation.

6. Control Strategy

A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure expected quality. Every process has a control strategy right now. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to carry out extensive in process tests, such as blend uniformity or tablet hardness. Manufacturers are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA. The rigidity of the current system is required because manufacturers may not understand how drug substance, excipients, and manufacturing process parameter s affect the quality of their product.[28]

Tools of Quality By Design

1.Design of Experiments (DOE): Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of putting the experiment in a fraction of the time. Application of DOE in QbD helps in obtaining maximum information from a minimum number of experiments. When DOE is applied to a pharmaceutical process, parameters are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes like blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is not possible to experimentally analyses all of them. DOE can help to identify optimal conditions, the critical factors that most influence CQAs and those who do not.[36-39]

2.PAT (Process Analytical Technology): For the sake of understanding scientific, risk-managed pharmaceutical development, manufacture, and quality assurance, many tools are available in the PAT framework. These tools can be categorized into four classes according to the PAT guidance.[22]

(1) Multivariate tools for design, data acquisition and analysis;
(2) Process analyzers;
(3) Process control tools;
(4) Continuous improvement and knowledge management tools.

As defined by FDA's PAT guidance document, whether to remove the sample or not,process analysis can be divided into three categories as : (1) Atline: Measurement where the sample is removed, isolated, and analyzed in close proximity to the process stream; (2) Online: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream; (3) In-line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive. It is obvious that PAT is definitely useful in helping QbD implement. It can do a job of real-time monitoring of process without interruption to get technological parameters and material parameters on-line. PAT enhances understanding of technology (including the relationship between CQA and CPP), which leads to accomplishment of quality improvement and register simplification.

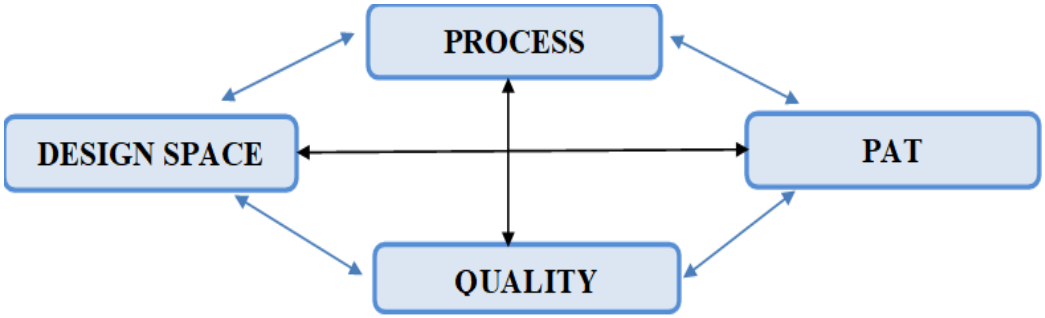

Figure 6: Process control.

Analytical QbD Method Validation[22,27,29]

A QbD method validation approach is that the validation of analytical method over a different API batch. It uses DoE and MODR knowledge for designing method validation for all kind of API manufacturing changes without revalidation. It provides the necessary ICH validation elements and information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach needs fewer resources than the traditional validation approach without compromising quality.

QbD can be applied for various analytical methods which include

1. Chromatographic techniques like HPLC for forced degradation studies, method development, and determination of impurities in pharmaceuticals.
2. Karl Fischer titration for determination of moisture content.
3. Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.
4. Chromatographic techniques like HPLC for stability studies, method development, and termination of impurities in pharmaceutical.
5. To Biopharmaceutical processes.
6. Dissolution studies.
7. Hyphenated technique like LC-MS.
8. Advanced techniques like mass spectroscopy, UHPLC, capillary electrophoresis.
9. Analysis of genotoxic impurity.

An analytical method development in an A QbD framework implement following five steps: **a. The 1st step**- Defines analytical target profile (ATP) where the method requirement and performance criteria are shown. Based upon the method, a suitable instrument technique can be selected which will permit the method to provide the main performance.

b. The 2nd step- After selecting a acceptable analytical technique, systematic method will be developed for the sample preparation and for analysis through different experiments. The objectives of activity experiment are to roughly obtain knowledge of robustness and the method condition.

c. The 3rd step- The knowledge gained in method development will then be implemented in risk assessment. The objective of risk assessment is to spot risk factors that should be experimentally evaluated in a design of experiment (DOE).

d. The 4th step- The DOEs help to establish Method operable design region (MODR) and a control strategy. Any place in the MODR will be consider as the Normal Operating Condition (NOC) for the method, and the MODR & NOC will be analyzed and Validated.

e. The 5th but continuous step in A QbD consist of knowledge management i.e. knowledge acquired from method optimization, development, verification, and use should be collected utilized and transferred thorough the life cycle of the method.

