

Analytical Quality by Design (AQbD) in Pharmaceutical Analysis: From Analytical target profile to method Lifecycle Management

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Abstract

Pharmaceutical analytical procedures are essential for establishing the identity, strength, purity, quality and stability of drug substances and drug products. Conventional analytical method development frequently relies on trial-and-error or one-factor-at-a-time experimentation, which may require repeated optimization and may not adequately reveal interactions among method variables. Analytical Quality by Design (AQbD) applies science-, risk- and knowledge-based principles to analytical procedure development. The approach begins with an Analytical Target Profile (ATP), followed by risk assessment, identification of critical method parameters and analytical performance attributes, Design of Experiments (DoE), method optimization, establishment of a Method Operable Design Region (MODR), control strategy, validation and lifecycle management. ICH Q14 and ICH Q2(R2) provide an important contemporary regulatory framework for analytical procedure development and validation. This review discusses the principles, workflow, statistical tools, chromatographic applications, validation, lifecycle management, advantages, limitations and emerging opportunities associated with AQbD. Particular emphasis is placed on RP-HPLC/UHPLC method development, risk assessment, DoE, MODR, green analytical chemistry and artificial intelligence.

Keywords

Analytical Quality by Design; AQbD, Analytical Target Profile, Design of Experiments, Critical Method Parameters, Method Operable Design Region.

1. Introduction

Pharmaceutical analytical procedures support drug development, quality control, stability testing, impurity determination and product release. Reliable analytical data are therefore fundamental to pharmaceutical quality decisions. Traditional analytical development commonly uses trial-and-error or one-factor-at-a-time (OFAT) experimentation. Although simple, OFAT can require many experiments and may fail to reveal interactions among variables[1,2].

Analytical Quality by Design (AQbD) extends Quality by Design concepts to analytical procedure development. It is a systematic, science- and risk-based approach intended to produce analytical procedures that are fit for their intended purpose and maintain performance throughout their lifecycle [2-4]. The modern AQbD framework connects analytical objectives with risk assessment, statistical experimentation, method understanding, control strategy and continued performance monitoring. Recent literature demonstrates growing application of AQbD in chromatographic analysis. A 2024 review identified more than 180 research articles published between 2019 and 2024 involving AQbD-based chromatographic methods [5]. ICH Q14, finalized in 2023, further formalizes a lifecycle-oriented approach to analytical procedure development, while ICH Q2(R2) provides the corresponding validation framework [6,7].

2. Concept and Evolution of AQbD

Quality by Design is a systematic development philosophy based on predefined objectives, product/process understanding and control founded on sound science and quality risk management [3]. When these concepts are applied specifically to analytical procedures, the resulting framework is commonly described as Analytical Quality by Design.

AQbD represents a shift from “quality by testing” toward proactive analytical design. Instead of developing a nominal method first and investigating robustness later, the method is designed with predefined performance objectives and an understanding of variables that may influence performance [2,8].

The typical workflow is: Analytical Target Profile (ATP) → risk assessment → identification of critical method parameters and analytical attributes → screening → DoE-based optimization → MODR/design region → control strategy → validation → continued performance verification [4,6,9].

3. Traditional Method Development versus AQbD

Traditional development generally changes one variable at a time until acceptable chromatographic performance is obtained. This may produce a working method, but the relationship between variables and responses may remain poorly understood.

AQbD uses structured experimentation and statistical modelling to investigate several factors together. It can identify significant variables, quantify interactions and define an operating region in which method performance remains acceptable [1,5].

4. Analytical Target Profile

The Analytical Target Profile (ATP) defines the intended purpose of an analytical procedure and the performance requirements needed to fulfil that purpose. It provides a foundation for method development and lifecycle management [6]. An ATP may describe the analyte or attribute to be measured, intended use, accuracy, precision, specificity/selectivity, range and sensitivity requirements where applicable. For example, an assay ATP may require accurate and precise quantification of an active pharmaceutical ingredient in a dosage form over a predefined range, with adequate specificity against excipients and degradation products. The ATP should be sufficiently clear to guide development but should not unnecessarily prescribe individual experimental settings. This distinction allows different analytical technologies or method conditions to be considered while maintaining the required analytical performance [6].

