Acta Scientific Pharmacology

Volume 5 Issue 1 January 2025

Review Article

Analytical Quality by Design (AQbD): A Detail Review

Ritu Tiwari[1]*, Gaurav Sanjay Mahalpure[1], Anuanshika Tiwari[2] and Sakshi Mahalpure[3]

[1]Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, Sector-23, Raj Nagar, Ghaziabad-201002, Uttar Pradesh, India

[2]SRMU University, Lucknow, Uttar Pradesh, India

[3]SVKM's Institute of Pharmacy, Dhule-424001, Maharashtra, India

***Corresponding Author:** Ritu Tiwari, Scientific Officer, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, Sector-23, Raj Nagar, Ghaziabad-201002, Uttar Pradesh, India.

Received: September 20, 2024

Published: December 21, 2024

Abstract

Applying advanced scientific and risk-based approaches to analytical methods yields significant benefits. Quality by Design (QbD) is a systematic approach that underscores the importance of comprehending and controlling product and process aspects. Adhering to the principles outlined in ICH guidelines can elevate the quality of drug substances and medicinal products, fostering ongoing enhancement and innovation across the product lifecycle. The development and regulation of analytical methods play a pivotal role in ensuring comprehensive product quality. It is crucial to grasp the impacts of variability on analytical method performance and outcomes.

Keywords: Analytical Quality by Design; Quality Risk Management; Pharmaceutical Quality System; Critical Quality Attributes; Design of Experiment

Introduction

The Food and Drug Administration (FDA) has recently granted approval for a number of new drug applications (NDAs) that incorporate regulatory flexibility through a quality by design (QbD)-based analytical approach. This QbD concept specifically applied to analytical method development, is now referred to as analytical quality by design (AQbD). This approach allows the analytical method to operate within the method operable design region (MODR). In contrast to current methods, an analytical method developed using the AQbD approach reduces occurrences of out-of-trend (OOT) and out-of-specification (OOS) results due to its method's robustness within the region. The adoption of AQbD in the method development process is a prevalent trend in the pharmaceutical industry, serving as a component of risk management, pharmaceutical development, and the pharmaceutical quality system. Given the limited availability of explanatory reviews, this paper aims to explore various perspectives of analytical scientists on the implementation of AQbD in the pharmaceutical quality system and its correlation with product QbD and pharmaceutical analytical technology (PAT).

Quality by design is a systematic approach that integrates quality risk management (QRM) and utilizes various design tools in conjunction with statistical analysis to ensure the production of high-quality products [1] (Figure 1).

In 2011, the FDA established a correlation between the analytical method and risk management (1CH Q9). This association highlighted that the quality of a product's risk factor depends on the severity of the drug's impact on patients due to lack of efficacy, the

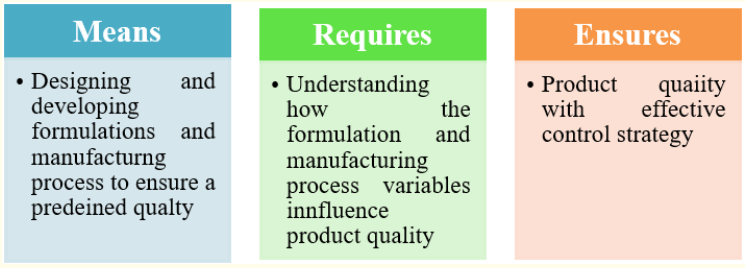

Figure 1: What is quality by design (QbD)?

uncertainty of new processes or products leading to a chance of failure, and poor detectability resulting from inappropriate analytical methods. Furthermore, the FDA has provided regulatory flexibility for select analytical procedures based on AQbD. In the pharmaceutical industry, QbD (Figure 2) has become a mandatory aspect of process and product design, as well as the optimization of analytical procedures [2,3].

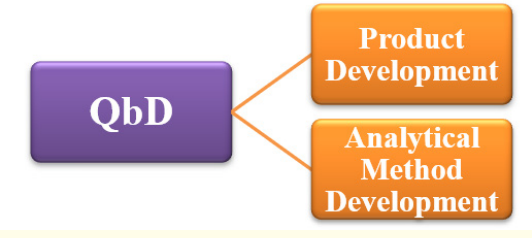

Figure 2: QbD in pharmaceutical industry.

