Review Article

QbD Approach: A Framework for Integrating Quality into Pharmaceutical Products

ABSTRACT

Introduction: The traditional development processes use a quality by testing (QbT) approach that needs continuous testing to determine quality. Such processes are fixed, averse to change, and focus only on process reproducibility. This approach does not allow variation in material and process controls. In order to overcome the shortcomings of the traditional process, regulatory bodies have issued guidelines for the industries to improve the understanding of the process and the quality of the product. It aims to shift from traditional process QbT to a scientific approach quality by design (QbD) to assure product quality in the pharmaceutical industry**.**

Methodology: Articles related to QbD published in many search engines such as Scopus, Google Scholar, and PubMed were reviewed.

Review Findings: In order to ensure the quality of pharmaceutical products, regulatory bodies have emphasized on the implementation of QbD. For this, various guidelines have been published from time to time. The Indian pharmaceutical industry has started to apply the principles of QbD. Implementation of QbD develops a detailed understanding of the manufacturing process. The design space is achieved by QbD within which the expected quality is achieved even with changes in process parameters.

Conclusion: In short, the QbD approach is a great tool for assuring pharmaceutical product quality and better understanding of the manufacturing process. Therefore, it is imperative to have a successful implementation of the QbD approach.

Key words: QbD, CQAs, Risk assessment, Design space, Design of experiment, ICH guidelines

1. INTRODUCTION

In the early 1990s, renowned quality expert Joseph M. Juran coined the term Quality by Design (QbD) [1]. Early in the 2000s, the FDA published a report called Pharmaceutical Quality for the 21st Century: A Risk-Based Approach, which aimed to enhance quality measures in any pharmaceutical manufacturing process in order to ensure product quality [2]. Every pharmaceutical company strives to formulate an end product with the best possible quality, which should meet all regulatory requirements. Therefore, formulation teams must consistently deliver the required quality to meet regulatory requirements. Developing a design space is strengthened through the establishment of acceptance criteria, specifications and formulation controls that can be achieved through scientific understanding based on pharmaceutical development and manufacturing experiences [1]. Janet Woodcock, chief scientific officer for the CDER, defined pharmaceutical quality in 2004 as "products that are free of contamination and deliver therapeutic benefits in accordance with their labels" [3]. For quality assurance, the ICH Q8, Q9, and Q10 guidelines emphasize QbD, a scientific method for formulating and fabricating products [4]. Quality by Design [Yu, 2008 #5] is outlined in Figure 1.

Quality by Design holds that only when critical sources of inconsistency have been identified and removed or controlled within certain parameters can the quality of the final formulation be ensured [2]. Based on the ICH Q8 guidelines, it can be observed that the quality of a product cannot be adequately assessed through testing; this reinforces the observation that appropriate formulation design can contribute to improving the quality of a final product [5]. The results of a recent study conducted on regulatory approaches to pharmaceutical manufacturing facilities suggest regulators are also sensitive to quality aspects of the process as well as the final products. Process Analytical Technology (PAT) is another FDA regulatory recommendation through its guidance, which can assist manufacturers in controlling manufacturing processes by enabling continuous, real-time monitoring.

