UPI Journal of Pharmaceutical Medical, and Health Sciences
Content Available at www.uniquepubinternational.com ISSN: 2581-4532

Open Access **Review Article**

Pharmaceutical Product Development: Quality by Design (QbD)

Valeru Chintu*, Korampalli Saida Rao, Chandu Babu Rao,and Balabhadrapatruni Sai Keerthana
Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur -522017.Andhra Pradesh, India.

DOI: https://doi.org/10.37022/jpmhs.v7i3.115

Article History
Received: 14-07-2024
Revised: 28-07-2024
Accepted: 14-08-2024

***Corresponding Author**
Valeru Chintu

Keywords: Quality by Design (QbD), ICH Guidelines, Target Product Quality Profile (TPQP), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Quality Risk Management (QRM).

Abstract

A popular modern strategy in pharmaceutical development is called "quality by design," or QBD, which started with established goals including the product's safety and efficacy. Safety and product efficacy are the primary goals of QBD in pharmaceutical development. With QBD, the design itself is emphasized for excellence. QBD was introduced by the Food and Drug Administration in order to comprehend the production process. An overview of the pharmaceutical quality system, quality risk management, and international council for harmonization (ICH) rules for product development is provided in this article in order to preserve product quality. The scientific foundation of QBD, regulatory industry perspectives, and QBD technologies were briefly discussed. There was a focus on excipients, manufacturing process development, container closure systems, and pharmacological substances. The Q9 guidelines for quality risk management, Q10 guidelines for pharmaceutical quality systems, and Q8 guidelines for pharmaceutical development form its basis. In the research and production of pharmaceuticals, it also provides an application of Quality by Design.

Introduction

Quality: In Quality by Design, Quality is important word. So Quality is “standard or suitability for intended use.” This term includes such attribute of the identity, potency, and purity.

Quality by Design: A lot of approaches to the development of pharmaceutical products and their subsequent manufacture has been advocated by the US FDA and the International Council Harmonization (ICH). This approach has been mounted ‘Quality by Design’ (QbD) and it defined as- “A systematic approach to development that begins with predefined objective and emphasizes product and process understanding and process control, based sound science and quality risk management”

Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. The concept of quality by design (QbD) has been recently adopted in the pharmaceutical industry through several initiatives {e.g., ICH Q8, Q9 and Q10, and the new regulatory documents, Process Analytical Technology (PAT), FDAs cGMP for the 21st Century}. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. [1]

In pharmaceutical science QbD was proposed by Food and Drug Administration (FDA) Generally QbD is a scientific approach it is mainly approached by the ICH (International council of harmonization) it follows three ICH guidelines.

The three approaches include the following ICH guidelines.Q8: Pharmaceutical development

Q9: Quality risk management

Q10: Pharmaceutical quality system

Quality was achieved final by the product testing and not by the process design QBD with knowledge of process and varying with the formulation variables. QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished

product. In the area of pharmaceutical quality; Food and drug administration (FDA) announced proposed amendments to "Current Good Manufacturing Practices" (cGMP) in 2002, with an emphasis on establishing a 21st century outlook on pharmaceutical manufacturing in order to establish a more systematic science and risk-based approach to the development of pharmaceutical products. The initiation of the cGMPs for the 21st Century and the publication of the Process Analytical Technology (PAT) guidance in 2004 by the FDA gave the way for the modernizationof the pharmaceutical industry. [2]

* Advantages of Quality by Design (QbD)

- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues

Key characteristics of Quality by Design (QbD)

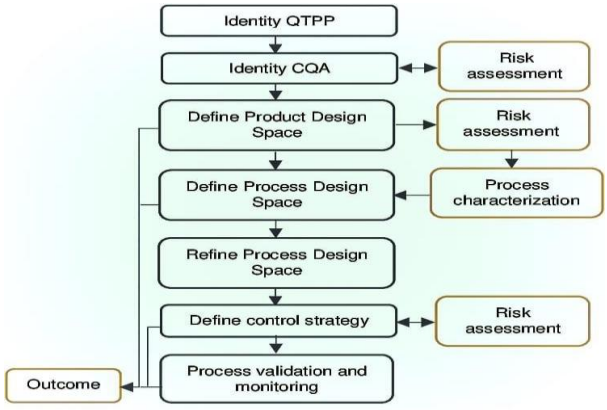

Fig 2: Tools of QbD

1] The Quality Target Product Profile (QTPP)

Quality Target Product Profile (QTPP): A future summary of the quality characteristics of a drug product that perfectly will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

* The concept of QTPP in this form and its application is novel in the QbD paradigm. QTPP forms the basis for product design in the following way.

