



QUALITY BY DESIGN APPROACHES TOWARDS THE DEVELOPMENT OF ANALYTICAL METHOD

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ABSTRACT

A modern approach for pharmaceutical product quality is called "quality by design." The creation of a high-quality product and a manufacturing process that reliably performs the product's intended function is the aim of drug development. Quality must be incorporated into the design because it cannot be tested in items. It plays a significant role in the current strategy for medical quality. It is critical to define the performance profile of the desired product [Target Product Profile (TPP), Target Product Quality Profile (TPQP)], Critical Quality Attribute (CQA) as part of the idea of QbD throughout the design and development of products. Based on this, we can create a product design and manufacturing procedure to satisfy product requirements. As a result, it is possible to learn about the effects of the CMAs, CPPs, and CQAs on the material as well as to identify and manage the causes of variation.

KEYWORDS: Quality By Design, Analytical Target Profile, Target Product Profile, Target Product Quality Profile, Critical Quality Attribute, etc.

INTRODUCTION¹⁻³

A systematic approach to drug development called Quality by Design (QbD) tries to ensure quality by incorporating analytical and risk-management techniques into the conception, creation, and production of new medications¹. To include quality into workflows from the outset is QbD's primary objective. Early on in a programme, a product's goals and key features are defined, and processes' potential impact on a product's attributes is assessed using risk and data analysis². As a result, QbD offers a strong framework for the creation and application of procedures that maintain a high level of quality and comply with predetermined standards. The US FDA and the International Council Harmonisation (ICH) have encouraged a variety of methods for the development of pharmaceutical goods and their subsequent production³. The term "Quality by Design" (QbD) has been mounted as this approach, and it is defined as "A systematic approach to development that begins with a predefined objective and emphasizes product and process⁴.

QbD incorporates a number of quality and statistical tools and techniques, including statistical designs of experiments, multivariate statistics, and statistical quality control⁵. To improve understanding of the processes and products in order to achieve product quality, process efficiency, and regulatory flexibility, Quality by testing (QbT) will be changed⁶. In the pharmaceutical industry, liquid chromatography (LC) is the most generally used separation method, and high-performance liquid chromatography (HPLC), particularly reversed-phase HPLC (RP-HPLC), is one of the most widely used analytical methods. The importance of QbD in achieving quality in HPLC procedures has increased⁷. To ensure method performance over the course of the product for the implementation of QbD, robustness and ruggedness should be established early in the method development stage for HPLC methods. Otherwise, if a non-robust or non-rugged method is adapted, a significant amount of time and resources may be needed to redevelop, revalidate, and retransfer analytical methods⁸.

HISTORICAL BACKGROUND

A remarkable increase in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological Licence Applications (BLAs), and Abbreviated New Drug Applications (ANDAs) was reported to FDA in 2007 with a total of 5000 supplements. The FDA noticed a rise in the number of firms submitting NDAs or ANDAs after their deadlines, and a significant number of additional applications were submitted for each manufacturing change. The primary focus on the data in both the original applications and the updates was chemistry. Other important aspects of manufacturing, such as engineering and product development, received the least importance. The FDA eventually came to relation with the idea that increasing numbers of controls were needed for drug manufacturing procedures in order to produce effective drugs and, without doubt, to improve regulatory decision-making. It led to a more stringent regulatory environment being created. The FDA changed procedures in 2002 under the Pharmaceutical cGMP (good manufacturing practise) for the 21st Century to address this problem. A system for developing, assessing, and managing manufacturing processes based on an understanding of science and elements that affect the quality of the finished product was discussed in Process Analytical Technology (PAT). In 2005, the USFDA asks some businesses to submit their CMC in QbD format as the time had come to deploy QbD for a more systematic approach. QbD's question base review (QbR) principle is built on this foundation. In a recent interview, Lawrence Yu, Deputy Director, Science and Chemistry, FDA, issued a warning that the deadline for generic manufacturers to implement Quality by Design is 2013.

BENEFITS OF QbD

For industries ⁷⁻⁹

1. The process will develop stronger in a variety of circumstances, increasing confidence.
2. It makes the procedure easier to understand.
3. When the procedure is transferred from the research level to the quality management department, this method has a higher success rate of transfer.
4. The design space idea prevents post-approval alterations, which may result in increased costs for any company.
5. It allows the development of novel processes through ongoing development throughout the life cycle.