According to the International Council on Organization (ICH) quality guidelines, the Analytical Quality by Design (AQbD) approach for analytical method development in the industry is a vital component of pharmaceutical development (Q8), quality risk management (Q9), and pharmaceutical quality system (Q10). The main goal of implementing AQbD is to develop a robust method, reduce the risk of method failure due to out-of-specification (OOS), out-of-trend (OOT) results, and out-of-control (OOC) situations, expedite product quality, achieve regulatory flexibility in changing method parameters within the method operable design region (MODR), and minimize the cost of analysis. While there is limited literature on QbD for drugs, some authors incorrectly interpret the implementation of design of experiments (DOEs) as an AQbD approach. It's important to note that DoE is just one aspect of the QbD approach [1,4].

In the pharmaceutical industry, chromatographic techniques like high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), and liquid chromatography-mass spectroscopy/mass spectrometry (LC-MS/MS) are commonly used for testing pharmaceuticals due to their precision and accuracy. However, creating new analytical methods using these techniques is challenging due to the variables' complexity. The Analytical Quality by Design (AQbD) process offers a solution by minimizing the impact of critical method variables (CMV) on method performance. By establishing a scientific relationship between CMVs and method responses, AQbD can design methods as regulatory bodies require, making it an essential tool for achieving highly robust analytical methods in the industry [5,6].

In the pharmaceutical industry, QbD is the concept that has been introduced to develop robust manufacturing processes, expedite product quality, and manufacture products in terms of "Six Sigma" [7]. The process of understanding the control and capability (PUCC) was implemented which is the loop process for constant improvement. "Six Sigma" is a system of practices developed for the systematic improvement of processes, which eliminates defects with statistical significance. Since it was originally developed, Six Sigma has become an important element of many total quality management (TQM) initiatives [8]. The significant number of reports on O0T results, OOS results, OOC, and out-of-statistical-control (OOSC), indicate that the present system of the pharmaceutical industry is not immune to these issues. At this stage, QbD implementation has been made obligatory in some countries, especially by the Europe Medicines Agency (EMA) and other ICH countries. The International Conference on Harmonization (ICH) Q8 (R1) guideline defines QbD as a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound

science and quality risk management" [9]. It indicates that scientifically designed product and process performance characteristics are needed to fulfill some specific objectives but not based on the performance of tests or quality control of release batches. QbD concepts are well-defined in ICH guidelines Q& (R1): Pharmaceutical Development, Q9: Quality Risk Management, and Q10: Pharmaceutical Quality System (Figure 3).

Figure 3: QbD bases.

The text highlights the increasing emphasis on the Quality by Design (QbD) concept in analytical method development within the pharmaceutical industry. It discusses the integration of QbD in developing efficient and high-quality analytical methods, referred to as Analytical Quality by Design (AQbD). The text recognizes the limited experience or exposure of analytical researchers to the AQbD approach, emphasizing the need for more discussions and guidance in its implementation within pharmaceutical quality systems. It also touches upon the key areas where the industry lacks sufficient knowledge, such as analytical target profile, method performance characteristics, risk assessment, Design of Experiments (DoE) tool selection, and MODR region optimization. Furthermore, it mentions the recent updates in USP and European Pharmacopeia related to flexibility in analytical methods when AQbD is implemented. The implications of system suitability testing (SST) and its relationship with AQbD are also outlined [10].

Regulatory perspective of QbD

The International Council for Harmonisation (ICH) Q8, Q9, and Q10 provides stringent requirements for product quality and emphasizes Process Analytical Technology (PAT) as a framework for pharmaceutical development, manufacturing, and quality assurance. QbD principles such as science and risk-based product development, life cycle approach, risk assessment, and product strategy are outlined in ICH Q8, Q9, and Q10 [11].

The pharmaceutical industry has implemented Quality by Design (QbD) through initiatives like the FDA's cGMP for the 21st century and process analytical technology (PAT). Analytical methods play a crucial role in ensuring predetermined performance and product quality. The FDA has approved numerous NDAs supported by QbD, emphasizing its importance in method development and product quality monitoring [12].

Figure 4: Principles of QbD.