5. Critical Method Attributes and Critical Method Parameters

Critical analytical performance attributes are characteristics that must meet predefined criteria to achieve the ATP. Depending on the method, these may include resolution, retention time, peak symmetry, accuracy, precision, sensitivity and selectivity [5,9]. Critical Method Parameters (CMPs) are method variables that can influence these performance attributes. For RP-HPLC, possible CMPs include mobile-phase composition, buffer pH, flow rate, column temperature, gradient conditions, injection volume and sample preparation variables.

Examples include: flow rate influencing retention time and resolution; pH influencing retention and selectivity; organic solvent percentage influencing retention and resolution; and column temperature influencing retention and efficiency. Not every variable is critical; its importance should be supported by risk assessment and experimental evidence [5,9].

6. Risk Assessment in AQbD

Risk assessment prioritizes variables that could have a meaningful effect on analytical performance. It is commonly performed before detailed optimization so that experimental resources can be focused on higher-risk

factors [1,3]. Common tools include Ishikawa (fishbone) diagrams, Failure Mode and Effects Analysis (FMEA), risk ranking and cause-and-effect matrices. FMEA evaluates potential failure modes using severity, occurrence and detectability. A commonly used risk priority number is calculated as

$$\text{RPN} = \text{Severity} \times \text{Occurrence} \times \text{Detectability} [1]$$

For an HPLC method, possible risks may arise from mobile-phase pH, organic-solvent ratio, flow rate, column temperature, column characteristics, sample preparation, standard preparation and instrument performance. Risk assessment should be revisited when new knowledge or performance data become available.

7. Design of Experiments in AQbD

Design of Experiments (DoE) is a central statistical tool in AQbD. It permits several factors to be varied systematically and can reveal interactions that may not be detected by OFAT experimentation [2,5]. Factors are controlled experimental variables, while responses are measurable outputs such as resolution, retention time, tailing factor, theoretical plates, peak area or recovery. Screening designs such as Plackett–Burman and factorial designs can identify important factors. Once significant factors are identified, response-surface designs such as Box–Behnken and Central Composite designs can be used for optimization [5,10]. A typical chromatographic study may investigate pH, organic-phase percentage and flow rate as factors, with resolution, retention time and tailing factor as responses. Statistical models can then be used to determine the effects and interactions of these variables and identify conditions satisfying the predefined analytical objectives.

8. AQbD-Based Chromatographic Method Development

HPLC and UHPLC are particularly suitable for AQbD because chromatographic performance is influenced by multiple interacting variables. A systematic workflow begins with defining the ATP, followed by identification of potential parameters and responses, risk assessment, screening, optimization and establishment of a design region [5,11]. For RP-HPLC, possible factors include buffer pH, organic-solvent ratio, flow rate and column temperature. Responses may include resolution of critical pairs, retention time, peak symmetry and analysis time. The selected experimental design should reflect the number of factors, desired information and available resources. Recent reviews report increasing use of AQbD in HPLC and UHPLC. A 2025 review specifically examining AQbD in UHPLC described improvements in robustness, efficiency and regulatory alignment and summarized methodological developments from 2014–2025 [11].

9. Method Operable Design Region

The Method Operable Design Region (MODR) represents a multidimensional region of method parameters within which predefined analytical performance requirements are met [6,9]. It is an important outcome of AQbD because it captures the relationship between method settings and analytical performance rather than defining a single nominal condition. For example, an optimized HPLC method might demonstrate acceptable performance over a range of pH, organic-solvent percentage and flow-rate combinations. The acceptable combinations, supported by experimental evidence and modelling, constitute the MODR. The MODR should not be interpreted as simply adding independent ranges for each parameter; interactions among parameters must be considered. Establishing an appropriate design region can support flexibility and scientifically justified lifecycle changes [6,9].

