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QUALITY BY DESIGN- A RECENT TREND IN PHARMACEUTICAL INDUSTRIES.

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ABSTRACT

The main objective of the present review article is to understand the concept of pharmaceutical Quality by Design (QbD) and discuss its application and implementation to ensure pharmaceutical quality & drug development. As it is known that pharmaceutical industries are constantly searching for different ways to ensure and improve product safety, quality and efficacy, regulatory bodies are therefore concentrating on implementing QbD, a science based approach that improves process understanding and enables process-control strategies. This new approach to drug development could increase efficiencies, provide regulatory relief and flexibility and offer important business benefits throughout the product's life cycle. Under this concept of QbD during designing and development of a product, a company needs to define Target product Profile (TPP), identify critical quality attributed (CQA) and Quality risk management (QRM). The pharmaceutical industry that follows QbD norms designs the product formulation and process to meet the product attributes, as results of all obtained details the company can continually monitor and update its manufacturing process to assure consistent product quality.

KEYWORDS: Quality by Design (QbD), Quality target product profile (QTPP), Critical Quality Attributes (CQA), Quality risk management (QRM), Design Space.

INTRODUCTION

It had been a long time since pharmaceutical companies were facing an increasingly difficult financial climatic condition, they had spend a lot of amount and efforts in obtaining predetermined product assured quality, achieve regulatory compliance and produce drugs as

cost-effectively as possible. But all these steps became effortless, as predetermined results were not obtained due to lack of comprehensive and rationale based understanding of these complex processes, associated critical variables and strategies to control these variables, which is pivotal in assuring quality of the product. Less importance was given to identify the main cause of manufacturing failures. Furthermore, no rationale-based approach was followed to predict the effects of scale-up on the final product. This has led to difference between product quality attributes and their clinical performances, resulting regulatory authorities to set stringent specifications and guidelines for approval of drug products.[1,2]

In order to overcome these hurdles, in the year 2002, US Food and Drug Administration (FDA) had announced a new initiative-Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, intended to modernize the FDAs regulation in regards to pharmaceutical manufacturing and product quality. The initiative challenged industry to look beyond quality by testing (QbT) for ensuring product quality and performance. Additionally, International Conference on Harmonization (ICH) Q8 guideline was published in May 2006 for pharmaceutical product development and has been complemented by the ICH Q9 on Quality Risk Management and ICH Q10 for a Pharmaceutical Quality System.

In basic QbT approach, pharmaceutical quality is defined as the product meeting the pre-specified quality and regulatory specification, QbT framework specifically focused on raw material testing, drug substance or drug product manufacturing process, in-process material testing, and end product testing, traditional testing methods were used to check quality of raw materials including drug substance and excipients. Since only limited numbers of drug product out of several millions were tested, drug manufacturers were usually required to conduct comprehensive in-process testing, such as blend uniformity, tablet hardness, tablet disintegration in order to ensure that the outcome of in-process testing meets the FDA approved testing specifications. Furthermore, due to lack of confidence, in the manufacturing processing, on part of FDA, the manufacturers were not permitted to make modifications to the operating parameters specified in the batch record without filing supplements with the FDA. Consequently, pharmaceutical companies incurred high cost associated with manufacturing failures while delaying the approval process due to stringent specification and additional paperwork required by regulatory authorities.[3,4]

Drug product of high quality is a product that is free from contamination and reproducibly produces the specified therapeutic use. ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity." A frequently used definition of quality is "Delighting the customer by fully meeting their needs and expectations.[5,6,7]

As it is well known that "The Quality cannot be tested into the product, but it should be built into it." Quality by design is a systematic approach for development that begins with predefined aim and emphasizes product and process understanding and process control, based on sound science and quality risk management.[8] The fundamental assumption underlying QbD is that the quality of the product can be assured only if critical sources of variability is understood and is suitably mitigated or controlled within a defined design space.[9] QBD can also be explained as a customer oriented work, that defines and control risk, creates reliable information & achieves optimum outcomes, by using facts, multifunctional teamwork & systematic methods to manage the process & decisions, helps in meeting regulatory requirements, robustly method development, meet commercial & quality performance targets, & quality products for customers. In this regards, with the assertion of regulatory authorities to implement QbD, pharmaceutical industry is undergoing a significant transformation to streamline their R&D process, provide greater manufacturing flexibility and control, and to reduce regulatory burden. Still, there is limited understanding and some major concerns regarding the implementation of QbD principles in the pharmaceutical field. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with its implementation.