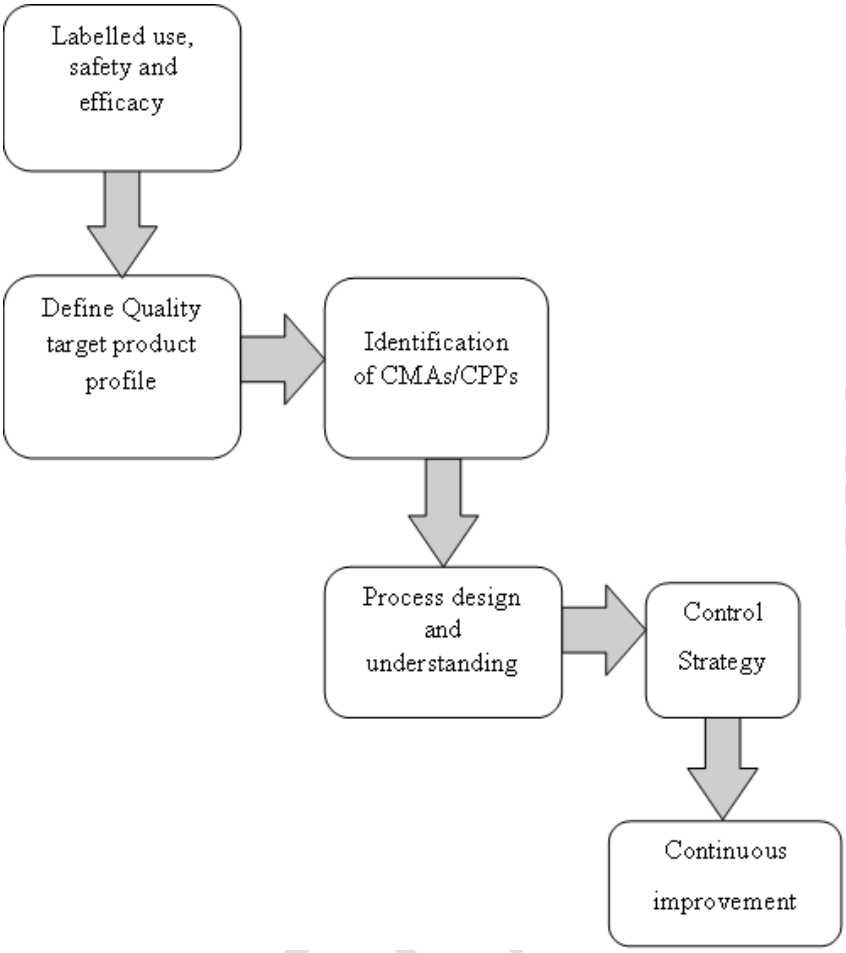

Figure 1: An overview of Quality by Design

Based on critical process parameters (CPP) and critical material attributes (CMA), real-time release testing (RTRT) is used to measure and ensure the quality of the resulting product [Christine, 2011 #7}. During a product's lifecycle, data should be collected, analysed, and evaluated continuously. A proposal for post-approval modifications can be justified based on the use of the collected data [6]. To contrast this, QbD is an approach which uses different ideologies and tools to understand the behaviour of formulas, which is based on a predefined target product profile (TPP).

Among the risk management tools are Failure mode effects analysis (FMEA), Fault tree analysis (FTA), Hazard analysis and critical control points (HACCP) etc. can be used to identify a first list of possible CQAs and critical process parameters (CPPs) [7]. The main purpose of CQAs is to identify quality attributes at various phases of the development life cycle, such as raw materials, intermediates, or final products. To ensure that the desired CQAs are met in product process optimization, a design of experiments (DOE) can be applied to evaluate effects of the design factors on manufacturer capability and final formulation CQAs, such as tablet blend flow and dissolution, and to determine the design space to ensure the desired CQAs [8]. Comparing the traditional and QbD desired approaches is illustrated in Figure 2 [9].