1. Dosage form
2. Route of administration
3. strength, maximum and minimum
4. Release/delivery of the drug
5. Pharmacological characteristic 6.Drug product quality criteria 7.Pharmaceutical elegance

2] Critical Quality Attribute (CQA)

A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed to ensure the desired product quality" Identification of CQAs is done through risk assessment as per the ICH guidance Q9. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenteral, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs. [3]

3] Critical Process Parameter (CPP)

CPP is outlined as any measurable input (input material attributes or operational parameter) or output (process state variable or output material attribute) of a method step that has got to be controlled to attain the required product quality and method uniformity. During this read, each item would be a method parameter. Parameters are monitored before or in processes that influence the looks, impurity, and yield of the ultimate product considerably.

4. Critical material attributes (CMAs)

A parameter is important once a true modification therein parameter will cause the product to fail to fullfill the Quality Target Product Profile (QTPP). Thus, whether or not a parameter is important or not depends on the however giant of an amendment one is willing to think about this as well as different properties or characteristics of associate input material. CMAs ought to be inside associate applicable limit, range, or distribution to make sure the required quality of that drug substance, excipient, or in-process material.

5. Design Space

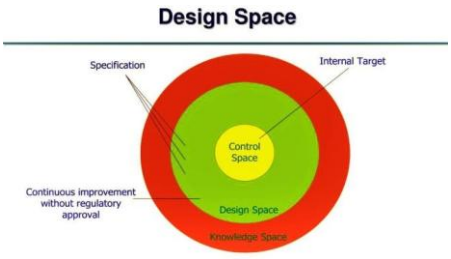

Fig 3: Design Space Development

A Design space is defined as, "Multidimensional combination and interaction of input variables (e.g. material attributes and process parameters) that have been demonstrated to provide assurance of quality". A design space may build 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 established without a formal design space, nevertheless, above approach can assist to better understanding and attain overallcontrol of a system. [4]

- Selection of Variables
- Describing a Design Space in a Submission
- Unit Operation Design Space(s)
- Relationship of Design Space to Scale and

Equipment

- Design Space versus Proven Acceptable Ranges
- Design Space and Edge of Failure.

6. Control Strategy

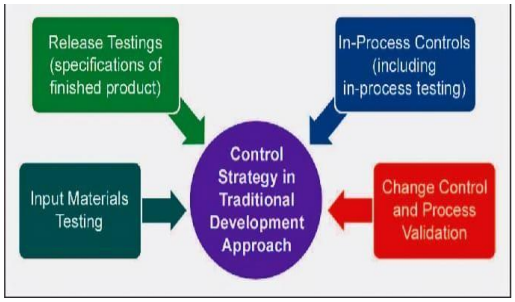

Fig 4: Control Strategy

An effective strategy should be designed and managed to make sure the specified quality product that embraces raw material specifications, method controls, in-method testing, and final product testing. Critical method parameters and significant material attributes are known by this method. For this purpose, PAT is often effectively used which will later scale back depending on the style house to observe quality.

- Risk based decision
- Continuous Improvement
- Product performance

7. Risk assessment

Risk is the combination of the chance of incidence of hurt and the severity of that hurt. Risk assessment helps to extend the quality of technique or process. A risk assessment will acknowledge crucial attributes that affect the ultimate quality of the product. Assessment of risk is useful for effective communication Between FDA And trades, research/development, and producing and among multiple producing sites at intervals the corporate. Methods of risk assessment: Some strategies of risk assessment square measure mentioned in ICH guideline Q9 as follows. [5]

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. This tool is further advanced with studying criticality of the consequences and providing clear indication of situation. [6]

- Failure Mode, Effects and Criticality Analysis (FMECA)

It is the extension of earlier said FMEA tool. Extending FEMA to incorporate an investigation of the degree of severity of consequences, their probabilities of occurrence and their detect-ability is Failure mode, effects and criticality analysis. In FMECA, each failure mode of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and if this level of risk is not acceptable, corrective action must be taken. This can be utilized for failure and risk associated with manufacturing processes. The tool can also be used to establish and optimize maintenance plans for repairable systems and/or contribute to control plans and other quality assurance procedures. [7]

- Fault Tree Analysis (FTA)

This tool assumes failure of the functionality of a product or process. The results are represented pictorially in the form of a tree of fault modes. This can be used to investigate complaints or deviation in order to fully understand their root cause and ensure that intended improvement will resolve the issues and not cause any other different problem.