The pharmaceutical industry is increasingly interested in Analytical Quality by Design (AQbD) as a solution to improve Quality Control (QC) processes and reduce the risk of method failure. This approach aims to enhance product quality and ensure high levels of assurance in pharmaceutical development and manufacturing. It is believed that applying Quality by Design (QbD) principles to analytical methods can lead to more robust and reliable analytical data, thus improving processes and product quality throughout their life cycle.

One factor at a time vs QbD in analytical method development

Currently, there is an increasing trend of method failure during method transfer and in quality control departments. This is believed to be due to the lack of robust test compliance as outlined in the ICH Q2 guidelines. Chromatographic methods, such as HPLC, UPLC, and RRLC, are commonly used for content uniformity, assay,

impurity profile, and stability-indicating assay. However, the complexity of method development, coupled with low sensitivity and selectivity, often leads to the need for revalidation protocols. The traditional one-factor-at-a-time (OFAT) approach to method development results in narrow method robustness, leading to increased costs [13]. The Analytical Quality by Design (AQbD) approach, which includes the Design of Experiments (DoE), is recommended for method development to improve robustness and cost-effectiveness, as well as to reduce out-of-specification (OOS) results [14].

Figure 5: Regulatory perspective: Product QbD vs Analytical QbD.

Implementation of AQbD

The Quality by Design (QbD) concept applies to analytical methods due to the numerous variables that can significantly impact the results. Implementing QbD offers an opportunity to attain regulatory flexibility, but it requires a high degree of robustness, product quality, and understanding of the analytical method. Implementing QbD in analytics is essential for achieving comprehensive quality improvement [15].

Table 1: Conventional approach vs product development QbD vs analytical QbD—cont'd.

Sr. No.	Parameter	Traditional	Product QbD	AQbD
1.	FDA Submission	Including only data for submission	Submission with product knowledge and process understanding	Submission with product knowledge and assuring by analytical target profile
2.	Specifications	Specifications are based on batch history	Specifications are based on product performance requirements	based on method performance to ATP criteria
3.	Process	Process is frozen and discourages changes	Flexible process with design space allows continuous improvement	Method flexibility with MODR and allowing continuous improvement
4.	Targeted Response	Focusing on reproducibility, ignoring variation	Focusing on robustness which understands control variation	Focus on robust and cost-effective method
5.	Advantage	Limited and simple	It is expended process analytical technology (PAT) tool that replaces the need for end product testing	Replacing the need of revalidation and minimizing OOT and OOS

Stages of quality by design

AQbD starts with an ATP, an analog to QTPP, defining the method's purpose. Once approved by regulatory authorities, ATP facilitates continuous improvement of analytical methods. In the pharmaceutical industry, the internal change control management system ensures effective ATP implementation for regulatory flexibility [2,16]. For example, CQA for a drug product is shown in Table 3.

Figure 6: Implementation of analytical QbD in pharmaceutical quality system.

Table 2: Implementation of analytical QbD.

Sr. No.	Implementation stage wise	Description
1.	Target measurement	Determine what to measure and where/when to measure it. Define ATP and develop measurement requirements based on product QTPP and CQA.
2.	Select technique	Select appropriate analytical technique for desired measurement defined in ATP. Define method performance criteria
3.	Risk assessment	Assess risks associated with method input variables, sample variation, and environmental conditions. Risk assessment tools (e.g., FMEA) can be used.
4.	Method development and validation	Examine potential multivariate interactions by DoE and define MODR to understand method robustness and ruggedness.
5.	Control strategy	Define control space and system suitability; meet Method performance criteria to meet ATP.
6.	Continual improvement	Monitor method performance that remains compliant with ATP criteria and thus analysts proactively identify and address the out-of-trend performance of the method. Update with new process and analytical technology.

Analytical Method Performance Characteristics

The method performance characteristics in ATP include bias, variance, accuracy, precision, specificity, linearity, and robustness. It's important to consider a joint criterion of two or more method performance characteristics. Linearity and specificity may not be directly linked to understanding the agreement of a measurement with the true value and may not need to be incorporated in the ATP. For example, an assay ATP should include a statement of accuracy and precision but not necessarily include linearity and specificity [17].

Table 3: Required analytical method performance for the CQA of drug product.

