Available online on 15.06.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

A Review on Quality by Design Approach in Analytical Methods

Vinayak Katekar [1], Dipali Sangule [2], Om Bhurbhure [3], Priyanka Ingle [2], Shivprasad Dhage [4], Krushna Jadhav [5]

[1] *Department of Quality Assurance, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (MS), India*

[2] *Department of Quality Assurance, Anuradha College of Pharmacy, Chikhli (MS), India*

[3] *Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (MS), India*

[4] *Department of Pharmaceutics, Pataldhamal Wadhwani College of Pharmacy, Yavatmal, 445001 (MS), India*

[5] *Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik (MS), India*

Article Info:

Article History:

Received 08 April 2022
Reviewed 16 May 2022
Accepted 22 May 2022
Published 15 June 2022

Cite this article as:

Katekar V, Sangule D, Bhurbhure O, Ingle P, Dhage S, Jadhav K, A Review on Quality by Design Approach in Analytical Methods, Journal of Drug Delivery and Therapeutics. 2022; 12(3-S):255-261

DOI: http://dx.doi.org/10.22270/jddt.v12i3-s.5386

Abstract

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives for a product, process understanding, and process control based on knowledge and quality risk management. All conventional methods may fail to the intended purpose during method development and validation. In a QbD approach, the impact and interactions between critical method variables are understood using a Design of Experiments (DOE) approach, which gives multivariate analysis and modeling leading to the consistent quality of drug products. QbD tools like risk assessment and design of experiments, enable better quality to be incorporated into the analytical method and facilitate prior understanding and identification of variables affecting method performance. The main objective of the present review article is to describe different steps involved in method development by the QbD approach for analytical method development. The QbD Approach for method development comprises various steps that include defining method intent, performing experimental design, evaluating experimental results, selecting proper method conditions, and performing risk assessment with changing analytical parameters and conditions for evaluation. The purpose of analytical QbD is to attain quality in measurement.

Keywords: Quality by Design (QbD), Design of Experiments (DOE), Critical attributes

*Address for Correspondence:

Vinayak Katekar, Department of Quality Assurance, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (MS), India

Introduction

Quality by Design (QbD) is a systematic method of drug development that aims to ensure quality by incorporating analytical and risk-management approaches into the design, development and manufacture of new medications [1]. The main goal of QbD is to build quality into workflows from the start. During the early stages of a program, a product's objectives and essential features are specified, and risk and data analysis are utilized to determine how processes can affect a product's characteristics [2]. As a result, QbD provides a solid foundation for the development and implementation of processes that achieve a constant level of quality and adhere to pre-defined criteria. Many approaches for the development of pharmaceutical products and their subsequent manufacture have been promoted by the US FDA and the International Council Harmonization (ICH) [3]. This approach has been mounted 'Quality by Design (QbD) and it is defined as "A systematic approach to development that begins with a predefined objective and emphasizes product and process [4].

Various quality and statistical tools and methods, such as statistical designs of experiments, multivariate statistics, and statistical quality control have been comprised in QbD [5]. The main goal for changing from Quality by testing (QbT) is to increase the understanding of the processes and products so that product quality, processes efficiency, and regulatory flexibility can be attained [6]. Liquid chromatography (LC) is the most commonly applied separation technique in the pharmaceutical industry and High-performance liquid chromatography (HPLC) particularly Reversed-Phase HPLC (RP-HPLC), is one of the widely accepted analytical techniques in the pharmaceutical industry. To accomplish the quality in HPLC methods QbD has become quite important [7]. In HPLC methods, robustness and ruggedness should be established early in the method development stage to make certain method performance over the lifetime of the product for the implementation of QbD or else, if a non-robust or non-rugged method is adapted, significant time and resources may be required to redevelop, revalidate and retransfer analytical methods [8].

Historical background

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 for the modernization of the pharmaceutical industry [9].