For Food and Drug Administration (FDA)¹⁰⁻¹¹

1. Increase decision-making flexibility
2. enhancing the research's scientific basis
3. Ensure that judgements are made using science rather than information that has been observed.
4. Increase stability.

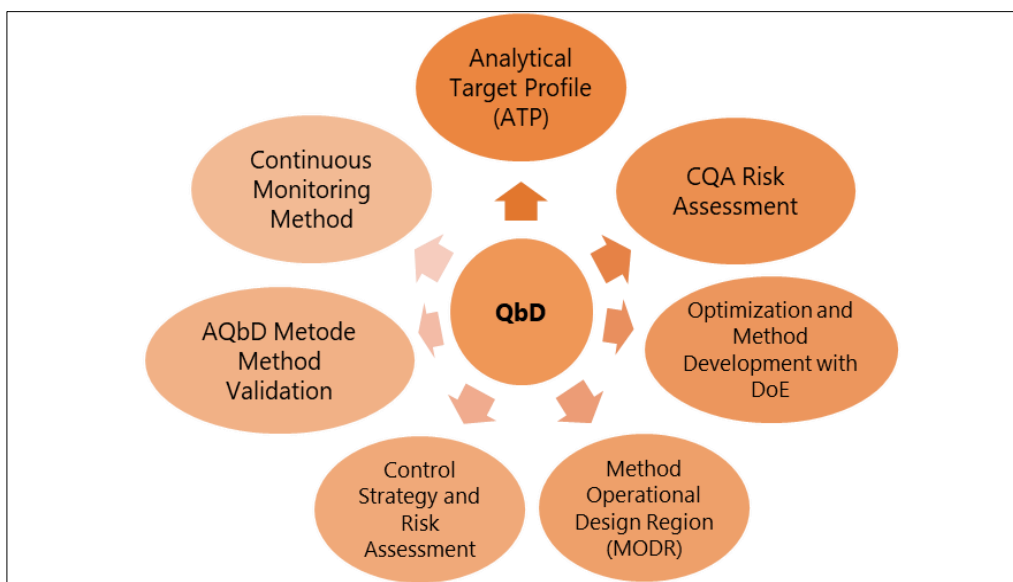


Figure no. 2: A QbD tools

4. Basic considerations of QbD¹²

The pharmaceutical sector places a high priority on patient safety and producing high-quality products. To help the industry accomplish this purpose, QbD uses a full understanding of the process, which is its ultimate objective.

The focus on patient safety and product efficacy is one way that QbD has advantages.

The pharmaceutical industry has developed a scientific understanding of its procedures.

Both process development and product design are involved.

Risk evaluation is done using scientific methods.

Critical quality characteristics are noted, and their impact on the final product's quality is examined.

It provides a reliable method or procedure.

Adoption of QbD is also driven by business benefits.

Using a method design concept can save costs associated with revisions made after approval.

4.1. Elements of pharmaceutical development

All aspects of pharmaceutical development listed in ICH guideline Q8 are included in QbD. The purpose of the Pharmaceutical Development section is to fully explain the product and manufacturing process to reviewers and inspectors. The goal of pharmaceutical development is to create a high-quality product and its manufacturing method to deliver the product's desired performance consistently. Scientific understanding is provided to support the construction of the specifications and manufacturing controls by the information and expertise gathered through pharmaceutical development research and manufacturing experience.

- Different elements of pharmaceutical development include,
- Defining an objective
- Determination of critical quality attributes (CQA)
- Risk assessment
- Development of experimental design– Designing and implementing control strategy – Continuous improvement.

Analytical target profile¹³⁻¹⁴

Similar to the Quality Target Product Profile (QTPP) element in QbD is Analytical Target Profile (ATP). The ICH Q8 R(2) guidelines highlight ATP as a means of method development. It specifies the requirements for the procedure that will be measured. ATP is a statement that specifies the method's purpose and is used to guide method selection, design, and development activities, according to a definition provided recently by PhRMA and EFPIA.¹²

General ATP for analytical procedures is as follows:¹³⁻¹⁴

- a. Selection of the target analytes (API and impurities),
- b. Technique (HPLC, GC, HPTLC, Ion Chromatography, chiral HPLC, etc.), and
- c. Selection of the method requirements (assay or impurity profile or residual solvents).