8.Process analytical technique (PAT)

PAT has been printed by the U.S. FDA as a mechanism to vogue, analyze, and manage pharmaceutical manufacturing methods through the activity of vital process Parameters (CPP) that have a sway on vital quality attributes (CQA). The thought very aims at understanding the processes of shaping their CPPs, and consequently observance them throughout a timely manner (preferably in-line or on-line) and so being plenty of economical in testing whereas at the identical time reducing over-processing, enhancing consistency, and minimizing rejects. The authority has created public a restrictive framework for PAT implementation.

Process Analytical Technology (PAT) Tools

To implement a productive PAT project, a mixture of 3 main PAT tools is essential: Multivariate knowledge acquisition and knowledge analysis tools: typically, advanced software packages, packages that aid in the design of experiments, an assortment of raw information and statistically analyzing this data to see what parameters are CPP.[21] Process analytical chemistry tools: In-line and on-line analytical instruments accustomed live those parameters that are outlined as CPP. These embrace at the main close to infrared spectrometry (NIRS); however conjointly embrace biosensors, Raman spectrometry, and fiber optics [8].

Applications of Quality by Design (QbD)

Quality by design (QbD) – a comprehensive systematic approach to pharmaceutical development and manufacturing

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable withi n

		desig n space; opportunities for innovation
Process Control	In process testing for go/on-go; offline	PAT utilized for feedback and feed forward at real time
	analysis wide or slow response	
Product Specification	Primary means quality control; basedon batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and product testing end	Risk based; controlled shifted up stream,real time release

Current Applications of Quality by Design (QbD)

QbD is applied on an oversized scale within the pharmaceutical trade. A number ofthe applications are as follows

1. Application of Pharmaceutical: QbD for the Solubility improvement and Dissolution of sophistication II BCS Drug, exploitation chemical compound, surfactants, and Crystallization Inhibitors: Development of Controlled-release Tablets [9].
2. Application of QbD to Development of Analytical Separation Methods: The necessity for the application of QbD to be applied to Analytical separation strategies was determined since these strategies are used for internal control analysis of API and drug products. The strategies used for investigation were HPLC and capillary electrophoresis strategies [10].
3. A QbD Approach on Starch-Based Nano capsules: A Promising Platform for Topical Drug Delivery: The analysis aimed to develop a novel Starch primarily based Nanoparticles Carrier System for topical delivery of lipotropic bioactive molecules.[20] The technique used to be the emulsification-solvent evaporation method

Quality by Design (QbD) for Food Processing

In recent days determining and predicting the quality, safety and nutritional values in both raw and processed foods is becoming more valuable information because of attacking severe diseases which leads to life threatening. Food quality will be identified based on the following criteria.[11]

Authenticity: Foods which comes naturally or traditionally that are synthesizes during production, storage Function: Quality of food based on the function like storage capacity and cooks well.[19]

Biological activity: Food interaction on the body both positively and negatively. Nutrition: Nutrition food interactions on both positive and negative aspects.

Sensual: supply of the food to the senses like smell, taste, texture of the food.Modelling techniques used in food processing is Design expert. [12]

Quality by Design (QbD) for Herbal Products

Herbal medicinal system is developed in olden days. In ancient days these herbal medicines used to treat various diseases. These Herbal products have played an important role in world health and make an important contribution to health care in spite of the great advances observed in modern medicine in recent decades. According to an estimate of the World HealthOrganization (WHO), about 80 % of the world population uses herbs and other traditional medicines. They are known for their safety, efficacy, cultural acceptability and lesser side effects. [18]This has led to phenomenal increase in the demand for herbal supplements in the last two decades and a need has been felt for ensuring the quality, safety and efficacy of herbal drugs. [13]

Office of New Drug Quality Assessment (ONDQA)