Regulatory aspects to QbD [4,5,6]

FDA Perspective

In 2005 USFDA asked participating firms to submit chemistry manufacturing control (CMC) information demonstrating the application of QbD as a part of the New Drug Application. QbD involves thorough all of the processes; a goal or objective is defined before the actual start of the process. Design space and real-time release risk assessment are other parameters for the implementation of QbD. International conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system give stringent requirements regarding the quality of a product [10]. FDA also states the importance of the quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.

QbD ultimately helps to implement Q8 and Q9. FDA's view of QbD is "QbD is a systematic approach to product and process design and development". This concept was accepted by FDA in 2004 and a detailed description was given in 'pharmaceutical cGMPs for the 21st century- a risk-based approach [11-12].

Product quality and performance can be assured by designing efficient manufacturing processes.

- Product and process specifications are based on a scientific understanding of how process factors affect product performance.
- Risk-based regulatory approaches are for scientific understanding and control related processes for product quality and performance.
- Related regulatory policies and measures are modified to accommodate the real-time scientific knowledge.

ICH guidelines and QbD

The underlying principles of QbD i.e., science- and risk-based product development, risk assessment, lifecycle approach, and method design are explained in the quality guidelines of an international conference on harmonization i.e., ICH Q8 Pharmaceutical Development, ICHQ9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System.

Analytical Quality by Design (AQbD)

As per ICH, QbD is defined as "A systemic 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". It implies that product and process performance characteristics need to be scientifically designed to fulfill the specific objectives. Analogous to process QbD, the outcome of AQbD is a well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its lifecycle, The broad knowledge obtained from this process is used to establish a method operable design (MODR), a multidimensional space based on the method factors and setting that provides suitable method performance. It is also used to establish meaningful method controls of which system suitability is one component high-level overview of the AQbD steps is depicted in [9] (**Figure 1)**.