CQA (Critical Quality Attributes)¹⁵

Method attributes and method parameters are part of the CQA for analytical methods. Every analytical method has a unique CQA. Mobile phase buffer, pH, diluent, column choice, organic modifier, and elution method are HPLC (UV or RID) CQA. GC processes Gas flow, oven programme and temperature, injection temperature, sample diluent, and concentration are examples of CQA. HPTLC techniques TLC plates, mobile phases, injection concentrations and volumes, plate development times, colour development reagents, and detection techniques are all components of CQA. For the creation of analytical methods, factors including solubility, pH value, charged functional groups, polarity, boiling point, and solution stability might define the CQA. The typical ATPs and CQA for an HPLC technique are shown in Table 3.

Risk Assessment¹⁶

After the technique has been identified, AQbD concentrates on a thorough risk evaluation of the variables that could affect the method's consistency, such as analyst methodologies, instrument setup, measurement and method parameters, sample characteristics, sample preparation, and environmental factors. While Analytical QbD mandates the risk assessment stage before to method transfer and throughout the product life cycle, traditional method development was predicated on testing the technique after transfer.

DoE Design of Experiments (Method Optimization and Development)¹⁷

The DoE may be created to support and facilitate critical change processes based on statistical requirements once the potential and critical analytical technique variables have been specified in the initial risk assessment. It is possible to determine the operation or combination of a number of chosen variable processes, as well as their communications and reactions (key method qualities). This technique gives you a decent chance to filter out different situations from a small number of studies. After that, data analysis employs crucial statistical methods to pinpoint crucial method variables in the best combination where a stable area for crucial method attributes can be attained. Process robustness is described in ICH Q8 recommendations as the "Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality." Robustness, impurity profile, physicochemical qualities, processing capability, and stability of the starting material are factors that will be impacted by the drug substance synthesis process. Understanding the process would give complete knowledge for defining robustness parameters by taking various operating situations, scales, and tools into consideration.

MODR (Method Operable Design Region)¹⁷

The creation of a multidimensional space based on method factors and settings is known as a method operable design region (MODR). MODR can demonstrate an effective technique. Important method controls like system appropriateness, RRT, and RRF are also established using it. It is possible to use additional method verification activities to develop ATP compliance and ultimately define the MODR.

Control Strategy and Risk Assessment¹⁸

Control strategy (31-34) is a predetermined set of controls that are derived from an understanding of MODR and the nature of the analyte. Based on the statistical information gathered throughout the aforementioned DoE and MODR procedures, a control strategy can be created. Connections between the procedure and the analysis quality for the ability to meet ATP criteria can be drawn using these experimental data. Control approach Using this method, the parameters (such as reagent grade, equipment brand or type, and column type) will be solved in an unpredictable way. In contrast to the conventional ways, the control strategy

method under the A QbD method does not seem to work very effectively. To create a better connection between system performance and goals, method controls are obtained based on experimental data from CQA, DoE, and MODR.

A QbD Method Validation¹⁹

Analytical methods are validated using a QbD (12–21) method validation over a variety of unique API batches. For creating method validation for all types of API manufacturing replacement without revalidation, it makes use of both DoE and MODR knowledge. This system offers the necessary ICH auxiliary information, social data, uncertainty measurement, control strategy, and ongoing improvement. While maintaining quality, this perspective calls for more expensive resources than the conventional validation perspective.

Continuous Method Monitoring (CMM) and Continual Improvement²⁰

Life cycle management is a control approach used for the commercial phase of design implementation. The CMM phase, which completes the A QbD life cycle, is a continuous procedure for exchanging information acquired throughout the creation and application of design space. This contains bridges between design spaces, MODR, control system, CQA, and ATP, assumptions based on prior knowledge, statistical analysis principles, and the outcomes of a risk assessment. Once a method has been validated, it can be utilised for normal purposes, and the system's performance can be regularly checked. Control charts, tracking systems, process-related analysis, and other tools should be used. The analyst is commended by CMM for being proactive in identifying and dealing with any out-of-trend operations.

Benefits and recommendations.

