

## QUALITY BY DESIGN (QBD) IN ANALYTICAL METHOD DEVELOPMENT: A SYSTEMATIC REVIEW OF PRINCIPLES, TOOLS AND REGULATORY PERSPECTIVES

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### ABSTRACT

Analytical Quality by Design (AQbD) represent a structured, science and risk-based frame work for the analytical method development in the pharmaceutical industry. This systematic review evaluates the principles, statistical tools, regulatory expectations, and lifecycle management strategies associated with AQbD. A structured literature search was conducted using an electronic database including PubMed, Scopus, and Google Scholar for publications between 2008 and 2025. The review highlights key elements such as Analytical Target Profile (ATP), Critical Quality Attributes (CQAs), Critical Method Parameters (CMPs), risk assessment tools, Design of Experiments (DoE), and Method Operable Design Region (MODR). Regulatory alignment with the ICH guidelines (Q-series) Q8, Q9, Q10, Q14, and Q2(R2) is critically discussed. The findings indicate that the AQbD improves robustness, reduces variability, and enhances regulatory flexibility. Despite implementation challenges, AQbD is emerging as an regulatory expectation in modern pharmaceutical analysis.

**KEYWORDS:** Analytical Quality by Design, AQbD, Design of Experiments, ICH Q14, MODR, Pharmaceutical Analysis.

### 1. INTRODUCTION

Traditional analytical method development often relied on the empirical and trial and error approaches. Such methods may frequently lacked comprehensive understanding of the method variability and robustness. Quality by Design (QbD), introduced through ICH Q8, emphasizes predefined objectives and systematic development. Analytical Quality by Design (AQbD) extends these principles to the analytical procedures, ensuring consistent method performance across the product lifecycle.

### 2. METHODOLOGY

#### • Search Strategy

A systematic literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar.

Keywords included 'Analytical Quality by Design', 'AQbD', 'Design of Experiments in pharmaceutical analysis', 'ICH Q14 analytical procedure development', and 'Method Operable Design Region'. Studies published between 2008 and 2025 were included.

#### • Inclusion and Exclusion Criteria

Inclusion criteria comprised peer-reviewed research articles, review papers, and regulatory guidance documents are focused on AQbD implementation in pharmaceutical analysis. Non-English publications and unrelated quality management articles were excluded.

- **Data Extraction and Analysis**

Relevant data were extracted regarding ATP definition, risk assessment tools, DoE models, regulatory perspectives, and lifecycle management practices.

### 3. Core Elements of AQbD

- **Analytical Target Profile (ATP)**

ATP defines the intended purpose and performance criteria of the analytical method, including accuracy, precision, specificity, and range etc.

- **Critical Quality Attributes (CQAs)**

CQAs represent measurable analytical responses such as resolution, tailing factor, and % RSD that ensure method suitability.

- **Critical Method Parameters (CMPs)**

CMPs include method variables such as mobile phase composition, pH, temperature, and flow rate that may influence the CQAs.

- **Risk Assessment Tools**

Risk management tools such as Ishikawa diagrams (Fish Bone diagram) and Failure Mode and Effects Analysis (FMEA) are used to identify high-risk parameters.

- **Design of Experiments (DoE)**

DoE enables simultaneous evaluation of multiple factors using the statistical models such as factorial design, Box–Behnken design, and Central Composite Design.

- **Method Operable Design Region (MODR)**

MODR defines the multi-dimensional region within which method performance meets ATP criteria, providing regulatory flexibility.

### 4. Regulatory Perspectives

AQbD aligns with ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System), ICH Q14 (Analytical Procedure Development), and ICH Q2(R2) (Validation of Analytical Procedures). ICH Q14 particularly emphasizes lifecycle management and robustness assessment.

### 5. Advantages and Challenges

Advantages include improved robustness, reduced out-of-specification(OOS) results, enhanced process understanding, and regulatory flexibility. Challenges involve statistical expertise requirements, training costs, and resistance to conventional approaches.

### 6. CONCLUSION

AQbD represents a transformative advancement in pharmaceutical analytical science. By integrating risk assessment, DoE, and lifecycle management principles, AQbD ensures robust and regulatory compliant analytical procedures. Future integration with artificial intelligence and predictive modeling may further strengthen analytical reliability.

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