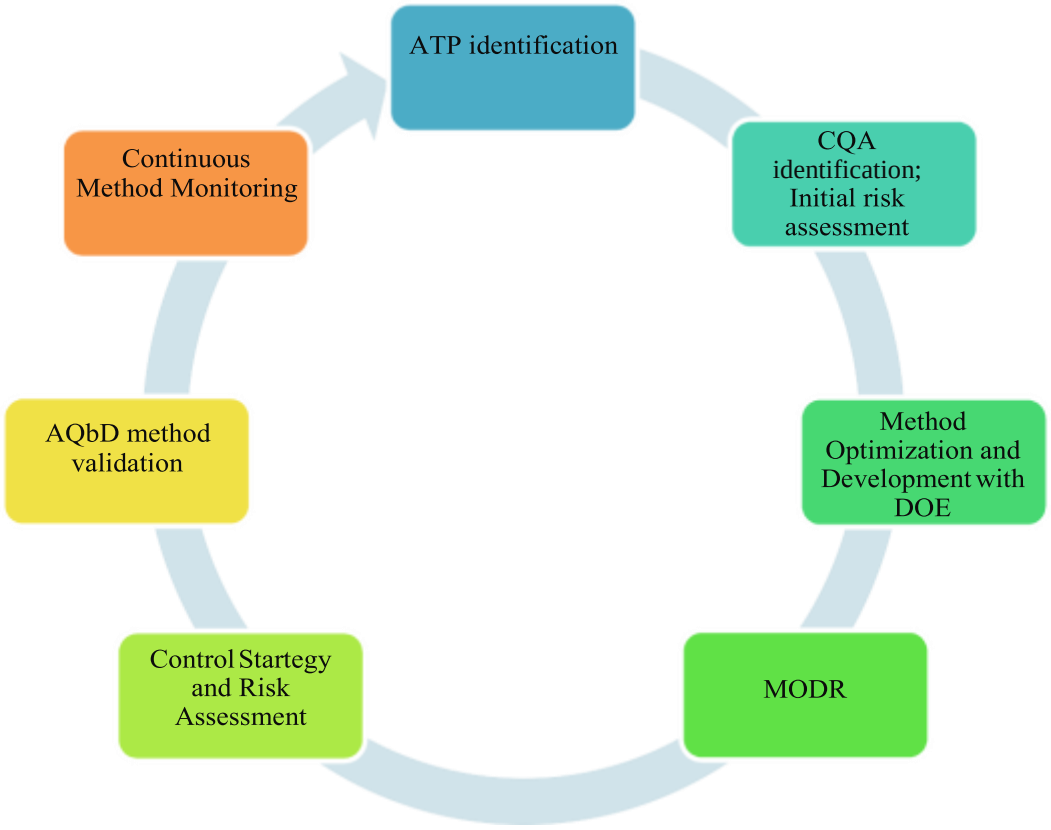

Figure 1: AQbD tools and life cycle

The expression of tools in QbD and AQbD is different for synthetic development and analytical development. Both QbD and AQbD tools are presented in (**Table 1)**.

Table 1: QbD tools for synthetic development and analytical development.

Steps	SyntheticDevelopment	Analytical Development
1	QTPP identification	ATP (Analytical Target Profile) identification
2	CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
3	Define Product Design Space	Method Optimization and Development with DOE
4	Refine Product Design Space	MODR (Method Operable Design Region)
5	Control Strategy and Risk Assessment	ATP (Analytical Target Profile) identification
6	Process validation	CQA identification, Initial Risk Assessment
7	Continuous Process Monitoring	Continuous Process Monitoring

Flow of Quality by Design

Key characteristics of QbD [13-14]

- A tool for focused & efficient drug development
- A dynamic and systematic process
- Relies on the concept that Quality can be built in as a continuum
- It is applicable to Drug Product and Drug Substance development (chemicals/biologics)
- It is applicable to analytical methods
- Can be implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Always encouraged by Regulators.

Applications of Quality by design are as follows [15]

- Applications of QbD in analytical method development
- Applications of QbD for drug substance development.
- Applications of QbD for clinical trials.
- Applications of QbD for bioequivalence studies.
- Applications of QbD for pharmaceutical manufacturing.
- Applications of QbD for formulation development, as shown in (**Figure 2**)

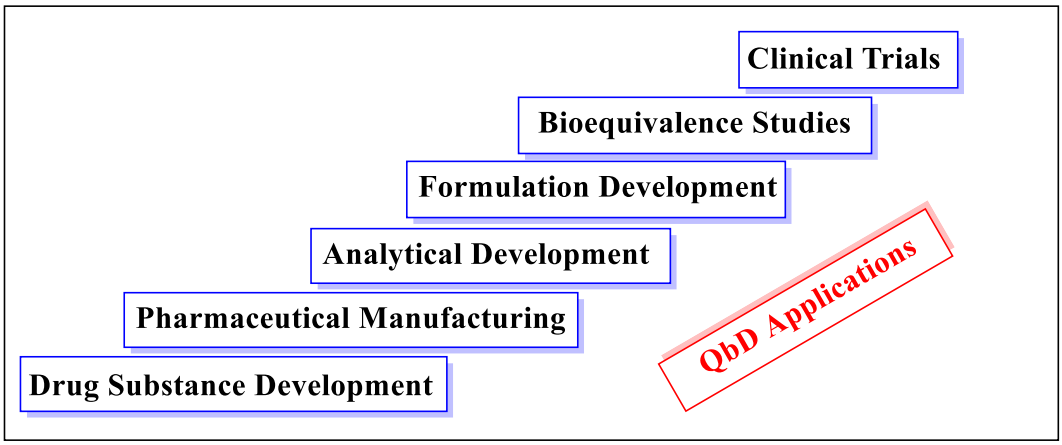

Figure 2: Different applications of QbD

QbD in analytical method development

Implementation of QbD helps to develop a rugged and robust/strong method that helps to go with ICH guidelines hence for that reason pharmaceutical industries are adopting this concept of QbD. This approach facilitates continuous improvement in the method [16-18].