A QbD is a technique that shifts from reactive problem-solving to proactive damage reduction. The project stage and the development time series affect the types and extent of risk assessments. The appropriate strategy is crucial to AQBD's success rate. using the right tools, timing your work execution, and doing proper planning. Applying the right risk assessment tools at the right time helps improve understanding of the design space and control strategy and prevent method failure.

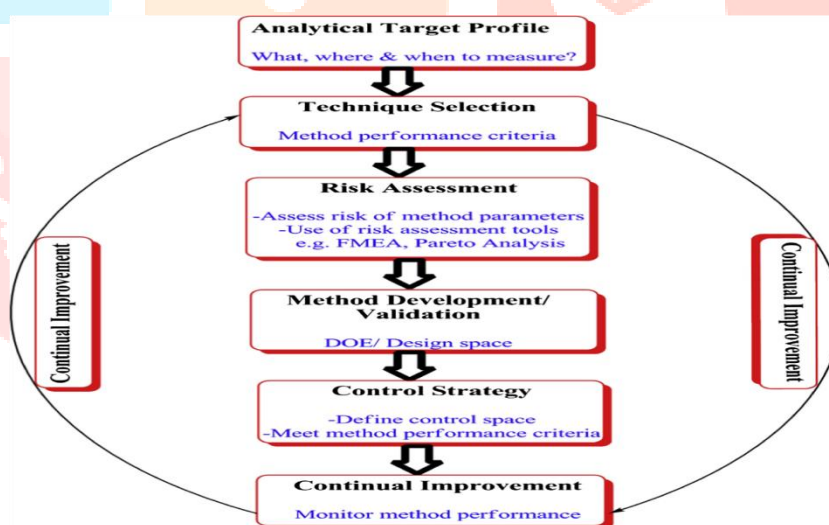


Figure 2 Analytical method development in QbD.

5.1.5. Method qualification²¹

The next phase is method qualification, which verifies that the technique is working as intended once the method has been designed with the analytical target profile (ATP) in mind and development risk taken into consideration. It covers technique qualification as well as equipment qualification. Method performance qualification (MPQ), method operational qualification (MPQ), and method installation qualification (MIQ) are the three categories.

HPLC instrument is taken into consideration for instrumental qualification demonstration. The following qualification can be completed while creating a chromatographic technique on HPLC.

1. Design Qualification
2. Installation Qualification
3. Operational Qualification
4. Performance Qualification

It is a component of DQ to take into account user requirement specifications (URS), which specify an instrument's design and technical specification. Since HPLC in this case is a commercially available technology, users must ensure that the instrument is appropriate for their intended uses. User must verify that the installation location satisfies all environmental specifications stated by the vendor. Here the IQ part starts. At the user's location, equipment is put together and all of its integrated components are tested to ensure appropriate operation. The combined parameters for operational qualification and performance qualification are given be

Application of QbD in analytical methods of measurement²²

QbD refers to the proper analysis carried out at the appropriate time and is based on science and risk assessment rather than necessarily referring to less analytical testing. Pharmaceutical firms are using this QbD concept since it helps to develop tough and reliable methods that aid to comply with ICH guidelines. When developing an analytical approach for the QbD environment, robustness-improving factors are taken into account. This strategy makes method improvement possible over time. In the literature, there are prospects for applying QbD to analytical methods in a manner similar to how it is applied to industrial processes. It implies that strategies like as target profiles, CQA, design spaces, and risk assessment are equally applicable to analytical methods. Although not all pharmaceutical industries have implemented it, it may do so in the future since regulatory agencies may make it mandatory. The multiple advantages of this approach and its simplicity in complying with regulatory authorities make it possible for industries to embrace it voluntarily. The Pharmaceutical Research and Manufacturers of America (PhRMA), the Analytical Technical Group (ATG), and the European Federation of Pharmaceutical Industries and Association (EFPIA) have all offered specific recommendations on how to employ QbD in conjunction with analytical techniques. QbD can be used with a variety of analytical techniques, such as,

- Chromatographic methods like HPLC (for determining contaminants in pharmaceuticals, method development, and stability studies).
- Hyphenated methods, such as LC-MS.
- cutting-edge methods including capillary electrophoresis, UHPLC, and mass spectrometry.
- Karl Fischer titration is used to calculate moisture content.
- Vibrational spectroscopy, such as the UV technique, for identifying and quantifying chemicals.
- Genotoxic impurity analysis. study on dissolution.