Quality by Design(QbD)

This concept was initially introduced by well-known quality expert Joseph M. Juran on Quality by Design (J.M.: "Juran on Quality by Design",). In the late 1990 FDAs internal discussion began and in the year 2002 the concept paper on 21st century Good Manufacturing Practice was published. With help of several biopharmaceutical companies, pilot programs were started to explore Quality by Design application and its understandings.[10,11]

As per ICH Q8 (R2) Pharmaceutical Development 2009, QbD can be defined as "A systematic approach to development that initiates with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" it means designing and developing formulations and manufacturing

processes to ensure predefined product quality objectives.[12] Furthermore, for technology transfer, QbD generated process understanding can make the transition more efficient.[13] This initiative intended to modernize the FDAs regulation of pharmaceutical quality and establish a new regulatory framework focused on QbD, risk management and quality system. An important part of QbD is to understand how process and formulation parameters affect the product characteristics and subsequent optimization of these parameters should be identified in order to monitor these parameters online in the production process. QbD requires an understanding of how product and process variables influence product quality. In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management. The former describes the expectations for the pharmaceutical development section of the Common Technical Document (CTD); the later presents approaches to producing quality pharmaceutical products using current scientific and risk based approaches. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry. Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. In 2002, the FDA announced a new initiative (cGMP for the 21st Century: A Risk based Approach.[14]

ADVANTAGES OF QbD[15]

- It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It provides a higher level of assurance of drug product quality.
- It offers cost savings and efficiency for the pharmaceutical industry.
- It makes the scale-up, validation and commercialization transparent, rational and predictable.
- It minimizes or eliminates potential compliance actions, costly penalties and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight.
- It streamlines post approval manufacturing changes and regulatory processes.
- It more focused post approval CGMP inspections.

It enhances opportunities for first cycle approval.

- It increases the transparency of the sponsor understands the control strategy for the drug product to obtain approval and ultimately commercialize.

THE BENEFITS OF QbD[16,17]

It has been found that if QbD is properly implemented, then it will lead to the following three benefits, ie:

- Increased efficient use of development time and expenses.
- Ability to meet FDA submission guidelines and expectations.
- Less approval time and decreased queries from the FDA.
- Innovation and Improvement encourage the use of new technologies which accelerate the change and enable a proactive product lifecycle marketing plan.

ENABLERS OF QUALITY BY DESIGN[18]

Quality risk management and Knowledge management are two main of enablers of QbD They play a vital role in development and implementation of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control and finally facilitating continual improvement.

Quality Risk Management

Quality risk management (QRM) is the basic enabler for Quality risk management (QRM), it enables resources to be focused on the perceived critical areas that affect product and process. It is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It also facilitates continual improvement in the product and process performance throughout the product life cycle.

Knowledge Management

Product and process knowledge management is an essential component of quality by design and must be managed from development through the commercial life of the product, including discontinuation. It is a systematic approach to acquiring, analizing, storing and disseminating information related to products, processes and components.

Components of QbD[19]

Quality target product profile (QTPP)

The quality target product profile (QTPP) as defined in ICH Q8(R1) it gives details about

quality characteristics or attributes of a drug product that ideally will be achieved and hence ensures the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the product and is developed with the end in mind. The FDA has published a guidance defining the Target Product Profile (TPP), that focuses on the consumer and the desired product label.[20,21,22] FDA defines QTPP as the quality attributes related to safety and efficacy of the product. It may include route of administration, dosage form, delivery systems, dosage strength(s), container closure critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size[23] For an NDA, the QTPP is under development while for the ANDA product, the QTPP is well established based on the properties of the drug substance (DS), characterization of the reference listed drug (RLD) products, RLD label and intended patient population. Therefore, a generic drug product is expected to have same QTPP as that of brand or product.[24]

Critical quality attributes (CQA)

After determination of QTPP, the next step is to identify the relevant CQAs. A CQA is defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality". This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables. Identification of CQA can be performed based on prior knowledge and/or quality risk management (QRM). Prior knowledge may be by literature review, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event report and recalls.

Quality risk management (QRM)

QRM is an essential part of QbD as it helps in determining the extent of impact of critical material attributes (CMA) and critical process parameter (CPP) on CQAs, which may eventually assist in prioritizing the CQAs. They are particularly important in complex processes, especially that are involved in cases of biologics or bio-similar. FDA defines QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. The goal of QRM is therefore to identify risks within a process or event, analyzing the significance of these risks, and take appropriate measures to mitigate such risks if deemed unacceptable.[25-28]

FDA suggest various tools that can be applied for QRM, among which the relevant ones are discussed below:[29]

Failure mode effects analysis (FMEA): FMEA is one of the most widely used risk-assessment tools in the pharmaceutical industry. This is 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. Risk control activities can then be performed to avoid such failures modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential.[30, 31]

Fault tree analysis (FTA)

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most commonly used methods in system reliability, maintainability and safety analysis. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top down fashion. In this method failures are listed at the top as main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified. The results are represented pictorially in the form of a tree of fault modes and their relationship are described with logical operators like "AND","OR", etc**.**

Hazard analysis and critical control points (HACCP)

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor. The definition of hazard includes both safety and quality concern in a process or product. HACCP consists of the following seven steps: (i) conduct a hazard analysis and identify preventive measures for each step of the process, (ii) determine the critical control points, (iii) establish critical limits, (iv) establish a system to monitor the critical control points, (v) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control, (vi) establish system to verify that the HACCP system is working effectively, (vii) establish a record-keeping system.