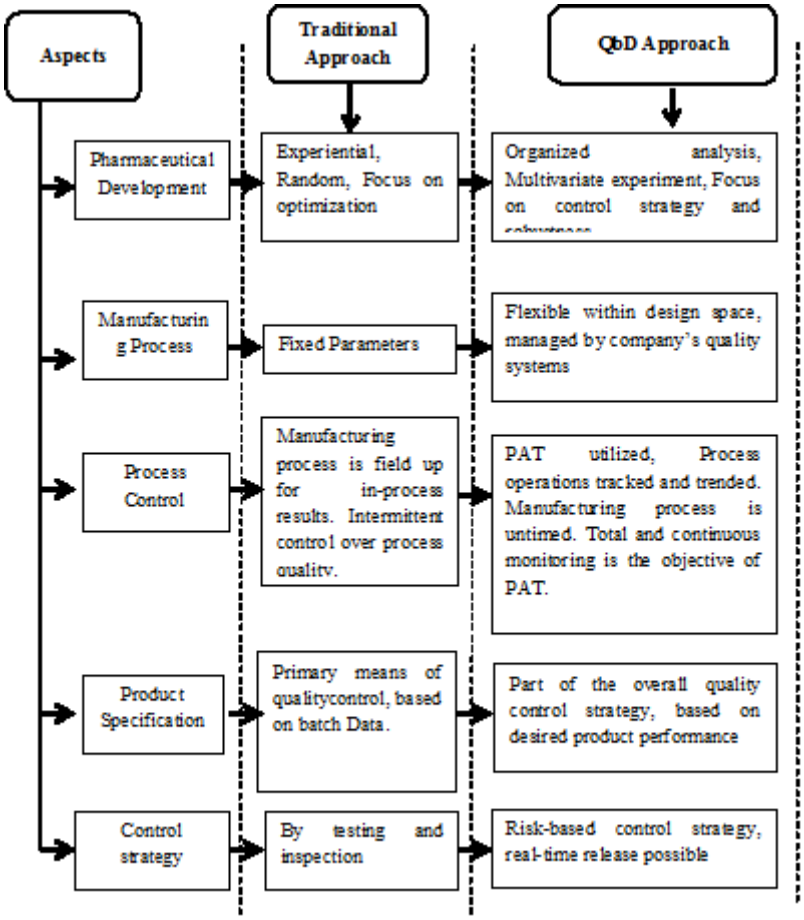

Figure 2: Comparison of traditional approach and QbD approach

The purpose of this review article is to provide a detailed overview of the components of the QbD approach and the guidelines issued by regulatory agencies. Along with this, there is also an assessment of the condition of the Indian pharmaceutical industry with respect to implementation of QbD. This is a descriptive study in which articles found from different search engines were reviewed.

2. KEY ELEMENTS OF QbD

2.1. Target Product Profile

It is a tool for pharmaceutical development called a Target Product Profile (TPP) - "planning with a view to the desirable end quality product before commencing the development" [4]. As an outline of the formulation development program, the target profile provides valuable guidance on how to achieve useful goals in the formulation development process.

Clinical terms such as clinical pharmacology, indications, contraindications, warnings, precautions, adverse reactions, abuse, dependence, overdosing, etc. are mainly used to describe TPP. [10]. The TPP is prepared based on the label's requirements. Current FDA guidelines state that the TPP provides the design sketch for the development of a formulation and details information on the

formulation at a specific time in the development cycle [11]. In TPP, Target Product Quality Profile (TPQP) is the next step that is mainly related to product quality.

It is crucial to consider how the term TPQP is linked to the words assay, stability, identity, dosage form, and purity on the label [12]. For example, an oral disintegrating tablet dosage form can serve as an example of a typical TPQP.

Hardness, wettability, tablet characteristics, identity, stability, assay, uniformity, dissolution, purity, and impurity are some of the attributes that make up TPQP for the orodispersible tablet. ‘

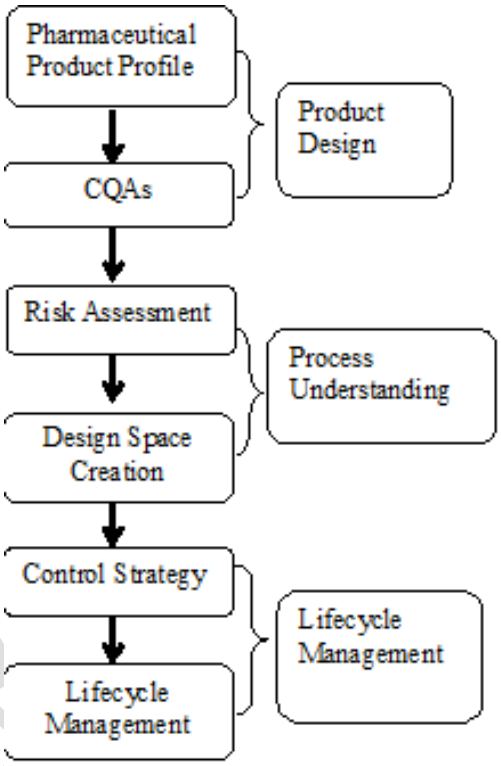

Figure 3: Steps to conduct pharmaceutical QbD

2.2. Identify critical quality attributes (CQAs)

In order to manufacture the required final formulation, the pharmaceutical formulation process generally includes a sequence of unit operations. In the development of a solid oral pharmaceutical dosage form, a unit operation might include milling, granulation, mixing, drying, compaction, and coating [13]. For a product to be of the desired quality, properties like physical, chemical, biological, and microbiological must be within the acceptable range. The ICH provides guidance to control the quality attributes that are considered as CQAs in order to ensure the product safety, efficacy, stability, and performance of the final formulation [14]. The intended safety, efficacy, stability, and performance are not part of this definition of CQA.