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals)
- Karl Fisher titration for determination of moisture content
- To Biopharmaceutical processes
- Dissolution studies
- Hyphenated techniques like LC-MS
- Advanced techniques like mass spectroscopy, UHPLC, capillary electrophoresis
- Analysis of genotoxic impurity

Various aspects explained in pharmaceutical development are also put into practice for the development of the analytical method in the QbD paradigm (**Figure 3**).

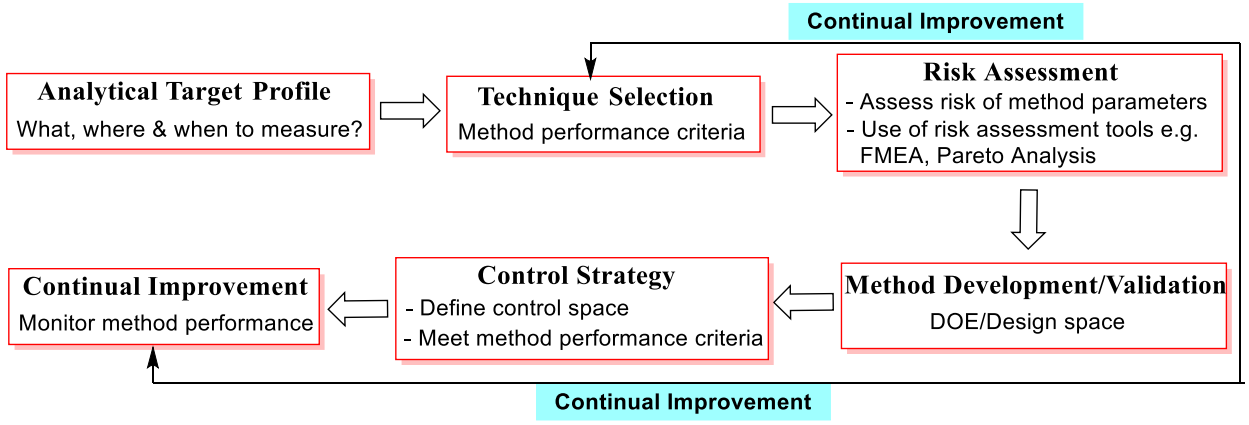

Figure 3: Aspects of application of QbD to analytical method

ATP (Analytical Target Profile)

Recognition of ATP comprises the selection of method requirements which include target analytes (product and impurities), type of analytical technique, and specifications of the product. A preliminary risk assessment would be carried out for the expectation of the method requirements and analytical criticalities [19].

ATP for analytical procedures comprises of

- Selection of target analytes (API and impurities),
- Assortment of analytical techniques (HPTLC, GC, HPLC, Ion Chromatography, chiral HPLC, etc.)
- Choice of method requirements.

Target Analytes Selection

Many regulatory bodies and ICH Q3 enlighten the deliberation of impurities in the API synthetic route.

Analytical method performance characteristics

Method requirements can differ from one method to another. There are various method performance characteristics. There are two types of method performance, that is, systematic (bias) and inherent random (variance) components. Commonly method performance is not evaluated by one but depends on both [16].

According to USP and ICH guidelines, there are many validation parameters for chromatographic separations, which are considered method performance characteristics that include accuracy and precision. These are quite commonly considered as method performance characteristics to quantify

the substance. No method can be accurate and precise without adequate specificity, linearity, and peak resolution but these do not signify robust behavior of the method. Another vital component that one has to be established based on acceptable behavior of both systematic and random performance characteristics is therange [20].

Robustness defines an operational range of method factors to give defined results. Other method performance characteristics such as linearity and specificity are not needed to be incorporated in the ATP, as they are not directly linked to understanding the agreement of a measurement with the true value [21, 22].