Design Space

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. The design space is proposed by the applicant and is subject to

regulatory assessment and approval, it is scale and equipment dependent, the design space determined on the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design-space verification at the commercial scale becomes essential unless it is confirmed that the design space is scale-independent. Currently, generic drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales.[32-36]

Control Strategies

ICH Q8 (R1) defines control strategy as: "A planned set of controls, derived from current product and process understanding that ensures process performance and product quality". The controls may include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control. The control strategy may include Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality, Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution), Procedural controls, Product specifications. The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution.[37-39]

Life cycle Management and Continuous improvement

In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product lifecycle with regard to process consistency and throughout could take place with fewer post approval submissions. In addition to regulatory flexibility, the enhanced understanding of the manufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations (excursions) on product quality.[40,41]

Tools of Quality by Design

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 observed that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors Factor at a time and Design of experiments.[42]

Process Analytical Technology (PAT)

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness. NIR act as a tool for PAT and useful in the RTRT (Real Time Release Testing) as it monitors the particle size, blend uniformity, granulation, content uniformity, polymorphism, dissolution and monitoring the process online, at the line and offline, thus it reduces the release testing of the product.[43,44]

Risk Management Methodology

Quality Risk Management is defined as "A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle". Risk assessment is a helpful science-based method, used in the quality risk management that can help in identifying the material attributes and process parameters that potentially have an effect on product CQAs. Risk assessment is typically performed in the

pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. In QbD, the management should be ensured and provided the risk- and science-based reviews, at critical milestones. For this purpose, the teams have to utilize risk assessment tools in the R&D lifecycle. Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data. The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools.[45,46]

CONCLUSION

Quality by design is an essential part of modern approach to pharmaceutical quality, it is an important tool that helps in process understanding which is pivotal in assuring product quality and performance. It includes various functions like technology transfer, control checks, deviation reduction and analytical methods development. Furthermore, since the quality is integrated in each process operation, regulatory authorities are more comfortable in approving the drug application. It is believed that the challenges and concerns associated with the implementation of QbD can only be resolved if there is proper communication between the industry and the regulatory bodies. QbD can be easily understood by the concepts of ICH Q8, Q9 and Q10 and will be essential in the process of formulation. The review explains the use of target product profile, risk assessment, identification the critical material attributes and clears the concept of critical process parameters, the control strategy and continues monitoring and updating the process. It also explains application of QbD principles and tools to drug product and process development. It can be concluded Quality by Design (QbD) principles and tools, play an important role in facilitating a higher level of process understanding and create opportunities for investigation and developing control strategies in formulation and process development.

REFERENCES

1. Rathore AS, Winkle H. “Quality by design for biopharmaceuticals”. Nat Biotechnol. 2009; 27(1): 26-34.
2. http//www.fda.gov.com/cder/gmp/gmp2004/GMP.
3. Chang RK, Raw A, Lionberger R, Yu L. “Generic development of topical dermatologic products, part II: quality by design for topical semisolid products”. AAPS J. 2013; 15(3): 674-83.

4. Yu LX. "Pharmaceutical quality by design: product and process development, understanding, and control". Pharm Res. 2008; 25(4): 781-91.
5. J Woodcock, "The concept of pharmaceutical quality", Am. Pharm. Rev. November-December, 1-3, 2004.
6. Juran JM. "On quality by design, The new steps for planning quality into goods and services." Newyork free press, 1992; 1-2.
7. Gawade A, Chemate S, and Kuchekar A. "Pharmaceutical Quality by Design: A New Approach in Product Development". Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences, 2013; 2(3): 5-12.
8. http://www.fda.gov/cder/guidance/6419fnl.pdf.
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". Eur J Pharm Sci. 2011; 42(1-2): 106-15.
10. http://www.fda.gov/ cder/ gmp/ gmp 2004/ GMP_ final report 2004.htm.
11. Bhatt D, Rane S. Int J Pharm Pharm Sci. 2011; 3(1).
12. US Food and Drug Administration. Guidance for industry: Q8(R2) pharmaceutical development. US Department of Health and Human Service (FDA, Rockville, MD, 2009).
13. Looby M, et al. "Application of quality by design principles to the development and technology transfer of a major process improvement for the manufacture of a recombinant protein". Biotechnology Progress. 2011; 27(6): 1718-29.
14. http://www.fda.gov/ cder/ gmp/ gmp 2004/ GMP_ final report 2004.htm.
15. ICH. Draft consensus guideline: pharmaceutical development annex to Q8. Available at:, MEDIA4349.pdf (accessed 11/21/2007).
16. Shanley A, "From the Editor: The Cost of Poor Quality, Too High a Price?" Pharmaceutical Manufacturing, March 2012.
17. R. Somma, "Development Knowledge Can Increase Manufacturing Capacity and Faciliate Quality by Design" J. Pharm. Innov. 2007; 2: 87-92.
18. ICH Harmonized Tripartite Guideline on Pharmaceutical Quality Systems Q10, step 4 version, dated June 4, 2008.
19. Lawrence X, AAPS Annual meeting and exposition, Los Angeles Convention Center, Los Angeles, CA, USA, 2009.
20. http://www.ich.org/LOB/media/ MEDIA4349.pdf (accessed 11/21/2007).
21. ICH Q8 (R1) Pharmaceutical Development: Quality by Design, May 2006.