10. Analytical Control Strategy

After optimization, a control strategy is established to maintain analytical performance during routine use. It can include method parameter ranges, system suitability criteria, instrument requirements, column specifications, mobile-phase preparation controls, standard and sample preparation requirements and monitoring procedures [6,9]. For HPLC procedures, control elements may include acceptable limits for resolution, retention time, tailing factor,

theoretical plates and injection precision. The control strategy converts development knowledge into practical routine controls.

11. AQbD and Analytical Procedure Validation

Analytical procedure validation demonstrates that a procedure is suitable for its intended purpose. ICH Q2(R2), finalized alongside ICH Q14, provides the contemporary framework for analytical procedure validation [6,7]. Depending on intended use, validation characteristics can include specificity/selectivity, accuracy, precision, response/range, detection capability and robustness. AQbD supports validation by providing prior knowledge about critical variables and their influence on analytical performance. Specificity evaluates the ability to distinguish the analyte from impurities, degradation products and matrix components. Accuracy assesses closeness to an accepted reference value, while precision addresses agreement among repeated measurements. Linearity/response and range establish the concentration interval over which the procedure meets relevant performance criteria. Detection and quantitation capability are especially important for trace impurities. Robustness evaluates the ability of the procedure to remain reliable under small deliberate variations in relevant parameters [7].

12. Analytical Procedure Lifecycle Management

AQbD treats an analytical procedure as a lifecycle-managed analytical asset rather than a static method. The lifecycle includes development, performance qualification and continued monitoring/improvement [4,9]. Lifecycle activities can include method transfer, continued performance monitoring, trend analysis, change management, investigation of atypical performance, revalidation where justified and method improvement. Knowledge generated during development can be used to understand the likely impact of changes and support scientifically justified decisions. The AAPS white paper on AQbD, lifecycle management and method control emphasized the value of systematic development, continuously validated analytical procedures and ongoing verification [9].

13. Applications of AQbD in Pharmaceutical Analysis

AQbD has been applied to RP-HPLC, UHPLC, LC-MS/MS, HPTLC, GC and spectroscopic methods. Chromatographic procedures remain the most extensively reported area because multiple method variables and responses can be investigated simultaneously [5,11]. In LC-MS/MS, AQbD can be applied to sample extraction, chromatographic separation and mass-spectrometric parameters.

In HPTLC, mobile-phase composition, chamber saturation and development distance may be studied. For GC, oven temperature, carrier-gas flow and injection conditions may be evaluated. Spectroscopic procedures can similarly investigate wavelength, solvent and sample-preparation variables.

14. AQbD in Stability-Indicating Methods

Stability-indicating methods must distinguish the active drug from degradation products and other components. AQbD can incorporate separation from likely degradation products as an important analytical performance objective from the beginning of development rather than treating forced degradation as a late-stage exercise.

For stability-indicating RP-HPLC, potential factors include pH, organic-solvent composition, gradient slope, flow rate and temperature. Responses can include resolution between the drug and critical degradation products, peak purity, retention time and peak symmetry. This approach can improve method robustness and reduce repeated optimization when new degradation behaviour is identified.

15. Advantages of AQbD

Major advantages include improved method understanding, systematic identification of critical variables, detection of factor interactions, improved robustness, efficient optimization, stronger scientific justification and better lifecycle management [5,9]. AQbD can also reduce the likelihood of method failure by identifying vulnerable parameters before routine implementation. It provides a documented rationale for selected method conditions and can facilitate communication among analytical development, quality control, quality assurance and regulatory teams.

16. Challenges and Limitations

Implementation of AQbD requires appropriate statistical knowledge, experimental planning and data interpretation. Software may be required for DoE and multivariate modelling. Initial development may appear more resource-intensive because structured experiments are deliberately planned. Another challenge is inconsistent implementation. Recent reviews have reported that some published AQbD studies use DoE but provide limited structured risk assessment or do not clearly establish a design region/MODR [5,12].

Therefore, using DoE alone should not automatically be considered full AQbD. Successful implementation also requires appropriate documentation, cross-functional knowledge and organizational acceptance. The statistical model must be experimentally verified, and predicted performance should not replace laboratory confirmation.