- Office of Generic Drugs (OGD)
- QbD contains the important scientific and regulatory review questions
- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product.
- 416 applications received using QbD by June 2007
- Successful in ensuring that questions address issues regarding QbDSteps Involved in Qb

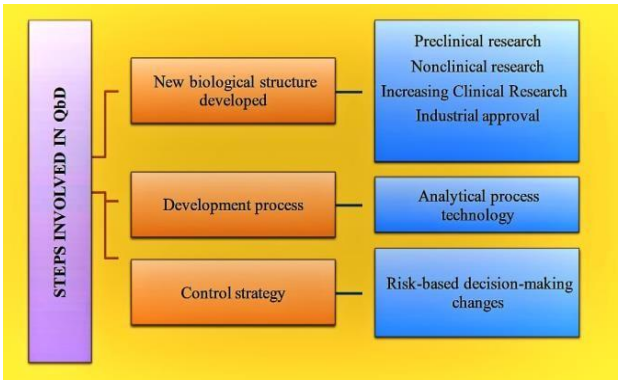

Fig 5: Steps involved in QbDBenefits of Implementing QbD for FDA

- Enhances scientific foundation for review
- Provides for better coordination across review, compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review (establishing a QMS for CMC)

- Provides for more flexibility in decision making
- Ensures decisions made on science and not on empirical information
- Involves various disciplines in decision making

Future perspective of QbD

In the future, the QbD is going to be easy to a far bigger extent. Collectively it will be additionally applied within the production space, as a result of presently, its often used within the growth space, wherever we tend to use the event approaches within the method.[17]

Moderately often it's seen that after we attend the assembly stage it stalls, either as a result of we have to travel into a plant that is presently existed for production purpose or as a result of they will be resistant towards new developments, particularly inside the PAT part. If we can keep the present production inside the instrumentation limits that we have then its fine. Some regulative Agencies conjointly initiate the QbD idea implementation like European Medicines Agency (EMA). The EU has conjointly discharged a document for "Real-Time Release."[16] The applications that embody quality intentionally square measure welcome by the EMA. The (EMA) is presentation partial interest in the applications that primarily support the idea of quality intentionally (QbD) [14]. U.S. authority/EMA refers to ICH guidelines Q8, Q9, Q10, Q11, and Q12 for QbD implementation [40,41]. Currently, ICH is functioning on "Q13- Continuous Manufacturing" and "Q14- Analytical technique Development." These new ICH tips square measures are expected close to the future [15].

Conclusion

Developing a dependable method that can be applied with a high level of assurance to consistently produce data matching predetermined criteria when operated within established parameters is the aim of a well-characterized method development endeavor. The creation and assessment of analytical techniques can be done using QbD. The following are examples of QbD tools: ATP, CQA, Method Optimization and Development using DoE, MODR, and Control Strategy incorporating Method validation, Continuous Method Monitoring (CMM), and continuous improvement in addition to Risk assessment. In addition to the required ATP, QbD calls for risk assessment, the use of the suitable tools, and the completion of the necessary amount of work within the allotted time frames. In order to guarantee the quality of the product, the pharmaceutical sector relies heavily on the development and validation of analytical methods through QbD. One may argue that the approach taken serves as an illustration of how to meet the intended technique performance criteria. Change control procedures inside the organization would apply to any modifications made to this strategy.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