For chromatographic technique

6.1.1. In determination of impurity²³⁻²⁴

Gavin offers a quality by design strategy for developing an impurity technique for atomoxetine hydrochloride. For the investigation of atomoxetine hydrochloride, an ion-pairing HPLC technique was created, and related system suitability parameters are investigated. For the separation of atomoxetine and contaminants, statistically designed experiments were utilised to demonstrate technique resilience and optimise settings. Weiyong Li outlines a three-step method development/optimization strategy, including multiple-column/mobile phase screening, further separation optimisation using multiple organic modifiers in the mobile phase, and multiple-factor method optimisation using Plackett-Burman experimental designs. Computer simulations were carried out using Dry Lab, chromatography optimisation software that is commercially accessible. The number of method development runs is drastically decreased by this strategy. Plackett-Burman experimental designs are used during method optimisation once a good separation has been achieved.

The development of a chromatographic method for the separation of impurities in vancomycin utilising specialised software and UPLC technology is given a QbD with Design-of-Experiments approach. 13 of these contaminants can be removed using conventional HPLC gradient methods, but as many as 26 pollutants may be removed using the QbD methodology and sub2-pm ACQUITY UPLC Column.

6.1.2. In screening of column used for chromatography

The specifics of the experimental design, the assessment standards applied, and some of the most popular analytical columns from reputable column manufacturers are described in. Seven RP-HPLC columns are assessed systematically against predetermined performance standards. The development of a QbD method must start with this strategy. The information supplied for frequently used columns assists working analysts in meeting the challenge of creating reliable and durable procedures for usage in a QbD context. Recently, UPLC has investigated better column selection utilising quality by design.

6.1.3. In development of HPLC method for drug products/ substances

In order to apply quality by design (QbD) concepts to the creation of high pressure reversed phase liquid chromatography (HPLC) technologies, Monks et al. (2011) describe a revolutionary method. Using computer modelling tools and a column database, four frequent essential HPLC parameters—gradient time, temperature, aqueous eluent pH, and stationary phase—are assessed within the quality by design framework. Application of quality by design features for the development and optimisation of an analytical technique for protamine sulphate was the focus of David et al. A reliable technique was created. The primary, interaction, and quadratic impacts of these three factors on the chosen responses were then assessed using a Box-Behnken experimental design and response surface approach. For the four peptide peaks of protamine sulphate, method requirements applied to the optimised circumstances projected peak resolutions between 1.99 and 3.61 and tailing factors between 1.02 and 1.45.

6.1.4. In capillary electrophoresis

Using capillary electrophoresis and experimental design, Yi-Hui et al. (2007) investigated the simultaneous analysis of arbutin, kojic acid, and hydroquinone in cosmetics. Method optimisation was done using statistical parameters.

6.1.5. In stability studies

For the creation of a stability-indicating HPLC method for a complex pain management drug product combining therapeutic ingredient, two preservatives, and their degradants, Karmarkar et al. (2011) presented an application of quality by design (QbD) concepts. The initial approach lacked any resolution in the peaks for preservative and another drug degradant, as well as drug degradant and preservative oxidative degradation peaks. With the aid of the DOE-based Fusion AE software, the optimisation of the procedure was carried out. The establishment of a design space and operating space with specifics of all method performance features and constraints as well as method robustness inside the operating space was made possible by the QbD-based method development.

6.1.6. In UHPLC²⁵⁻²⁶

In order to demonstrate the accuracy of retention time prediction at high pressure (enhanced flow-rate), Szabolcs et al. (2009) developed Rapid high performance liquid chromatography with high prediction accuracy, with design space computer modelling. This study also demonstrates that computer-assisted simulation can be effective with sufficient precision for UHPLC applications.

6.2. For hyphenated technique²⁷⁻²⁸

6.2.1. In LC–MS method development

The QbD method is described by Joseph Turpin for developing liquid chromatographic methods. The article is organised into three sections: the experimental region, knowledge space, design space coverage, data treatments to quantify the column screening experiment, and estimation of the robustness of the quantitative method. According to how they affect separation, parameters are divided into two categories: (1) The main factors in separation are column type (column screening), pH, organic solvent type, and gradient time (controls slope). Pump flow, gradient conditions, temperature, and ion pairing agent are secondary effectors of separation.