22. FDA CDER. Draft guidance for industry and review staff. Target product profile-strategic development process tool, March 2007.
23. Yu LX, Lionberger R, Olson MC, Johnston G, Buehler G, Winkle H. "Quality by Design for Generic Drugs". Pharmaceutical Technology. 2009; 33(10): 122-27.
24. Lionberger RA, *et al*, "Quality by design: concepts for ANDAs". AAPS J. 2008; 10(2): 268-76.
25. US Food and Drug Administration. Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms. US Department of Health and Human Service (FDA, Rockville, MD, 2012).
26. McConnell J *et al*, "Quality risk management and variability reduction". Journal of Validation Technology. 2011; 12-6.
27. Mollah H, Baseman H, Long M. "Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing" Wiley; 2013.
28. Fahmy R et al, "Quality by design I: Application of failure mode effect analysis (FMEA) and Plackett-Burman design of experiments in the identification of "main factors" in the formulation and process design space for roller-compacted ciprofloxacin hydrochloride immediate-release tablets". AAPS Pharm Sci Tech. 2012; 13(4): 1243-54.
29. Wu H, White M, Khan MA, "Quality-by-Design (QbD): An integrated process analytical technology(PAT)approach for a dynamic pharmaceutical co-precipitation process characterization and process design space development". Int J Pharm. 2011; 405(1-2): 63-78.
30. Jain S. "Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development". International Journal of Pharmacy and Pharmaceutical Sciences. 2014; 6(1): 29-35.
31. White E. Risk Management for Aseptic Processing. Journal of Validation Technology. 2009; 15(2): 25-33.
32. Keizer JA et al, "Risks in new product development: devising a reference tool. R&D Management". 2005; 35(3): 297-309.
33. US Food and Drug Administration. guidance for industry: Q10 quality systems approach to pharmaceutical cGMP regulations, FDA, Rockville, MD, September 2006.
34. Gibson, M., "Product Optimization: Pharmaceutical Preformulation and Formulation". Taylor & Francis, New York, 2001.
35. US Food and Drug Administration. Guidance for industry:Q8(R2) pharmaceutical development. US Department of Health and Human Service, FDA, Rockville, MD, 2009.

36. Altan S, "Statistical Considerations in Design Space Development Part I of III". Pharmaceutical Technology. 2010; 34(7): 66-70.
37. Harms J et al, "Defining Process Design Space for Biotech Products: Case Study of Pichia pastoris Fermentation". Biotechnology Progress. 2008; 24(3): 655-62.
38. Trivedi B. "Quality by desing (QbD) in pharmaceuticals". Int J Pharm Pharm Sci. 2012; 4(1): 17-29.
39. US Food and Drug Administration, guidance for industry: Q10 quality systems approach to pharmaceutical cGMP regulations, FDA, Rockville, MD, September 2006.
40. Seely, R.J et al, "Process Validation in Manufacturing of Biopharmaceuticals", Taylor & Francis, Boca Raton, FL 2005; 13-50
41. International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, TopicQ9: Quality Risk Management, ICH, Geneva, Switzerland, 2005.
42. Scidenfeid T, RA Fisher. The Design of Experiment and Statistical Estimation. The Founder of Evolutionary Genetics. 1992; 23-26.
43. US Food and Drug Administration. PAT guidance for industry-a framework for innovative pharmaceutical development, manufacturing and quality assurance (US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine, Office of Regulatory Affairs, Rockville, MD, September, 2004).
44. Watts C., Clark, J. E., J Pro Ana Tech, 2006; 3: 6-9.
45. US Food and Drug Administration. Guidance for industry: Q9 quality risk management, US Department of Health and Human Service (FDA, Rockville, MD, June 2006).
46. Ian House Process Understanding: for Scale-up and Manufacturing of Active Ingredients, First edition, Wiley-VCH Verlag GMbH & Co. KGaA (2011).