2.1.1. Critical Material Attribute (CMA)

Critical material attributes refer to the characteristics of the material (physical, chemical, biological or microbiological property or characteristic) used in the formulation that should be within the specified range or limit to ensure good product quality.

2.1.2.Critical Process Parameters (CPP)

Critical process parameters include all parameters that have an impact on critical quality attributes directly or indirectly. In order for the process to produce the desired quality daily, these parameters need to be monitored or controlled [15].

As a result of the different levels of the process input whose variations in prescribed operation range could exercise significant influence on CQAs, these are known as CPP. Independent CMAs are the most effective and practical method of capturing the relationship between the product quality and the overall quality of the process in the manufacturing process [1].

2.3. Risk Assessment

As part of its Q9 guidance document, the ICH recommends risk assessment and management. Quality risk management (QRM) is a systematic approach to evaluating, managing, communicating, and evaluating quality risks. Risk is inversely proportional to process and product understanding [16]. The better the knowledge of the process and the performance of the product, the lower the risk. An assessment of the risk should include an analysis of product performance with respect to a variety of material attributes (e.g., moisture content, particle size distribution, flow properties), processing options, and processing parameters and critical characteristics of raw materials, solvents, APIs, and packaging materials [15]. In quality risk management, the skill of risk assessment is a critical method which can aid in the identification of the material attributes and process parameters that will directly affect the quality of the end product [3]. Identifying the variables to be experimentally examined is the result of the risk assessment.

Risk Factor = (Occurrence) x (Detectability) x (Severity)

Where,

1. In contrast to the impact of a manufacturing fault, **severity** is the effect that relates to the patient, with respect to safety and efficacy (CQAs).
2. **Occurrence** refers to a possibility of product or process malfunctions, including doubts about new processes or lack of changes in processes.
3. **Detectability** is the ability to detect a failure, as well as the capability and correctness of the analytical methods [17].

2.3.1. Risk Estimation Matrix

The risk assessment procedure can be performed easily by setting up a matrix in which the probable risks that could occur due to CMAs and CPPs are placed/arranged and the impact they have on the CQAs of a product is evaluated. Therefore, the matrix is used in order to identify which variables and unit operations are most likely to impact the quality of the final product. Identified risks are color-coded as high, medium, or low risk, as detailed below:

- **Color Red:** Indicates high risk and is not acceptable. More evaluation is needed to determine whether the risk can be eliminated or reduced.
- **Color Yellow:** Indicates medium risk, which may be reduced through risk assessment.
- **Color green:** indicates low risk and is acceptable. No further investigation is needed.

At the time of risk assessment, the attributes (CMAs or CPPs) that are identified in red (high impact on CQAs of products) require investigation and mitigation plans to lower any residual risk to acceptable levels (if any). acceptable range. The green color indicates those that present little risk to critical quality attributes of the product and this is based on our prior experience with prior knowledge of the product [18].

2.3.2. Fish Bone Technique

A quality risk management tool that was developed in the 1960s by Kaoru Ishikawa is one of the seven basics of quality management [19]. Alternatively, this process is referred to as Ishikawa diagram, cause and effect diagram, etc. An effective method for identifying potential causes of effects (problems) in a process is via this tool. The structured approach identifies and organizes potential areas/causes of variation in a process that need to be evaluated for root cause determination for root cause analysis. Methods such as this illustrate the relationship between the result and all of the factors that contribute to the outcome. By creating the structure for group participation to take place, this technique encourages group members to engage in a systematic and orderly approach to the problem's potential cause [19]. On the right-hand side of every basic fishbone diagram, there is a box where the effect to be examined is written. This diagram has a horizontal axis at the center that is broken into branches to the left, and the branches are generally depicted as bones. The bones represent the potential factors that may influence the outcome described on the right hand side of the diagram and that need to be discussed and investigated. The limitation of this technique lies in the fact that, despite its simplicity and orderliness, it is difficult to document in some very difficult situations the connection between troubles and causes, and that its textual design makes it difficult to explore without a large space on which to draw the cause and effect diagram [20].