Applications of Quality by Design[30]

1. For Chromatographic technique
a) In determination of impurity
b) In screening of column used for chromatography
c) In method Development of drug product substance using HPLC
d) In stability studies
e) In UHPLC
2. For hyphenated technique likr LC-MS
3. In bioanalytical method development with precision and accuracy
4. In dissolution studies for testing release of drug
5. For spectroscopic measurement
a) In mass spectroscopy
b) In IR spectroscopy
c) In handling complex spectroscopic data
6. In modified release products
7. In tableting process
8. In compatibility study analaysis of API and Excipients
9. In Biopharmaceuticals
10. For Biotechnological Products
11. In formulation and processing of protein liposomes
12. Screening of critical variables, and establishment of design space on liposomes containing hydrophilic API

CONCLUSION

Quality by design is an important part of the modern approach to pharmaceutical quality. QbD, if properly performed and taken together with the current world wide harmonization of regulations and risk should be taken for what it has to offer, rather than what its concerns. The goal of a well-characterized method development effort is to establish a reliable method that can be implemented with a high degree of assurance to consistently produce data meeting predefined criteria

when operated within defined boundaries. 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. QbD has expanded in recent years from pharmaceutical processing to analytical chemistry. Beyond online process analytical technology, off-line assays including immunoassays are also getting benefits from QbD. The backbone for pharmaceutical companies is the quality of the products. The robust design space helps to minimize both intra- and inter-batch variations, which are quite common in the pharmaceutical industry. The QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement with a decrease in variability.

13. REFERENCES

1. Kalyan S, Vihar P. Quality By Design: Changing Outlook of Pharmaceutical Development, Int J pharmaceutical Sci Res, 2019; 10(9): 4100–8.
2. Woodcock J. The concept of pharmaceutical quality. Am Pharm Rev, 2004; 7(6): 10–5.
3. Nadpara NP, Thumar R V., Kalola VN, Patel PB. Quality by design (QBD): A complete review. Int J Pharm Sci Rev Res, 2012; 17(2): 20–8.
4. European Medicines Agency (EMA). ICH guideline Q10 on pharmaceutical quality system, 2014; 44(1): 1–20.
5. European Medicines Agency (EMA). ICH Guideline Q9 on quality risk management, 2014; 44(1): 1–20.
6. Kamemura N. Butylated hydroxytoluene, a food additive, modulates membrane potential and increases the susceptibility of rat thymocytes to oxidative stress. Comput Toxicol, 2018; 6(8): 32–8.
7. Purohit P, Shah K. Quality By Design (Qbd): New Parameter for Quality Improvement & Pharmaceutical Drug Development. Pharma Sci Monit [Internet], 2013; (2): 1–19.
8. Bindhu M. Rayaprolu*, Quality by Design: A Brief Introduction, Bindhu, J Pharmacovigilance, 2015; 3(4): 112.
9. Vemuri Pavan Kumar, N. Vishal Gupta*, A Review on quality by design approach (QBD) for Pharmaceuticals, Int J Drug Development and Research, 2015; 7(1): 52-60.
10. Lionberger RA, Lee SL, Lee LM, Raw A, Yu LX. Quality by design: Concepts for ANDAs. AAPS J, 2008; 10(2): 268–76.
11. Development S, Tool P, Fda. Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool. US Dep Heal Hum Serv Food Drug Adm Cent Drug Eval Res, 2007; (March): 1–22.
12. Abhinandana P, Nadendla R. Application of Quality by Design and its Parameters for Pharmaceutical Products. Int J pharma Chem Res, 2017; 3(3): 505–15.
13. Jyotsna Balasaheb Jadhav[1]*, Nitin NamdeoGirawale[2] and Rakesh Ashok Chaudhari[3], Quality by Design (QBD) Approach used in Development of Pharmaceuticals, Int. J. Pure App. Biosci, 2014; 2(5): 214-223.
14. . Vijay Mishra, Sourav Thakur, Akshay Patil & Anshuman Shukla, Quality by design (QbD) approaches in current pharmaceutical set-up, Expert Opinion on Drug Delivery, 2018; 15(8): 737-758.
15. Amit S. Patil, Anil M. Pethe, Quality by Design (QbD): A new concept for development of quality pharmaceuticals, International Journal of Pharmaceutical Quality Assurance, 4(2): 13-19.
16. Lalit Singh and Vijay Sharma*, Quality by Design (QbD) Approach in Pharmaceuticals: Status, Challenges and Next Steps, Drug Delivery Letters, 2015 4(3): 2-8.
17. Mimansha Patel, REVIEW ARTICLE: QUALITY BY DESIGN (QbD),Indo American Journal of Pharmaceutical Research, 2018; 8(11): 1357-1360.
18. Sharmada S. Sinai Kakodkar*, Dr. Shilpa Bhilegaonkar, Dr. Ajeet M. Godbole, Pankaj Gajare, Pharmaceutical Quality-by-Design (QbD): Basic Principle, Ijrm. Human, 2015; 1(1): 1-19.
19. Kengar MD, Tamboli JA, Magdum CS. Quality by Design- A Review. pharma Tutor, 2019; 7(4): 48–51.
20. Gholve SB, Ajgunde RR, Bhusnure OG, Thonte SS. Analytical method development and validation by QbD approach – A review Pelagia Research Library. pelagia Res Libr, 2015; 6(8): 18–24.
21. Lan Zhang, Shirui Mao *, Application of quality by design in the current drug development, Asian Journal of Pharmaceutical Sciences, 2017; 12(1): 1-82016.
22. Mayur Ashok Chordiya, Hemant Hiraman Gangurde, Vikram Nirmal Sancheti, Quality by Design: A Roadmap for Quality Pharmaceutical Products, Journal of Reports in Pharmaceutical Sciences, 2019; 8(2): 289-294.
23. Callls J, Deborah L, Kowalski BR. Process analyticle chemistry. Anal Chem, 1987; 59(9): 624–37.
24. Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control. Pharm Res, 2008; 25(4): 781–91.
25. Munson J, Freeman Stanfield C, Gujral B. A Review of Process Analytical Technology (PAT) in the U.S.Pharmaceutical Industry. Curr Pharm Anal, 2006; 2(4): 405–14.
26. R. M. Narke, R. P. Singh, OVERVIEW OF QbD: A CHALLENGE TO THE PHARMACEUTICAL INDUSTRY, Asian Journal of Pharmaceutical Research and Development, 2014; 2(4): 42-53.
27. Sachin L. Darkunde, A review on quality by design, International Journal of Pharmaceutical Chemistry and Analysis, 2018; 5(1): 1-6.
28. Bhattacharya J. Quality Risk Management – Understanding and Control the Risk in Pharmaceutical Manufacturing Industry.