17. AQbD and Green Analytical Chemistry

Sustainability is an emerging consideration in analytical development. Chromatographic methods may consume significant amounts of organic solvent and generate waste. AQbD can incorporate solvent consumption, analysis time and waste generation as additional considerations during optimization. Potential strategies include reducing flow rate where performance permits, shortening analysis time, reducing sample and solvent volumes, selecting safer solvents and considering miniaturized approaches. Green analytical assessment tools such as Analytical Eco-Scale, GAPI and AGREE can complement AQbD by evaluating environmental performance. Future method development may therefore optimize analytical performance, robustness and sustainability together rather than treating environmental considerations as an afterthought.

18. AQbD, Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning may extend AQbD by using historical analytical data to predict chromatographic behaviour and recommend experimental conditions. Potential applications include retention-time prediction, peak recognition, chromatographic optimization, automated integration, prediction of robustness and detection of abnormal performance. A future workflow may involve historical data → model-based prediction → risk assessment → DoE → experimental confirmation → design region → automated monitoring. However, AI predictions require experimental verification and appropriate governance before use in regulated pharmaceutical environments. The integration of AI with AQbD is therefore a promising but developing area.

19. Regulatory Perspective

ICH Q14 provides a harmonized framework for analytical procedure development and describes approaches including minimal and enhanced development strategies, analytical procedure understanding, risk assessment, robustness and lifecycle management [6]. ICH Q2(R2) addresses validation of analytical procedures and should be considered together with Q14 rather than as an isolated activity [7]. AQbD is also closely connected to broader ICH quality principles, including Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, Q10 Pharmaceutical Quality System and Q12 Product Lifecycle Management [13-16]. Together, these guidelines support a science- and risk-based pharmaceutical development environment.

20. Future Perspectives

The future of AQbD is likely to involve increased automation, digitalization, artificial intelligence, green analytical chemistry and continuous analytical performance monitoring. Automated instruments can execute structured experiments, while data systems can support trend analysis and lifecycle decision-making.

Integration with Process Analytical Technology and real-time release approaches may further expand the role of analytical procedures from laboratory testing toward continuous process understanding. Standardized terminology and implementation strategies will also be important for broader industry adoption [9,12].

21. Conclusion

Analytical Quality by Design provides a comprehensive framework for developing robust, reliable and fit-for-purpose analytical procedures. The approach begins with an Analytical Target Profile and integrates risk assessment, critical parameter identification, Design of Experiments, optimization, MODR, control strategy, validation and lifecycle management. The increasing use of AQbD in chromatographic analysis and the publication of ICH Q14 and Q2(R2) demonstrate the growing importance of systematic analytical procedure development [5-7]. Nevertheless, AQbD should not be reduced to the use of statistical software or DoE alone. Its value lies in the integration of scientific understanding, risk management, experimental evidence and continued monitoring. Future integration with artificial intelligence, automation and green analytical chemistry may further improve the efficiency, sustainability and adaptability of pharmaceutical analytical procedures.

Table 1. Comparison of traditional analytical method development and AQbD

Parameter	Traditional approach	AQbD approach
Development strategy	Trial and error	Systematic, science- and risk-based
Experimental approach	OFAT	Multivariate DoE
Risk assessment	Often limited	Structured
Variable interactions	May remain unidentified	Evaluated
Robustness	Often assessed later	Considered during development
Method understanding	Limited	Enhanced
Design region	Usually absent	MODR/design region may be established
Lifecycle management	Limited	Integrated

Table 2. Representative AQbD applications in pharmaceutical analysis

Technique	Typical factors	Typical responses	Purpose
RP-HPLC	pH, organic phase, flow rate, temperature	Resolution, retention, tailing	Assay/impurities
UHPLC	Gradient, flow rate, temperature	Resolution, run time	Rapid separation
LC-MS/MS	Extraction, mobile phase, MS parameters	Recovery, sensitivity	Bioanalysis/trace analysis
HPTLC	Mobile phase, saturation, development distance	Peak area, resolution	Quantitative analysis
GC	Oven temperature, carrier flow, injection	Resolution, peak shape	Volatile analytes
UV-Vis	Wavelength, solvent,	Absorbance, accuracy	Assay/quantification

	concentration		
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