2.4 Design of experiments (DOE) for formulation and development

Normally, DOE involves assessing the impact of planned changes to input variables on some predetermined output to determine the extent of the impact of varying inputs or input mixtures (CPPs and CMAs) on the outcome [21]. Accordingly, DOE exhibits a relationship between input factors and

output responses. DOE is critical as it helps provide the greatest amount of information from the smallest amount of resources. The purpose of DOE is to plan and execute experiments so that information can be evaluated. To evaluate variables that affect processing, an experimental design must be used. Excluding variables based on earlier information is extremely important as well as specifying the range within which experiments are performed and excluding experimental areas that cannot be investigated [22]. DOE enables an assessment of effects of the design factors on the CQAs of final product and the manufacturability of final product [17]. DOE is being used in recent publications to design products and processes [23].

DOE provides an excellent method for understanding a process and controlling production of a desired product [24].

It Providing scientific understanding of procedural parameters and RM attributes on product quality enables establishment of a design space and manufacturing control strategy [25]. DOE does not only optimize, but also establishes a thorough understanding of the environment in which execution can take place. The following activities are planned for DOE:

1. In order to optimize formulation.

2. For the purpose of optimizing the production process.

3. Testing operational variables robustly

DoE designs are mainly divided into two categories, screening and optimization designs. The objective of screening design is mainly the selection of critical factors, Plackett-Burman design, Taguchi design and factorial design are mainly used as screening design[26]. The objective of optimization design is to determine the optimum level of critical factors, Central Composite Design, Box-Behnken design, Mixture design and D-optimal design are the most frequently used optimization designs[26]. Over the past decade, DoE has also been used in the optimization of many analytical methods. Some of the studies are summarized in Table 1, which used the DoE design for the optimization of the formulation and the analytical method.

Table 1: Recent studies employing DoE designs for optimization of formulation and analytical method.

S.no	Objective of study	Dosage form	Drug	Design used	Ref
1.	Optimization of formulation	Microspheres	Fucoxanthin	Face centered central composite design	[27]
2.	Optimization of input variables	Nanoantibiotic formulation	Ampicillin/sulbactam	Central composite design	[28]
3.	Optimization of formulation and process parameter	Nanosuspension	Carvedilol	Box-Behnken design	[29]
4.	Optimization of formulation for solubility enhancement	Solid dispersion	Nevirapine	Plackett-Burman design and Central composite design	[30]
5.	Optimization of formulation	Release modulating matrix tablet	Losartan Potassium	Box-Behnken design	[31]
6.	Optimization of formulation	Self-nanoemulsifying drug delivery system	Ezetimibe	Box-Behnken design	[32]
7.	Development of stability indicating RP-HPLC method using QbD approach	Bulk and pharmaceutical dosage form	Clofazimine	Taguchi design, Box-Behnken design	[33]
8.	Optimization of RP-HPLC method	Tablet dosage form	Pseudoephedrine Sulphate	Central composite design	[34]

2.5 Design Space

Design space refers to the interaction between input variables and parameters that has a direct or indirect impact on the product quality [14]. This design space allows for a variety of variables to be changed by numerous regulatory bodies [14]. Any modification of parameters outside the design space is considered a change that may affect the product quality, so it must be approved prior to implementation. Regulatory bodies must review and approve variations of this type in design space before they can be accepted. Design spaces can be prepared for the entirety of the process, for separate unit operations, or for different unit operations within the same design space. In addition, QbD can be implemented without building a design space if the knowledge of the product and process are well understood. DOE examines interactions between variables simultaneously, whereas various input variables vary simultaneously, which is a more effective analysis of variables [11]. A one-factor-at-a-time (OFAT) approach is useful here, where only one variable varies at a time while the rest remain constant. A design of experiment (DOE) approach, however, varies several input variables simultaneously and is more effective when studying interactions between two or more variables. It is characteristic of this type of application to use factorial designs (full or fractional) and response surface methodology (RSM) [3]. CQA and design space are associated based on the risk assessment results. CQAs and CPPs are interconnected in this model, and their impacts on the different operational operations are also illustrated [16].