Sr. No.	CQA	Detection Methods	Detectability approach	Required method performance
1.	Appearance	Visual	Qualitative	Specificity, LOD
2.	Identification	Analytical method	Qualitative	Specificity, LOD
3.	Assay	Analytical method	Quantitative	Specificity, precision, accuracy, linearity
4.	Impurity	Analytical method	Quantitative	Specificity, LOD, LOQ, Precision, accuracy,linearity
5.	Heavy metals	Analytical method	Quantitative	Specificity, LOD, LOQ,Precision, accuracy,linearity
6.	Dissolution	Analytical method	Quantitative	Specificity, Precision, accuracy, linearity
7.	Disintegration	Disintegration apparatus	Quantitative	Reproducibility, accuracy
8.	Hardness	Hardness tester	Quantitative	Reproducibility, accuracy
9.	Friability	Friability apparatus	Quantitative	Reproducibility, accuracy
10.	Moisture content	Analytical methods	Quantitative	Specificity, LOD,Precision, accuracy,linearity

Table 4: Type of method performance characteristics as per USP and ICH Q2 (R1).

Sr. No.	Defined by ICH and USP	Method performance characteristics
1.	Systematic variability	Accuracy, specificity, and linearity
2.	Inherent random variability	Precision, detection limit, and quantification limit
3.	Not applicable	Range and robustness

Selection of analytical techniques

This must be done concerning the needs, which are defined in the ATP. On the other side, the selected analytical technique should satisfy the required method validation parameters as required by regulatory requirements. For example, specificity may not be included in ATP, but the analytical technique should satisfy the specificity. Hence, the chromatographic method can satisfy the required method performance defined in ATP and the validation requirement of ICH. Instead, the UV spectrophotometric method can fulfill the needs of ATP but may not satisfy ICH Q2 [18].

For example, considered analytical method performance characteristics and possible analytical techniques for dosage form are shown in Table 5.

Table 5: Analytical target profile for assay of tablet.

Targeted CQA	Possible analytical methods	Required method performance as per ICH Q2	Expected method response
Simultaneous assay of PRO and ETZ	UV-Visible method, HPLC UPLC, LC-MS/MS, HPTLC	Specificity (Pass), Linearity ($r^2 \geq 0.99$), Precision (% RSD < 2), Accuracy (98%–102%), Robustness (Pass)	Resolution > 2, Plate count > 3000, Tailing factor < 2, tR (PRO) = 3–5 min, tR (ETZ) ≥ 7-10 min

Establishing CQAS by risk assessment

The risk assessment process identifies critical method variables and focuses on method development. It involves assessing risks associated with various factors such as analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. The assessment strategy should follow the ICH Q9 guideline and is typically performed at the end of the method development stage [19]. It's crucial for method transfer and routine laboratory practices. Three methods for risk assessment are knowledge-based, cause and effect analysis, and failure mode and effect analysis. Various tools are utilized for risk management, and a Box-Behnken design is used for the systematic optimization of critical method variables.

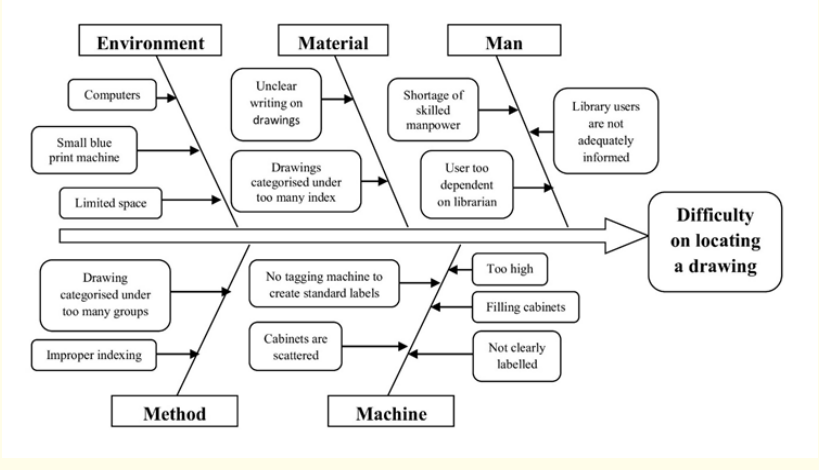

Figure 7: Ishikawa fishbone diagram (Cause and effect analysis).