6.3. In bioanalytical method development²⁹⁻³¹

A HPLC-fluorimetric bioanalytical method for quantifying telmisartan in urine was developed by Torrealday et al. (2003) utilising an experimental design approach for the optimisation of chromatographic factors that affected the fluorescent response. The central composite design was used to create the response surface from which the ideal circumstances for the goal response could be inferred, and the fractional factorial design was used to assess which of the researched factors had an impact on the response.

6.4. In dissolution studies

In order to show the robustness of the method, Miroslav et al. (2010) devised an HPLC method for digoxin measurement in dissolving samples. Full factorial design is used to determine the effects of small adjustments in the acetonitrile fraction, mobile phase flow rate, column temperature, and column length on the properties of the digoxin peak (24). The digoxin quality and stability testing using the HPLC technique was done. In order to study tablet dissolution shift upon accelerated stability by multivariate approaches, Jun et al. (2011) used the quality by design methodology. A case study using quality by design, an integrated multivariate approach to drug product and process development, was also presented.

6.5. For spectroscopic measurements

6.5.1. In handling complex spectroscopic data

For the objective of better understanding the process, concerns and challenges. Pharmaceutical and biotechnology industries are increasingly discovering and utilising process analytical technologies (PAT). Information can be gleaned from sophisticated spectroscopic data in detail. The resilience of the process control system and overall control strategy are improved by a number of novel methods that circumvent the drawbacks of the calibration and modelling methodology now in use.

6.5.2. In mass spectroscopy

Lianming and Frederick (2012) explain the practical projection and current challenges in quantitative chiral MS techniques for QbD (Quality-by-Design) based pharmaceutical applications in their review of recent advances in mass spectrometric methods for gas-phase chiral analysis of pharmaceutical and biological compounds.

CONCLUSION

When employed within predetermined parameters, a well-characterized method development attempt to create a trustworthy technique that can be used with a high degree of assurance to produce data in a methodical manner that fits set criteria. The development and assessment of analytic data methods can be done using QbD. Tools for AQbD include ATP, CQA, method creation and optimisation through DoE, risk assessment and control strategy for MODR, method validation and continuous method monitoring (CMM), and continuous improvement. Accurate ATP, risk assessment, the use of appropriate tools, and fast completion of work are all required by AQbD. Greater future constitutional amendments are possible thanks to the new QbD mechanism. Instead of saving the system itself, performance values of the system might be saved. The technique utilised can be used as an illustration of how to get the system to perform as desired. Pharmaceutical processes like drug development, formulations, analytical methods, and biopharmaceuticals have seen a rise in the importance of QbD. The key driver of QbD adoption is the need to comply with regulations. In the pharmaceutical sector, Analytical Quality by Design (AQbD) is crucial for ensuring the quality of the final product. Understanding from product development to commercial production is the result of AQbD. The AQbD tools are the ATP, CQA, MODR, and Control Strategy with Risk Assessment, Method Validation, and Continuous Improvement.

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Disclosure of conflict of interest

The authors have no conflict of interest to declare.

