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ANALYTICAL QUALITY BY DESIGN (AQBD) APPROACH FOR LIFECYCLE MANAGEMENT OF PHARMACEUTICAL ANALYTICAL METHODS

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ABSTRACT

The pharmaceutical industry has increasingly adopted science- and risk-based approaches to ensure the quality, safety, and efficacy of pharmaceutical products. One of the most widely implemented strategies is Quality by Design (QbD), which emphasises systematic product and process understanding during drug development. Regulatory guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, particularly ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, ICH Q10 Pharmaceutical Quality System, and ICH Q11 Development and Manufacture of Drug Substances, encourage the implementation of QbD principles in both drug substance synthesis and formulation development. In parallel, the concept of Analytical Quality by Design (AQbD) has emerged to improve the robustness and reliability of analytical methods throughout their lifecycle. AQbD involves defining an Analytical Target Profile (ATP), identifying Critical Quality Attributes (CQAs), performing risk assessment, and optimizing analytical parameters using Design of Experiments (DoE). This approach helps establish a Method Operable Design Region (MODR) and implement an effective control strategy for consistent analytical performance. The simultaneous application of QbD and AQbD in API synthesis and analytical method development enhances process understanding, minimizes risks, and supports regulatory expectations. Ultimately, these approaches

contribute to the development of high- quality pharmaceutical products and facilitate continuous improvement in pharmaceutical manufacturing.

KEYWORDS: Analytical Quality by Design (AQbD); Analytical Target Profile (ATP); Design of Experiments (DoE); Method Operable Design Region (MODR); Critical Method Parameters (CMP); Lifecycle Management; Quality Risk Management; Analytical Method Validation.

1. INTRODUCTION[1-10]

The concept of Quality by Design (QbD) was first introduced by the renowned quality expert Joseph M. Juran, who emphasized that quality should be designed into a product rather than tested into it. According to Juran's philosophy, most quality problems arise from inadequate product design and insufficient understanding of the manufacturing process. Therefore, quality must be built into the product during the development stage through systematic planning and scientific understanding. Juran's principles, described in his influential work Juran on Quality by Design, have been widely applied across various industries, including automotive and manufacturing, and have more recently been adopted by the pharmaceutical sector.

In the pharmaceutical industry, the concept of QbD has gained significant importance as a strategy to improve product quality, safety, and efficacy. Regulatory authorities such as the United States Food and Drug Administration (USFDA) strongly encourage the use of risk-based and science-driven approaches during pharmaceutical development and manufacturing.

The FDA recognizes that product quality cannot be ensured solely by extensive end-product testing; instead, quality must be built into the product through robust process design, improved process understanding, and effective control strategies.

QbD is defined as a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding, as well as process control, based on sound scientific principles and quality risk management. This concept has been formally incorporated into regulatory guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), particularly ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, ICH Q10 Pharmaceutical Quality System, and ICH Q11 Development and Manufacture of Drug Substances. These guidelines provide a comprehensive framework for implementing QbD

principles in drug substance and drug product development.

One of the key components of the QbD approach is the application of statistical and experimental tools such as Design of Experiments (DoE) and Response Surface Methodology (RSM). These tools enable systematic investigation of the relationships between critical input variables and product quality attributes. Compared to traditional experimentation methods, where one factor is varied at a time, DoE allows simultaneous evaluation of multiple factors, resulting in more efficient data collection and improved process understanding. The use of DoE and RSM facilitates the establishment of a design space, within which the combination of input variables ensures consistent product quality and optimal process performance.

Furthermore, the knowledge and scientific understanding generated during development support the establishment of appropriate control strategies and risk management practices. By integrating QbD principles into pharmaceutical development, manufacturers can achieve greater process robustness, regulatory flexibility, and continuous improvement in product quality. The differences between the traditional development approach and the QbD-based approach are commonly highlighted to demonstrate the advantages of systematic and science-driven product development.

Traditional Approach vs QbD Approach Table1.