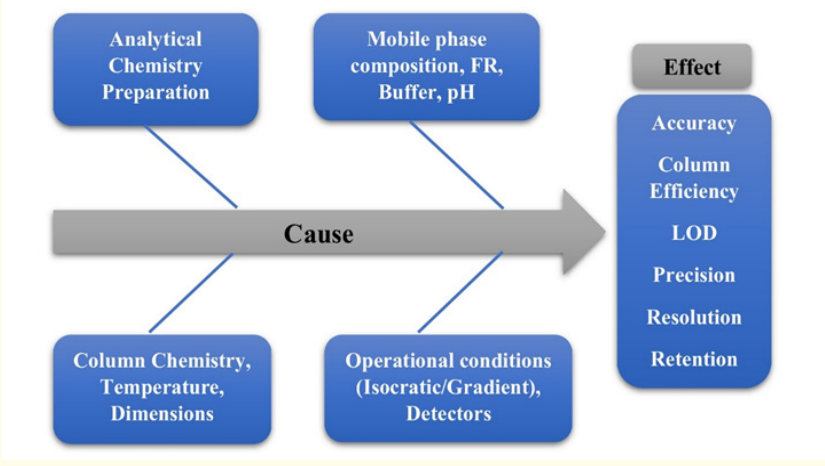

Figure 8: Diagram representing cause and effect analysis.

Risk assessment for the drug product was performed for the selection of CMVs shown in Tables 6 and Table 7.

Table 6: Risk assessment: critical method variables vs HPLC method responses.

Sr. No.	Input method variables (Xn)	Method Responses (Yn)		Consideration
		Theoretical plates (N)	Retention time (tR)	
	Flow rate	H	H	Optimized
	pH	H	H	Optimized
	% Aqueous phase	H	H	Optimized
	Buffer concentration	H	M	Optimized
	Column temperature	M	M	Controlled
	Type of organic phase	M	M	Controlled
	Column type	H	H	Controlled
	% Carbon load	H	H	Controlled
	Column make	H	H	Default
	Buffer type	H	H	Controlled
	Column length	M	M	Default
	Column particle size	H	M	Default
	Detector	N/A	N/A	Default
	Injection volume	L	L	Default
	Reagent purity	L	L	Controlled
	Vendors (reagents)	L	L	Controlled
	Reference drug	L	L	Controlled

Table 7: Risk assessment: gas chromatography.

Sr. No.	Input Method Variables	Method Responses		Consideration
		Retention time	Area	
	Flow rate	H	H	Controlled
	Temperature of headspace	H	H	Controlled
	Temperature of the oven	H	H	Controlled
	Injection port temperature	H	H	Controlled
	Column	H	H	Controlled
	Column temperature	H	H	Controlled
	Column particle size	H	H	Default
	Detector	H	H	Default
	Carrier gas	H	H	Controlled

This analysis is important in reliability engineering, safety engineering, and quality engineering as it helps in identifying potential failure modes and their consequences. It is widely used in the development and manufacturing industries to mitigate risks and reduce the probability of failure. The Failure Modes and Effects (FME) Analysis is a design tool used to systematically analyze postulated component failures and their effects on system operations. It consists of two sub-analyses: Failure Modes and Effects Analysis (FMEA) and Criticality Analysis (CA). FMEAs can be performed at various levels, from system to part level. Timely completion of the FMECA is crucial for guiding design decisions and eliminating or minimizing critical failure modes. Additionally, for more comprehensive scenario modelling, a fault tree analysis (FTA) may be considered, which incorporates multiple failures and external factors.

Functional analysis

The analysis starts at the functional level and extends to the hardware level once the design has matured. The hardware level FMECA assumes that interfacing hardware is operating within specification. Multiple FMEAs are conducted to evaluate the impact of lower-level failures on system operation and to prevent irreversible damage across interfaces due to failures. FMECA combines FMEA and CA, with the latter requiring the identification of system-level critical failure in the former.

Ground rules

The ground rules for FMEA include project procedures, analysis assumptions, included and excluded hardware, exclusions rationale, indenture level, hardware status, and system success criteria [2,20]. It's important to define these rules before starting, but they can be expanded as the analysis progresses. Typical assumptions include one failure mode at a time, all inputs at nominal values, sufficient consumables, and available nominal power.