International Journal of Pharmaceutical Science Invention, 2015; 4: 29-41.
29. P. J. Purohit*, K. V. Shah, Quality By Design (Qbd): New Parameter For Quality Improvement & Pharmaceutical Drug Development, 2013; 4(3): 12-23.
30. Rakesh A. Chaudhari[1]*, Ashok P. Pingle[2], Chetan S. Chaudhari[3], Chetan Yewale[4], Kantilal A. Patil[5], Quality By Design (Qbd): An Emerging Paradigm For Development Of Pharmaceuticals, Int J Pharm, 2014; 4(2): 138-146.
31. Gandhi A, Roy C. Quality by Design (QbD) in Pharmaceutical Industry : Tools, Perspectives and Challenges. pharma Tutor, 2016; 4(11): 12–20.
32. Shashank Jain, Quality By Design:A Comprehensive Understand-Ing Of Implementation And Challenges In Pharmaceuticals Development, 2014; 6(1).
33. Hardik Patel*1,Shraddha Pawar[1], Bhavna Patel[1],A Comprehensive Review on Quality by Design(QbD) in Pharmaceuticals, Int. J. Pharm. Sci. Res, 2013; 21(1).
34. Nishendu P.Nadpara*, Rakshit V. Thumar, Vidhi N. Kalola, Parula B.Patel, QUALITY BY DESIGN(QBD): A COMPLETE REVIEW, Int. J. Pharm. Sci. Res, 2012; 17(2).
35. Chavan SD, Pimpodkar N V, Kadam AS, Gaikwad PS, Pharm PD. Quality by Design. Res Rev J Pharm Qual Assur, 2015; 1(2): 18–24.
36. Lawrence X. Yu, Robert A. Lionberger, Sau Lawrence Lee, LaiMing Lee, Andre Raw Quality by Design: Concepts for ANDAs. The AAPS Journal, 2008; 10(2): 268-276.
37. Determining Criticality-Process Parameters and Quality Attributes (2013) BioPharm International, 2013; 26(12): 13-18.
38. Rathore AS, Winkle H () Quality by design for biopharmaceuticals. Nature Biotechnology, 2009; 27: 26-34.
39. FDA CDER. Guidance for industry. Pharmaceutical development, May 2006.