Aspect	Traditional Approach	QbD Approach
Development strategy	Empirical, trial-and-error approach	Systematic and science-based approach
Quality concept	Quality tested in final product	Quality built into product and process
Process understanding	Limited understanding of process variables	Extensive understanding of process and product
Risk management	Minimal risk assessment	Structured risk assessment and management

Aspect	Traditional Approach	QbD Approach
Experimental design	One-factor-at-a-time experiments	Statistical tools such as Design of Experiments (DoE)
Process control	Fixed operating conditions	Flexible operation within design space
Regulatory flexibility	Limited flexibility for changes	Greater regulatory flexibility if within design space
Product robustness	Less robust processes	Robust and reliable processes
Data utilization	Limited data analysis	Multivariate data analysis and modeling
Lifecycle management	Minimal lifecycle monitoring	Continuous Improvement and lifecycle management

2. Flow Diagram of QbD Steps[11-16]

Define Quality Target Product Profile (QTPP)

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Identify Critical Quality Attributes (CQAs)

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Risk Assessment and Identification of Critical Variables

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Design of Experiments (DoE) for Process Optimization

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Establish Design Space

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Develop Control Strategy

↓

Process Validation

↓

Lifecycle Management and Continuous Improvement

3. QbD Tools for Synthetic Development and Analytical Development[17-20]

The application of Quality by Design (QbD) in pharmaceutical development involves the use of systematic scientific and statistical tools to ensure product quality and process robustness.

These tools are applied during both drug substance (synthetic) development and analytical method development to achieve better process understanding, risk control, and regulatory compliance. The integration of QbD tools improves product quality, reduces variability, and facilitates continuous improvement throughout the product lifecycle.

3.1 QbD Tools in Synthetic (API) Development

During active pharmaceutical ingredient (API) synthesis, QbD tools help identify critical process parameters and optimize reaction conditions to ensure consistent product quality.

Quality Target Product Profile (QTPP)

The QTPP defines the desired characteristics of the final pharmaceutical product, including dosage form, strength, purity, stability, and safety.

Critical Quality Attributes (CQAs)

CQAs are the physical, chemical, biological, or microbiological properties that must be controlled within defined limits to ensure product quality.

Risk Assessment

Risk assessment tools are used to identify and prioritize variables that may affect CQAs. Common tools include

- Failure Mode and Effects Analysis (FMEA)
- Ishikawa (Fishbone) diagram
- Risk ranking and filtering

These tools help identify **critical process parameters (CPPs)** that significantly influence product quality.

Design of Experiments (DoE)

Design of Experiments (DoE) is a statistical approach used to evaluate the effects of multiple process variables simultaneously. It allows optimization of reaction conditions such as temperature, pH, solvent composition, and reaction time.

Design Space

Design space represents the multidimensional combination of input variables and process parameters that ensure product quality. Operation within the design space provides regulatory flexibility.

Control Strategy

A control strategy is developed to maintain process performance and product quality through monitoring and controlling critical parameters during manufacturing.

3.1 QbD Tools in Analytical Development

The concept of Analytical Quality by Design (AQbD) applies QbD principles to analytical method development to ensure reliable and robust analytical procedures.

Analytical Target Profile (ATP)

ATP defines the performance requirements of the analytical method, such as accuracy, precision, sensitivity, and specificity.

Identification of Analytical CQAs

Analytical CQAs refer to parameters that influence the reliability of analytical results, such as resolution, retention time, and signal-to-noise ratio.

Risk Assessment

Risk assessment is used to identify critical analytical method variables such as

- Mobile phase composition
- Column type
- Flow rate
- Detection wavelength

Method Optimization using DoE

Statistical tools such as DoE are used to evaluate the impact of analytical variables and optimize chromatographic conditions.

Method Operable Design Region (MODR)

MODR defines the range of analytical parameters within which the method performs reliably and produces acceptable results.

Control Strategy and Method Validation

A control strategy is established to ensure consistent analytical performance, followed by validation of the method according to regulatory guidelines.

Continuous Method Monitoring

Continuous monitoring ensures long-term method robustness and supports lifecycle management of analytical procedures.

3.1.1 Quality Target Product Profile (QTPP)[21-22]

The Quality Target Product Profile (QTPP) is a fundamental element of the Quality by Design (QbD) approach in pharmaceutical development. QTPP represents a prospective summary of the quality characteristics that a drug product should possess to ensure the desired quality, safety, and efficacy. It serves as the foundation for identifying critical quality attributes and guiding the development of a robust pharmaceutical product and manufacturing process.

QTPP includes key attributes related to the final drug product, such as dosage form, route of administration, strength, purity, stability, pharmacokinetic characteristics, and therapeutic

performance. These attributes are defined early in the product development stage based on clinical requirements, regulatory expectations, and patient needs. Establishing a well-defined QTPP helps ensure that the product consistently meets its intended performance throughout its lifecycle.