Benefits

The major benefits of properly implemented FMECA efforts include:

- Selecting a design with a high probability of successful operation and safety.
- Assessing potential failure mechanisms and their impact on system operation.
- Identifying single-failure points and system interface problems.
- Evaluating proposed design changes and operational procedures.
- Developing in-flight troubleshooting procedures and locating fault-detection devices.
- Planning tests early.

Early identification of single-failure points, input to troubleshooting procedures, and locating performance monitoring and fault-detection devices are the most important benefits.

Design of experiments

By ICHQ8 guidelines, MODR can be established in the method development phase, serving as a source for a robust and cost-effective method. MODR is the operating range for critical method input variables that consistently meet the goals set in the ATP. It is science-based and permits flexibility in method parameters, ensuring expected method performance without resubmission to the FDA. The FDA recommends conducting MODR together with method validation. Once defined, appropriate method controls can be put in place. This approach requires a deep understanding of input variables and output response selection.

Selection of DoE tools

During optimization, different approaches can be used to derive a mathematical relationship (model). The choice of design of experiments (DoE) tool depends on the number of input variables, knowledge of controlled parameters, and the relationship between variables and results. Statistical knowledge is essential to interpret variable interactions and their contributions to method responses. Different methods like factorial design, response surface methodology (RSM), Taguchi method, and Plackett-Burman design can be used based on the specific requirements of the study Table 8.

Table 8: Selection of DOE tools in analytical quality by design.

Sr. No.	Design	Number of variables and usage	Advantage	Disadvantage
1.	Full factorial design	Optimization/2–5 variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables
2.	Fractional factorial design or Taguchi methods	Optimization/and screening variables	Requiring lower number of experimental runs	Resolving confounding effects of interactions is a difficult job
3.	Plackett-Burman Method Screening/or identifying	Screening/or identifying vital few factors from large number of variables	Requiring very few runs for large number of variables	It does not reveal Interaction effect
4.	Pseudo-Monte Carlo sampling (pseudorandom sampling) method	Quantitative risk analysis/ optimization	Behaviour and changes to the model can be investigated with great ease and speed. This is preferred where exact calculation is possible	For nonconvex design spaces, this method of sampling can be more difficult to employ. Random numbers that can be produced from a random number-generating algorithm
5.	Box-Behnken design	Three levels of each factor (-1, 0, +1) was used.	Design points fall within design region	Two factor design was not given
6.	Doehlert design	Optimization of variables	Used in response surface analysis	

John Bennet Lawes and Joseph Henry Gilbert used factorial designs in the 19th century. In 1926, Ronald Fisher argued that factorial designs were more efficient than studying OFAT.

Advantages of factorial designs

Factorial experiments offer several advantages over OFAT experiments, such as efficiency, the ability to examine additional factors at no extra cost, the detection of interactions between factors, and the estimation of factor effects at different levels. Additionally, Box-Behnken designs are experimental designs for response surface methodology (RSM) that were devised in 1960 to achieve specific goals, including placing each factor at three equally spaced values, fitting a quadratic model, maintaining a reasonable ratio of experimental points to coefficients, and ensuring that estimation variance depends mainly on the distance from the centre.

The design involves a combination of a two-level factorial design with an incomplete block design. Each block varies a certain number of factors through all combinations for the factorial design while keeping the other factors at central values [21]. Centre points are also included. The design for 8 factors was not in the original paper, but using the 9-factor design and deleting one column pro-

duces an 81-run design. Designs for other numbers of factors have also been invented, at least up to 21. For example, a 16-factor design exists with only 256 factorial points, and using Plackett-Burmans to construct a 16-factor design requires only 221 points.

The Doehlert design is chosen for its advantages of a spherical experimental domain with uniform space-filling, the ability to explore the entire domain, and the potential for sequential experiment use [22]. It is easily applied to optimized variables and offers

Table 9: Box-Behnken design for 3 factors.