References

1. Lawrence XY, Raw A, Lionberger R, Rajagopalan R, Lai ML, Holcombe F, Patel R, Fang F, Sayeed V, Schwartz P, Adams R. US FDA question-based review for generic drugs: A new pharmaceutical quality assessment system. Journal of Generic Medicines. 2007 Jul 1;4(4):239
2. Bhadoriya A. Quality by design–A Systematic Approach to Enhance Quality Matrix. BR Nahata Smriti Sansthan International Journal of Phramaceutical Sciences & Clinical Research. 2023 Dec 15;3(04). https://pubs.acs.org/doi/10.1021/ac00136a001
3. Rathore AS. Roadmap for implementation of quality by design (QbD) for biotechnology products. Trends in biotechnology. 2009 Sep 1;27(9):546-53.
4. Nadpara NP, Thumar RV, Kalola VN, Patel PB. Quality by design (QBD): A complete review. Int J Pharm Sci Rev Res. 2012;17(2):20-8. https://globalresearchonline.net/journalcontents/v17-2/04.pdf
5. Gawade A, Chemate S, Kuchekar A. Pharmaceutical Quality by Design: A new approach in product development. Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences. 2013 Jul;2(3):5-12.
6. Juran JM. Juran on quality by design: the new steps for planning quality into goods and services. Simon and Schuster; 1992 May 4. https://www.jpsr.pharmainfo.in/Documents/Volumes/vol13issue04/jpsr13042101.pdf
7. Hwisa NT, Adiki SK, Katakam P, Chandu BR. Design of dissolution media for in-vitro bioequivalence testing of Lamivudine. Journal of Applied Pharmaceutical Science. 2013 Jun 27;3(6):106-10.
8. Roy S. Quality by design: A holistic concept of building quality in pharmaceuticals. International Journal of Pharmaceutical and Biomedical Research. 2012;3(2):100-8. https://www.researchgate.net/publication/331270567_Quality_by_Design_A_new_practice_f
9. Adam S, Suzzi D, Radeke C, Khinast JG. An integrated Quality by Design (QbD) approach towards design space definition of a blending unit operation by Discrete Element Method (DEM) simulation. European Journal of Pharmaceutical Sciences. 2011 Jan 18;42(1-2):106-15.
10. Cubero-Leon E, De Rudder O, Maquet A. Metabolomics for organic food authentication: Results from a long-term field study in carrots. Food chemistry. 2018 Jan 15;239:760-70.

11. Sangshetti JN, Deshpande M, Zaheer Z, Shinde DB, Arote R. Quality by design approach: Regulatory need. Arabian Journal of chemistry. 2017 May 1;10:S3412-25.
12. Vogt FG, Kord AS. Development of quality-by-design analytical methods. Journal of pharmaceutical sciences. 2011 Mar 1;100(3):797-812.
13. Aucamp M, Milne M. The physical stability of drugs linked to quality-by-design (QbD) and in-process technology (PAT) perspectives. European Journal of Pharmaceutical Sciences. 2019 Nov 1;139:105057.
14. Sarvani V, Elisha RP, Nama S, Pola LM, Rao CB. Process validation: An essential process in pharmaceutical industry. International Journal of Medicinal Chemistry and Analysis. 2013;3(2):49-52.
15. Warude D, Patwardhan B. Botanicals: quality and regulatory issues. https://www.researchgate.net/publication/228624425_Botanicals_Quality_and_Regulatory_issues
16. Basalious EB, El-Sebaie W, El-Gazayerly O. Application of pharmaceutical QbD for enhancement of the solubility and dissolution of a class II BCS drug using polymeric surfactants and crystallization inhibitors: development of controlled-release tablets. Aaps Pharmscitech. 2011 Sep;12:799-810.
17. Orlandini S, Pinzauti S, Furlanetto S. Application of quality by design to the development of analytical separation methods. Analytical and bioanalytical chemistry. 2013 Jan;405:443-50.
18. Marto J, Gouveia LF, Gonçalves LM, Gaspar DP, Pinto P, Carvalho FA, Oliveira E, Ribeiro HM, Almeida AJ. A quality by design (QbD) approach on starch-based nanocapsules: a promising platform for topical drug delivery. Colloids and surfaces B: Biointerfaces. 2016 Jul 1;143:177-85.
19. Mantanus J, Rozet E, Van Butsele K, De Bleye C, Ceccato A, Evrard B, Hubert P, Ziémons E. Near infrared and Raman spectroscopy as Process Analytical Technology tools for the manufacturing of silicone-based drug reservoirs. Analytica chimica acta. 2011 Aug 5;699(1):96-106.
20. Chowdary KP, Chandra DU, Mahesh N, Reddy TM, Gopaiah KV. Enhancement of dissolution rate and formulation development of pioglitazone-a BCS class II drug. J. Pharm. Res. 2011 Nov;4:3862-3.
21. Kadam VR, Patil MP, Pawar VV, Kshirsagar S. A review on: Quality by design (QbD). Asian J. Res. Pharm. Sci. 2017 Dec 24;7(4):197-204. https://www.academia.edu/20037579/Quality_by_design_approach_for_optimizing_the_formulation_and_physical_properties_of_extemporaneously_prepared_orodispersible_films