2.6. Control strategy

Through the application of knowledge acquired during earlier stages of QbD, a control strategy is developed. This is defined by ICH Q8 (R2) as "a planned set of controls, derived from current product and process understanding, that ensure the quality and performance of a process and product." [13]. These are derived from the studies of CMAs and CPPs, as well as facility and end product acceptance criteria. The control strategy aims at ensuring that the process meets the CQA within the design space. In accordance with ICH Q8 [Jain, 2013 #3], the following tools can be used for control strategy:

- Material control
- By controlling equipment and operating conditions, each manufacturing step can be controlled
- Testing of control systems includes both end-product testing and process testing, as well as stability testing.
- Process monitoring program (evaluate whole process at regular time interval).

2.7. Incessant improvement and life cycle management

PALM (post approval lifecycle management) describes how QbD activity will continue after regulatory approval. As part of the design of PALM, the following points are taken into consideration [3].

- In what ways will the product and process be within their limits.
- During the course of the change process, how can it be ensured that all the changes will be within the design space
- Regularly updated control strategies will be developed as the knowledge increases.

3. REGULATORY TOOLS OF QbD

The FDA acknowledged that lapses in NDA or ANDA submissions have increased, with more applications being submitted for each change in formulation. The focus of the submitted dossier was on analysis and the least attention was given to process design and development. The regulatory body acknowledged that better understanding of processes is essential for continuous manufacture of quality products, as well as addressing regulatory challenges. As a consequence, the USFDA implemented the Current Good Manufacturing Practice (cGMP) in 2002 [35]. As part of CGMPs, processes are controlled to ensure product quality. It consists of raw material control, process design and monitoring, and reliable testing facilities. In addition, the USFDA developed the Process Analytical Technology (PAT) concept to better understand and monitor the manufacturing process. As a result, the manufacturing process is continually monitored by testing to ensure quality [36]. In response, ICH released three guidelines: "ICH Q8 (R2) (Pharmaceutical development), "ICH Q9 (Quality risk management)" and "ICH Q10 (Pharmaceutical quality system)" [37]. There are various regulatory guidelines that specify the components of QbD and they are provided in table 2.

Table 2. A summary of the components of QbD as specified by various regulatory guidelines

Date	Guideline Reference	Scope
Aug 2009	ICH Q8	Pharmaceutical development
Nov 2005	ICH Q9	Quality risk management
June 2008	ICHQ10	Pharmaceutical quality system
Jan 2011	FDA	Process validation. General principal and practices
Dec 2011	ICH Q8/Q9/Q10	Guide for implementation
March 2012	EMA/CHMP/QWP/811210	Real time release testing
Feb. 2014	EMA/CHMP/QWP/CVMP/70287	Process validation for finished products

4. QbD CONCEPT, UNDERSTANDING & ADAPTATION: CURRENT STATUS IN INDIAN PHARMACEUTICAL INDUSTRY

In order to get a quality product, pharmaceutical manufacturers need to follow cGMP guidelines and other guidelines issued by the regulatory authority. By developing better quality medicines, these guidelines aim to provide safer and more effective treatment for patients. Pharma industries are required to comply with cGMP and as a result, they often develop strategies to do so. The pharma industry generally uses three modalities to control and regulate quality: Quality Control (QC), Quality Assurance (QA), and Quality Management. The QC department is inspection-based and tends to justify quality by running tests. The quality control process compares certain parameters of in-process and finished products with available standards. This component determines if there is non-compliance and checks for defects in the final product, discarding the defective products. To some extent, QA is an effort to prevent defects and ensure the quality of the end product. QA examines every step of the process in order to obtain the best results. In order to minimize quality defects in the final product, companies use QA to confirm that the product is being made in the most efficient manner. Quality assurance and quality control are traditionally used together by companies to produce superior products [38]. Essentially these methods follow the Quality after Design model and they are not adequate. Apart from some pharma giants, most Indian pharma companies rely on QC for quality control. Small Indian pharma companies have yet to adopt the concept of QbD. Indian pharma giants, however, with multinational presence, have already started to implement a quality management system based on quality by design.