REFERENCE

1. 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; Yu 57:342-66. <https://doi.org/10.1016/j.ejps.2013.08.024>
2. 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/s12248014-9598-3>.
3. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
4. Sinica DP, Gholve SB, Ajgunde RR, Bhusnure OG, Thonte SS. Pelagia Research Library Analytical method development and validation by QbD approach.
5. "ICH Q8 Quality guidance: Pharmaceutical Development".
6. "ICH Q9 Quality guidance: Quality Risk Management".
7. "ICH Q10 Quality guidance: Pharmaceutical Quality System".
8. "ICH Q11 Quality guidance: Development and Manufacture of Drug Substance".
9. Jadhav JB, Girawale NN (2014) QbD approach used in development of pharmaceutical. *Int J of Pure and Applied Biosci* 2(5): 214-223.
10. Ashrani S, Goyal A, Rajat V (2018) QbD and process analytical technology: Important Tools for Building quality in pharmaceutical Products. *Journal of Scientific & Technical Research* 2(1): 2408-2412.
11. Janet W (2004) The concept of pharmaceutical quality. *American Pharmaceutical Review* 7(6): 10-15.
12. *J Pharm Anal*. 2016; 5: 22-8.
13. Malviya R, Bansal V, Pal OP, Sharma PK. High performance liquid chromatography: a short review. *Journal of global pharma technology* 2010; 2(5): 22-26.
14. Liu Y, Lee ML. Ultrahigh pressure liquid chromatography using elevated temperature. *Journal of Chromatography* 2006; 1104 (1-2): 198–202.
15. Abidi SL. High-performance liquid chromatography of phosphatidic acids and related polar lipids. *J. Chromatography* 1991; 587: 193-203.
16. International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use, Pharmaceutical Development Q8 (R2). ICH harmonized tripartite guideline, Draft Step 4. 2008, 13-15.
17. Yu L. Pharmaceutical quality by design: Product and process development, understanding and control. *Pharm Res*. 25, 2008, 781–791.
18. Lee SL, Raw AS, Yu L. Significance of drug substance physiochemical properties in regulatory quality by design. In *Drugs and the Pharmaceutical Sciences 78 (Pre formulation in Solid Dosage Form Development)*, London: Informa Healthcare, 2008, 571–583.
19. Mhatre R, Rathore AS. Quality by design: An overview of the basic concepts. In *Quality by design for biopharmaceuticals*. New York: Wiley, 2009, 1–8.
20. Sousa, L.V.E.; Gonçalves, R.; Menezes, J.C.; Ramos, A. Analytical method lifecycle management in pharmaceutical industry: A review. *AAPS PharmSciTech* 2021, 22, 128. [Cross Ref](2015) ICH. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. *European Medicines Agency Science Medicines Health*, p. 1-20.
21. Gupta V, Jain ADKJ, Gill NS, Guptan K. Development and validation of HPLC method—a review. *International research journal of pharmaceutical and applied sciences* 2012; 2(4): 17
22. Thamman M. A review on high-performance liquid chromatography (HPLC). *Res Rev*:
23. Deidda, R.; Orlandini, S.; Hubert, P.; Hubert, C. Risk-based approach for method development in pharmaceutical quality control context: A critical review. *J. Pharm. Biomed. Anal.* 2018, 161, 110–121.
24. Jayagopal, B.; Shivashankar, M. Analytical quality by design—A legitimate paradigm for pharmaceutical analytical method development and validation. *Mech. Mater. Sci. Eng. J.*

- 2017, 9. Available online: [https://hal.archives-ouvertes.fr/hal-01504765 /document](https://hal.archives-ouvertes.fr/hal-01504765/document)(accessed on 16 September 2022).
25. Rignall, A. Analytical Procedure Lifecycle Management: Current Status and Opportunities. *Pharm. Technol.* 2018, 42, 18–23.
 26. European Medicines Agency. ICH Guideline Q9(R1) on Quality Risk Management. Step 2b, Amsterdam, The Netherlands. 2021.
 27. Ramalinagn, P.; Shakir Basha, S.; Bhaddraya, K.; Beg, S. Risk assessment and design space consideration in analytical quality by design. In *Handbook of Analytical Quality by Design*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 167–189.
 28. United States Pharmacopeia. General Chapter, <1220> Analytical Procedure Lifecycle USP-NF; United States Pharmacopeia: Rockville, MD, USA, 2022.
 29. Elder, D.; Borman, P. Improving Analytical Method Reliability Across the Entire Product Lifecycle Using QbD Approaches. *Pharmaceutical Outsourcing*. 2013. Available online: <https://www.pharmoutsourcing.com/Featured-Articles/142484-ImprovingAnalytical-Method-Reliability-Across-the-Entire-Product-Lifecycle-Using-QbD-Approaches/>(accessed on 7 August 2013).
 30. Hubert, C.; Lebrun, P.; Houari, S.; Ziemons, E.; Rozet, E.; Hubert, P. Improvement of a stability-indicating method by Quality-by Design versus Quality-by-Testing: A case of a learning process. *J. Pharm. Biomed. Anal.* 2014, 88, 401–409.
 31. Tome, T.; Žigart, N.; Casar, Z.; Obreza, A. Development and optimization of liquid chromatography analytical methods by using AQbD principles: Overview and recent advances. *Org. Process Res. Dev.* 2019, 23, 1784–1802.