Within the QbD framework, the QTPP guides the identification of Critical Quality Attributes (CQAs), which are the physical, chemical, biological, or microbiological properties that must be controlled within specified limits to achieve the desired product quality. By clearly defining QTPP, pharmaceutical scientists can systematically evaluate the relationship between formulation variables, process parameters, and product quality.

Regulatory guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, particularly ICH Q8(R2) Pharmaceutical Development, emphasize the importance of defining QTPP during pharmaceutical development. A well-established QTPP enables a more structured and risk-based development strategy, facilitates regulatory flexibility, and supports continuous improvement in product quality.

Example Elements of QTPP

QTPP Element	Description
Dosage form	Tablet, capsule, injection, etc.
Route of administration	Oral, intravenous, topical, etc.
Strength	Amount of active pharmaceutical ingredient
Stability	Shelf life and storage conditions
Purity	Acceptable impurity limits
Release profile	Immediate or controlled drug release

3.1.2 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) for analytical methods encompass both method characteristics and method parameters that influence the accuracy, precision, and reliability of the results. The specific CQAs vary depending on the analytical technique employed. For instance

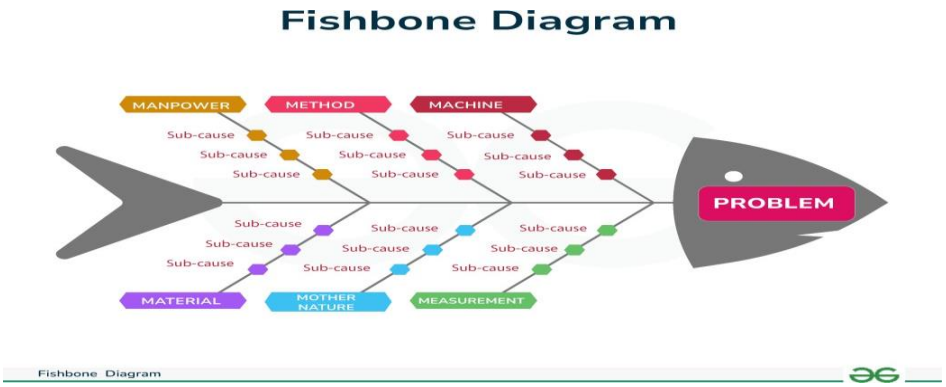
- **HPLC (UV or RID)**: Key CQAs include mobile phase composition and buffer, pH, choice of diluent, column type, organic modifier, and the elution program.
- **GC**: Important CQAs include carrier gas flow rate, oven temperature and programming, injector temperature, sample diluent, and sample concentration.

- **HPTLC**: Relevant CQAs include the type of TLC plate, mobile phase, sample concentration and volume, plate development time, color development reagents, and detection method.

The nature of the drug substance (DS) and potential impurities also influences analytical CQAs. Factors such as solubility, pH, polarity, presence of charged functional groups, boiling point, and solution stability must be considered during method development.

3.1.3 Risk Assessment

Risk assessment is a science-based process within quality risk management that helps identify critical material attributes and method parameters impacting the Analytical Target Profile (ATP). In the context of Analytical Quality by Design (AQbD), risk assessment is applied from the earliest stages of method development and continues through continuous method monitoring. The AQb D framework emphasizes early identification of potential risks, followed by the implementation of appropriate mitigation strategies and control measures to ensure reliable and consistent analytical performance. Tools commonly used for risk identification and evaluation include the Ishikawa (fishbone) diagram, which provides a structured visual representation of potential sources of variability affecting analytical procedures.



3.1.4 Design of Experiments (DoE)[23-25]

Design of Experiments (DoE) is a statistical tool widely used in Quality by Design (QbD) and Analytical Quality by Design (AQbD) to systematically study the relationship between input variables and output responses. Unlike traditional one-factor-at-a-time experiments, DoE allows multiple factors to be varied simultaneously, providing a more efficient and comprehensive understanding of the process or analytical method.

In pharmaceutical development, DoE is used to

1. Identify critical factors: Determine which process parameters or method variables significantly affect product quality or analytical performance.
2. Optimize conditions: Find the optimal combination of variables to achieve the desired quality attributes.
3. Establish design space: Define the multidimensional range of parameters where the process or method consistently produces acceptable results.
4. Support risk management: Quantitatively evaluate the effect of variability in input parameters on product performance and method reliability.