5. CONCLUSION

Quality by Design (QbD) is becoming increasingly popular and widely used in the development of pharmaceutical products. Having QbD implemented at the product/process design level is highly effective, but it should also be applied at the manufacturing and quality assurance levels. When QbD concept is implemented in product development patients will benefit from high quality medicines, manufacturers will improve production with a dramatic reduction in batch failures, and regulators will be more confident in the quality of drugs. As a strategic process for product development and manufacturing, Quality, QbD promotes product quality by design. It is designed to ensure that the intended performance of a final drug product will perform as expected - both in terms of purity and effectiveness. In order to successfully achieve this, clear objectives must be established, as well as proper risk management.

REFERENCES

1. Patel H, Parmar S, Patel B. A Comprehensive Review on Quality by Design (QbD) in Pharmaceuticals. Int J Pharm Sci Rev Res. 2013;21:223-36.

2. Nadpara NP, Thumar RV, Kalola TV, Patel PB. Quality by design (QBD): A complete review. Int J Pharm Sci Rev Res. 2012;17:20-8.

3. Jain S. Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development. Int J Pharm Pharm Sci. 2013;6:29-35.

4. Anuj G, Fuloria NK. Short review on Quality by design: A new Era of Pharmaceutical drug Development. Int J Drug Dev & Res. 2012;4:19-26.

5. Karanakov L, Ribarska J, Dodov M, Trajkovic-Jolevska S. Analysis and critical review of ICH Q8, Q9 and Q10 from a generic pharmaceutical industry view point. Macedonian Pharmaceutical Bulletin. 2011;57:85-96.

6. McCurdy V. Process Understanding: For Scale-Up and Manufacture of Active Ingredients: Wiley-VCH Verlag GmbH & Co; 2011.

7. Jones R. Pharmaceutical Manufacturing: how to understand risk and assess the risk to patient safety. Pharmaceutical Engineering. 2009;29:1-10.

8. Roy S. Quality by design: A holistic concept of building quality in pharmaceuticals. Int JPharm Biomed Res 2012;3:100-8.

9. Ghodke DV, Bhusnure OG, Kulkarni AA, Makne PD. Quality by Design: Better Approach for pharmaceuticals quality development. International Journal of Universal Pharmacy and Life Sciences. 2013;3:341-8.

10. Siddiqua SA, Kumar GP, Kumar MS. QbD - A challenge to the Pharma industry. International journal of innovative pharmaceutical science and research. 2013;31:1-21.

11. Trivedi B. Quality by design (QbD) in Pharmaceutical. Int J Pharm Pharm Sci. 2012;4(1):17-29.

12. Nasr M. Pharmaceutical Development: ICH Q8/Q(8)R. Workshop on Implementation of ICH Q8/Q9/Q10; Beijing, China: Office of new Drug Quality Assessment Centre for Drug Evaluation and Research (CDER) food and Drug Administration (FDA); 2010.

13. Yu LX. Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. Pharm Res. 2008;25:781-91.

14. Guidance for industry: Q8 Pharmaceutical Development. US Department of Health and Human Service Food and Drug Administration; 2010.

15. Tiwari R, Kulkarni S, Panda A. Application of quality by design (QBD) approach to pharmaceutical industry. Int J Pharm Res Bio-Sci. 2013;2:11-28.

16. Gutidance for Industry: Q9 Quality Risk Management: US Department of Health and Human Service Food and Drug Administration; 2005 [Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf.

17. Sun D, Lawrence X, Hussain M, Wall D, Smith R, Amidon G. In Vitro testing of drug absorption for drug “develop ability” assessment: Forming an interface between in vitro preclinical data and clinical outcome. Curr Opin Drug Discovery Dev. 2004;7:75–85.

18. Pharmaceutical Development Case Study: “ACE Tablets” CMC-IM working group; 2008

19. Jain A, Jain SK, Ganesh N, Barve J, Beg AM. Design and development of ligand-appended polysaccharidic nanoparticles for the delivery of oxaliplatin in colorectal cancer. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;6(1):179-90.

20. Sleezer CM, Russ–Eft DF, Gupta.K. Practical Guide to Needs Assessment. 3 ed. Hoboken, New Jersey: John Wiley & Sons; 2007.