Critical quality attributes (CQA)

Factors that directly affect the quality and safety of the product are first sorted out, and their possible effect on method development is studied. Understanding the product and method will help to sort the CQA. If a drug product contains an impurity that may have a direct effect on the quality and safety of the drug product it is being considered the critical quality attribute for the HPLC method development of that particular drug compound. Safety and efficacy can be achieved by demonstrating measurable control of quality attributes i.e., product specification, intermediate specification, and process control. CQA for analytical methods comprises, method attributes and method parameters. CQA can diverge from one analytical technique to another [23].

- HPLC (UV or RID) CQA are buffers used in the mobile phase, pH of mobile phase, diluent, column selection, organic modifier, and elution method.
- CQA for GC methods are oven temperature and program, injection temperature, the flow of gas, sample diluent, and concentration.
- TLC plate, mobile phase, injection concentration and volume, time taken for plate development, reagent for color development, and detection methods are the CQA for HPTLC.

Risk Management

Quality Risk Management (ICH Q9) is "a systematic process for the assessment, control, communication and review of risks to the quality across the lifecycle". Risk assessments are a vital part of the Analytical QbD process. Risk assessments smooth the progress of recognition and ranking of parameters that could brunt method performance and conformance to the ATP. Risk assessments are often iterative throughout the lifecycle of a method and are typically performed at the end of method development, with product changes (e.g., route, formulation, or process) and as a precursor to method transfer. These RAs emphasize potential differences (e.g., laboratory practices, environment, testing cycle times, reagents sources). During the technique selection and method development stages major differences (e.g., availability of equipment) should be recognized and factored in [24].

Some methods of risk assessment are mentioned in ICH guideline Q9 as follows:

- Failure Mode Effects Analysis (FMEA).
- Failure Mode, Effects and Criticality Analysis (FMECA); Fault Tree Analysis (FTA).
- Hazard Analysis and Critical Control Points (HACCP).
- Hazard Operability Analysis (HAZOP).
- Preliminary Hazard Analysis (PHA).
- Risk ranking and filtering.
- Supporting statistical tool.

Method development by QbD approach

Step 1: Defining method intent

Since pharmaceutical QbD is a systematic, scientific, holistic, menace-based, and practical approach that begins with predefined objectives and lays emphasis on product and process understanding and control so the goals of HPLC method development have to be clearly defined. The eventual goal of the analytical method is to separate and quantify the maincompound [24].

Step 2: Performing experimental design

Experimental design can be efficiently used for rapid and systematic method optimization. A systematic experimental design is considered necessary to aid in obtaining profound method understanding and performing optimization. It forms a chromatographic database that will help out with method understanding, optimization, and selection. In addition, it can be used to evaluate and implement the change of the method, should it be needed in the future, for example, should the chromatographic column used no longer be commercially available, or impurity is no longer relevant.

Step 3: Evaluation of experimental results and selection of final method conditions

The conditions for the method need to be evaluated using the three-tiered approach. At first, the conditions should be evaluated for peak symmetry, peaks fronting and peaks tailing. Later these conditions should be further evaluated by using more stringent criteria, such as the tailing factor should be less than 1.5, etc.

Step 4: Performing risk assessment with robustness and ruggedness evaluation

Once the final method is selected against method attributes, it is highly likely that the selected method is reliable and will remain operational over the lifetime of the product. The fourth step of method development is mainly for the method verification and finalization and the evaluation of method robustness and ruggedness to be carried out.

Method qualification

Once the method is designed keeping analytical target profile (ATP) in mind with taking care of the risk involved in the development, the next step comes is method qualification this is to ensure that method is being performed as intended. It involves equipment qualification which is part of method qualification. It is divided into method installation qualification (MIQ), method operational qualification (MPQ), and method performance qualification (MPQ).

For a demonstration of instrumental qualification HPLC instrument is considered. While developing a chromatographic method on HPLC following qualification can be done Design Qualification

i. Installation Qualification
ii. Operational Qualification
iii. Performance Qualification

Considering user requirement specifications (URS), the design and technical specification of an instrument are defined, it is part of DQ. As HPLC is a commercial-off-the-shelf system in this case the users should make sure that the instrument is suitable for their desired applications. The user must confirm that the installation site fulfill all vendor-specified environmental requirements. Here IQ part

begins. Equipment is assembled at the user's site and checked for the proper working of all the assembled parts.