Factors	M	No. of Blocks	Factorial points per block	Total with 1 centre point	Typical total with extra centre points	No. of coefficients in quadratic model
3	2	3	4	13	15, 17	10
4	2	6	4	25	27, 29	15
5	2	10	4	41	46	21
6	3	6	8	49	54	28
7	3	7	8	57	62	36
8	4	14	8	113	120	45
9	3	12	8	97	105	55
10	4	10	16	161	170	66
11	5	11	16	177	188	78
12	4	12	16	193	204	97
16	4	24	16	385	396	153

advantages over other designs in response surface analysis. The number of experiments required is determined by the number of variables and centre points. The design allows for screening out qualitative input variables and incorporating quantitative measures for critical method variables in the optimization phase.

Model validation

Before choosing between contour and graph, the predicted values for the method response need to be confirmed by actual experimental runs. After that, regression analysis must be conducted to statistically validate the model.

Method validation should be carried out according to ICHQ2 (R1) guidelines under normal operating conditions or optimized conditions with set variables at one point. Additionally, method verification can be performed through accuracy and precision assessment at different points within the chromatographic separation space [23]. This multipoint verification should go beyond regular robust test limits to ensure the method's ability to meet requirements. The experiments should demonstrate robustness across parameter ranges, such as verifying column temperature between 35°C and 45°C, percentage of aqueous or organic components in the mobile phase, and pH levels. If the performance characteristics are satisfactory and meet the acceptance criteria, the method's operable range can be established based on the validation and verification results.

Control strategy/conformance to ATP

In product QbD, the control strategy ensures instant production with the required quality. It's derived from data collected during method development and verification and predicts the method's ability to meet ATP criteria and control strategy. The implemented control strategy considers parameters and their impact on product quality for changes within and outside the design space. The method control strategy of the AQbD approach does not differ from the traditional control strategy [24].

Continuous monitoring/life-cycle management

The establishment of an analytical method for quality control involves monitoring method performance over time to ensure it complies with defined criteria. In the pharmaceutical industry, con-

trol charts and other tools are used to track system suitability data. This monitoring allows the detection and addressing of abnormal or OOT performance of the method, critical from raw material testing to stability testing Table 10.

Table 10: Role of analytical method in pharmaceutical testing and control strategy.

Sr. No.	Control	Strategy
1.	Raw material testing	Specification based on product QTPP and CQA Effects of variability, including supplier variations, on process and method development are understood
2.	In-process testing	Real time (at-, on-, or in-line) measurements Active control of process to minimize product variation Criteria based on multivariate process understanding
3.	Release testing	Quality attributes predictable from process inputs(design space) Specification is only part of the quality control strategy Specification based on patient needs (quality, safety, efficacy, and performance)
4.	Stability testing	Predictive models at release minimize stability failures Specification set on desired product performance with time

PAT and AQbD

The Process Analytical Technology (PAT) system is a method defined by the USFDA to measure critical process parameters that affect Critical Quality Attributes (CQA) and involves designing, analyzing, and controlling the manufacturing process. It aims to reduce production cycle time, prevent batch rejections, enable continuous processing, improve material usage, promote automation, and reduce risks. The FDA recommends that pharmaceutical manufacturing processes ensure product quality and performance through continuous and real-time quality assurance. PAT initiatives serve as the foundation for the Design of Experiments (DOE) and Multivariate Analysis (MVDA). Pharmaceutical industries are working on developing specific process understanding and designing process analytical control strategies to enhance the effectiveness of the PAT approach [25].

Conclusion

The methods outlined in pharmacopoeias are intended to be suitable for a wide variety of available formulations. This often necessitates a review of registered methods to ensure their applicability for pharmacopoeial use. The case study accomplished these objectives, demonstrating the value of employing AQbD to enhance quality and effectiveness in monograph development. The concepts expounded in this study can help determine whether a published pharmacopoeial method is appropriate for its intended purpose and can be utilized for the specific product under examination. The principles and methodologies delineated in this study not only provide guidance but also have the potential to significantly augment the work of the analyst or organization, encouraging their adoption and use.

Acknowledgements

The authors acknowledge the Secretary-cum-Scientific Director, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, for providing the platform for developing the manuscript.

Competing Interests

All authors declare that they have no conflicts of interest.

Ethical Approval

Not applicable.

Funding

None.

Bibliography

1. Mishra V., *et al*. "Quality by design (QbD) approaches in current pharmaceutical set-up". *Expert Opinion on Drug Delivery* 15.8 (2018): 737-758.