21. Ranga S, Jaimini M, Sharma SK, Chauhan BS, Kumar A. A Review on Design of Experiments (DOE). International Journal of Pharmaceutical and Chemical Sciences. 2013;3:216-24.
22. Rantanen J, Khinast J. The Future of Pharmaceutical Manufacturing Sciences. J Pharm Sci. 2015:1-27.
23. Shivhare M, McCreath G. Practical Considerations for DoE Implementation in Quality by Design 2010 [Available from: http://www.bioprocessintl.com/manufacturing/information-technology/practical-considerations-for-doe-implementation-in-quality-by-design-297328/.
24. Failure Mode and Effects Analysis (FMEA): A Guide for Continuous Improvement for the Semiconductor Equipment Industry Technology Transfer: Sematech; 1992 [Available from: http://www.sematech.org/docubase/document/0963beng.
25. Chen C. Implementation of ICH Q8 and QbD – An FDA Perspective Food and Drug Administration ISPE, Yokohama, Japan2006 [Available from: http://www.nihs.go.jp/drug/PhForum/Yokohama060609-02.pdf.
26. S NP, Colombo P, Colombo G, D MR. Design of experiments (DoE) in pharmaceutical development. Drug development and industrial pharmacy. 2017;43(6):889-901.
27. Jaswir I, Noviendri D, Taher M, Mohamed F, Octavianti F, Lestari W, et al. Optimization and Formulation of Fucoxanthin-Loaded Microsphere (F-LM) Using Response Surface Methodology (RSM) and Analysis of Its Fucoxanthin Release Profile. Molecules (Basel, Switzerland). 2019;24(5).
28. Sharma N, Singh V, Pandey AK, Mishra BN, Kulsoom M, Dasgupta N, et al. Preparation and Evaluation of the ZnO NP–Ampicillin/Sulbactam Nanoantibiotic: Optimization of Formulation Variables Using RSM Coupled GA Method and Antibacterial Activities. Biomolecules. 2019;9(12):764.
29. Medarević D, Djuriš J, Ibrić S, Mitrić M, Kachrimanis K. Optimization of formulation and process parameters for the production of carvedilol nanosuspension by wet media milling. International Journal of Pharmaceutics. 2018;540(1):150-61.
30. Mahajan A, Surti N, Patel P, Gheewala N, Patel A, Shah D. Optimization of formulation and process variables using central composite design for the production of nevirapine spray dried solid dispersion. Drying Technology. 2021:1-14.
31. Kalbhare SB, Redasani VK, Bhandwalkar MJ, Pawar RK, Bhagwat AM. Optimization of Formulation using Box-Behnken Design. Asian Journal of Pharmaceutical Research. 2021;11(2).
32. Yadav P, Rastogi V, Verma A. Application of Box–Behnken design and desirability function in the development and optimization of self-nanoemulsifying drug delivery system for enhanced dissolution of ezetimibe. Future Journal of Pharmaceutical Sciences. 2020;6(1):7.
33. Patil TS, Deshpande AS. Development of an Innovative Quality by Design (QbD) Based Stability-Indicating HPLC Method and its Validation for Clofazimine from its Bulk and Pharmaceutical Dosage Forms. Chromatographia. 2019;82(2):579-90.
34. Dongala T, Katakam LNR, Palakurthi AK, Katari NK. RP-HPLC Stability Indicating Method Development and Validation of Pseudoephedrine Sulfate and Related Organic Impurities in Tablet Dosage Forms, Robustness by QbD Approach. Analytical Chemistry Letters. 2019;9(5):697-710.

35. Manufacturing Technology Committee – Risk Management Working Group Risk Management Training Guides. Failure Modes and Effects Analysis Guide 2008 [Available from: http://www.pharmtech.com/pharmtech/data/articlestandard//pharmtech/252011/727766/article.pdf.

36. Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality: U.S. Department of Health and Human Services Food and Drug Administration; 2004 [Available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf.

37. Aksu B. Quality by design (QbD) and new ICH Guidelines [Available from: http://www.crsic.org/pdf/buket-aksu-abstract.pdf.

38. Lawrence XY. Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceutical research. 2008;25(4):781-91.