Control strategy

It is important that the set method performs as intended and consistently gives accurate results, for that purpose control of the method is required. A factor identified to have risk has to be controlled. More attention is given to the high-risk factors. System suitability, the risk assessment can also help identify a specific control strategy.

Life cycle approach

The life cycle approach differs from that of the traditional approach of method development. According to More field, it includes continuous improvement of method performance and the design space allows flexibility for Continuous improvement in the analytical method can be done without prior regulatory approval because of design space made previously [25].

QbD for various analytical methods which include,

- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- Hyphenated techniques like LC-MS
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g., UV method.
- Analysis of genotoxic impurity.
- Dissolution studies
- Biopharmaceutical processes

Benefits of QBD [26-28]

- Eliminate batch failures.
- Minimize deviations and costly investigations.
- Avoid regulatory compliance problems.
- Empowerment of technical staff.
- Efficient, agile, flexible system.

Conclusion

The application of the QbD concept to the analytical method is important because many variables significantly affect the method results which include instrument settings, sample characteristics, method parameters, and choice of calibration models. Being chromatographic technique is the most common analytical tool in pharmaceutical quality control, and the number of variables involved in the analytical method development phase is almost equivalent to the number of variables involved in formulation and development protocols for dosage form so implementation of QbD provides an opportunity to achieve regulatory flexibility but requires a high degree of robustness, product quality, and analytical method understanding**.** Method transfers in QbD are feasible for analytical methods and will enable better, more efficient, and continuous improvements for future methods.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and /or publication of this article.

Funding: No Funds, Grants, or Other Support Was Received.

References

1. Patil AS, Pethe AM. Quality by Design (QbD): A new concept for the development of quality pharmaceuticals. International journal of pharmaceutical quality assurance. 2013; 4(2):13-9.

2. Verch T, Campa C, Chéry CC, Frenkel R, Graul T, Jaya N, Nakhle B, Springall J, Starkey J, Wypych J, Ranheim T. Analytical Quality by Design, Life Cycle Management, and Method Control. The AAPS Journal. 2022; 24(1):1-21. https://doi.org/10.1208/s12248-022-00685-2

3. Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, Dickinson PA, Dressman J, Holm R, Klein S, Mann J. In vitro models for the prediction of in vivo performance of oral dosage forms. European Journal of Pharmaceutical Sciences. 2014; 57:342-66. https://doi.org/10.1016/j.ejps.2013.08.024

4. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. The AAPS journal. 2014; 16(4):771-83. https://doi.org/10.1208/s12248-014-9598-3

5. Huang J, Kaul G, Cai C, Chatlapalli R, Hernandez-Abad P, Ghosh K, Nagi A. Quality by design case study: an integrated multivariate approach to drug product and process development. International journal of pharmaceutics. 2009 Dec; 382(1-2):23-32. https://doi.org/10.1016/j.ijpharm.2009.07.031

6. Jain S. Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development. Int. J. Pharm. Pharm. Sci. 2014; 6:29-35. 7. Nikolin B, Imamović B, Medanhodžić-Vuk S, Sober M. High performance liquid chromatography in pharmaceutical analyses. Bosnian journal of basic medical sciences. 2004; 4(2):5. https://doi.org/10.17305/bjbms.2004.3405

8. Patel KY, Dedania ZR, Dedania RR, Patel U. QbD approach to HPLC method development and validation of ceftriaxone sodium. Future Journal of Pharmaceutical Sciences. 2021; 7(1):1-0. https://doi.org/10.1186/s43094-021-00286-4

9. Sangshetti JN, Deshpande M, Zaheer Z, Shinde DB, Arote R. Quality by design approach: Regulatory need. Arabian Journal of Chemistry. 2017; 10: S3412-25. https://doi.org/10.1016/j.arabjc.2014.01.025

10. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.

11. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.

12. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.

13. Anuj G, Fuloria NK. Short review on Quality by design: A new Era of Pharmaceutical drug development. Int J Pharm Pharm Sci. 2012; 4(3):19-26.

14. Elliott P, Bi J, Zhang H. Quality by design for biopharmaceuticals: a historical review and guide for implementation.

15. Åsberg D, Karlsson A, Samuelsson J, Kaczmarski K, Fornstedt T. Analytical method development in the quality by design framework. American Laboratory. 2014; 46(9):12-5.

16. Peraman R, Bhadraya K, Padmanabha Reddy Y. Analytical quality by design: a tool for regulatory flexibility and robust analytics. International Journal of Analytical chemistry. 2015. https://doi.org/10.1155/2015/868727

17. Ambhore JP, Chaudhari SR, Cheke RS, Kharkar PS. A Concise Analytical Profile of Efavirenz: Analytical Methodologies. Critical Reviews in Analytical Chemistry. 2021; 27:1-0. https://doi.org/10.1080/10408347.2021.1895711

18. Reid GL, Morgado J, Barnett K, Harrington B, Wang J, Harwood J, Fortin D. Analytical quality by design (AQbD) in pharmaceutical development. Am. Pharm. Rev. 2013; 144191.

19. Dispas A, Avohou HT, Lebrun P, Hubert P, Hubert C. 'Quality by Design'approach for the analysis of impurities in pharmaceutical drug products and drug substances. TrAC Trends in Analytical Chemistry. 2018; 101:24-33. https://doi.org/10.1016/j.trac.2017.10.028

20. Ravisankar P, Gowthami S, Rao GD. A review on analytical method development. Indian journal of research in pharmacy and biotechnology. 2014; 2(3):1183.

21. Ramalingam P, Jahnavi B. QbD considerations for analytical development. InPharmaceutical Quality by Design 2019 Jan 1 (pp. 77-108). Academic Press. https://doi.org/10.1016/B978-0-12-815799-2.00005-8

22. Adhao VS, Chaudhari SR, Ambhore JP, Sangolkar S, Thenge RR, Cheke RS, Patil AS. Reverse phase-liquid chromatography assisted protocol for simultaneous determination of lamivudine and tenofovir disoproxil fumarate in combined medication used to control HIV infection: an investigative approach. Future Journal of Pharmaceutical Sciences. 2021; 7(1):1-1. https://doi.org/10.1186/s43094-021-00233-3

23. Mazumder S, Pavurala N, Manda P, Xu X, Cruz CN, Krishnaiah YS. Quality by Design approach for studying the impact of formulation and process variables on product quality of oral disintegrating films. International Journal of Pharmaceutics. 2017; 527(1-2):151-60. https://doi.org/10.1016/j.ijpharm.2017.05.048

24. Raman NV, Mallu UR, Bapatu HR. Analytical quality by design approach to test method development and validation in drug substance manufacturing. Journal of chemistry. 202015.

25. Jackson P, Borman P, Campa C, Chatfield M, Godfrey M, Hamilton P, Hoyer W, Norelli F, Orr R, Schofield T. Using the analytical target profile to drive the analytical method lifecycle. Analytical chemistry. 2019 Jan 9; 91(4):2577-85. https://doi.org/10.1021/acs.analchem.8b04596

26. 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.

27. Ambhore JP, Adhao VS, Cheke RS, Popat RR, Gandhi SJ. Futuristic review on progress in force degradation studies and stability-indicating assay method for some antiviral drugs. GSC Biological and Pharmaceutical Sciences. 2021; 16(1):133-49. https://doi.org/10.30574/gscbps.2021.16.1.0172

28. Pharm B, Pharm M. Quality by design (QbD): manufacturing and product quality of Generics drugs perspective. Journal of Global Trends in Pharmaceutical Sciences. 2013 Oct; 4(4):1257-62.