2. Ramalingam P and Jahnavi B. "QbD considerations for analytical development. In *Pharmaceutical Quality by Design* (2019): 77-108.

3. J Ermer. Quality by design in pharmaceutical analysis, Conference organized by European Compliance Academy, Vienna, Austria.

4. Fukuda IM., *et al*. "Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD)". *Brazilian Journal of Pharmaceutical Sciences 54* (2018): e01006.

5. Vandana P and Harish D. "Product lifecycle management in pharmaceuticals". *Journal of Medical Marketing* 12 (2012): 150-158.

6. Todd Hein. Oracle life sciences. Product lifecycle Management for the Pharmaceutical Industry. Improving clinical development and manufacturing processes in pharmaceutical R and D organization.

7. Pramod K., *et al*. "Pharmaceutical product development: A quality by design approach. *International journal of Pharmaceutical Investigation 6*.3 (2016): 129.

8. Green FB. "Six-Sigma and the revival of TQM". *Total Quality Management and Business Excellence* 17.10 (2006): 1281-1286.

9. Aksu B and Mesut B. "Quality by design (QbD) for pharmaceutical area". *Journal of Faculty of Pharmacy of Istanbul University* 45.2 (2015): 233-251.

10. Tome T., *et al*. "Development and optimization of liquid chromatography analytical methods by using AQbD principles: Overview and recent advances". *Organic Process Research and Development 23*.9 (2019): 1784-1802.

11. Hasnain MS., *et al*. "Pharmaceutical product development: A quality by design (QbD) approach". In Advances and challenges in pharmaceutical technology (2021): 131-146.

12. Bondi Jr RW and Drennen III JK. "Quality by Design and the Importance of PAT in QbD". In Separation Science and Technology 10 (2011): 195-224.

13. Tome T., *et al*. "Development and optimization of liquid chromatography analytical methods by using AQbD principles: Overview and recent advances". *Organic Process Research and Development* 23.9 (2019): 1784-1802.

14. Chiarentin L., *et al*. "Drilling into "Quality by Design" approach for analytical methods". *Critical Reviews in Analytical Chemistry* (2023): 1-42.

15. Peraman R., *et al*. "Analytical quality by design: a tool for regulatory flexibility and robust analytics". *International Journal of Analytical Chemistry* 1 (2015): 868727.

16. Das V., *et al*. "Quality by design approaches to analytical method development". *Research Journal of Pharmacy and Technology* 10.9 (2017): 3188-3194.

17. Ermer J., *et al*. "Method Performance Qualification". *Method Validation in Pharmaceutical Analysis: A Guide to Best Practice* (2014): 303-376.

18. Jadhav ML and Tambe SR. "Implementation of QbD approach to the analytical method development and validation for the estimation of propafenone hydrochloride in tablet dosage form". *Chromatography Research International* 1 (2013): 676501.

19. McMahon ME., *et al*. "Considerations for updates to ICH Q1 and Q5C stability guidelines: Embracing current technology and risk assessment strategies". *The AAPS journal 23* (2021): 1-9.

20. Bouti A and Kadi DA. "A state-of-the-art review of FMEA/FMECA". *International Journal of Reliability, Quality and Safety Engineering* 1.4 (1994): 515-543.

21. Abbar AH. "Effect of Electrolysis Parameters on the Specific Surface Area of Nickel Powder: Optimization using Box-Behnken Design". *International Journal of Electrochemical Science* 14.1 (2019): 662-678.

22. Dejaegher B., *et al*. "Experimental design in method optimization and robustness testing". *Chemometric Methods in Capillary Electrophoresis* (2010): 11-74.

23. Ashritha N and Rajitha G. "Analytical Quality by Design Approach for the Development and Validation of Liquid Chromatographic Procedure for the Estimation of Abrocitinib". *Pharmaceutical Chemistry Journal* (2024): 1-10.

24. Vogt FG and Kord AS. "Development of quality-by-design analytical methods". *Journal of Pharmaceutical Sciences* 100.3 (2011): 797-812.

25. Rosas JG., *et al*. "Real-time determination of critical quality attributes using near-infrared spectroscopy: A contribution for Process Analytical Technology (PAT)". *Talanta* 97 (2012): 163-170.