Common DoE approaches include

- Full factorial designs: Study all possible combinations of selected factors.
- Fractional factorial designs: Examine a subset of combinations to reduce experimental runs while still identifying critical factors.
- Response surface methodology (RSM): Model and optimize responses when relationships between factors are nonlinear.
- Plackett–Burman design: Screen a large number of factors to identify the most influential ones.

In AQbD, DoE is crucial for method development and optimization, as it helps define the Method Operable Design Region (MODR) and ensures the analytical method is robust, reproducible, and capable of consistently delivering reliable results.

3.1.5 Design Space (26-28)

The Design Space is a core concept in Quality by Design (QbD) that defines the multidimensional combination of input variables (e.g., process parameters, formulation factors) and their ranges that have been demonstrated to consistently ensure the desired product quality. Operating within this space provides flexibility in manufacturing or analytical processes without compromising quality, while movements outside the design space may require regulatory notification.

In pharmaceutical development, the design space is established using knowledge gained from experimental studies, risk assessments, and statistical tools such as Design of Experiments (DoE) and Response Surface Methodology (RSM). By systematically evaluating the effect of critical process parameters (CPPs) on critical quality attributes (CQAs), developers can

determine the safe and effective operating ranges that yield a robust and reproducible product. For analytical method development (AQbD), the design space is referred to as the Method Operable Design Region (MODR). The MODR defines the acceptable ranges of analytical method parameters (e.g., mobile phase composition, pH, flow rate, temperature) within which the method remains robust, accurate, precise, and reliable. Establishing a MODR ensures that small, intentional variations in method parameters do not negatively impact analytical performance, supporting consistent and regulatory-compliant results.

Key advantages of defining a design space include

- Provides operational flexibility and reduces the need for regulatory post-approval changes.
- Enhances process understanding and control.
- Supports robust, reproducible, and high-quality products and analytical methods.
- Integrates seamlessly with risk assessment and control strategies.

3.1.6 Control Strategy[29-31]

A Control Strategy is a planned set of controls, derived from product and process understanding, that ensures a pharmaceutical product or analytical method consistently meets predefined quality requirements. In the context of Quality by Design (QbD) and Analytical Quality by Design (AQbD), a control strategy integrates knowledge from Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), risk assessments, and experimental studies to manage variability and maintain product quality throughout its lifecycle.

The key components of a control strategy include

1. Input Material Controls: Specifications and quality checks for raw materials, excipients, and reagents.
2. Process Controls: Monitoring and adjustment of critical process parameters to ensure product quality.
3. In-Process Controls: Real-time checks during manufacturing or analytical procedures to detect deviations early.
4. Analytical Controls: Validated methods to ensure the quality, purity, and potency of the product or sample.
5. Finished Product Controls: Final product testing to confirm that quality objectives are met.
6. Continuous Monitoring: Ongoing observation and evaluation to detect trends, support

continuous improvement, and ensure regulatory compliance.

In AQbD, the control strategy is closely linked to the Method Operable Design Region (MODR). By defining acceptable operating ranges for analytical method parameters and monitoring them, the control strategy ensures that the analytical method performs reliably under routine conditions.

A robust control strategy minimizes risk, ensures process consistency, and supports regulatory flexibility, allowing adjustments within the design space without the need for post-approval submissions. This aligns with the principles of risk-based pharmaceutical development, enhancing overall product and analytical method quality.

3.1.1 Analytical Target Profile (ATP)[32-34]

The Analytical Target Profile (ATP) is the cornerstone of Analytical Quality by Design (AQbD). It defines the intended purpose and performance requirements of an analytical method, analogous to the Quality Target Product Profile (QTPP) in product development. By clearly specifying the ATP, pharmaceutical scientists can ensure that the analytical method is designed to produce reliable, accurate, and reproducible results that support product quality, safety, and efficacy.

The ATP typically includes key performance characteristics, such as:

- Accuracy: The closeness of measured values to the true value.
- Precision: The degree of repeatability or reproducibility under normal operating conditions.
- Specificity/Selectivity: The ability to measure the analyte of interest in the presence of other components, such as impurities, excipients, or matrix components.
- Sensitivity/Detection Limit: The lowest amount of analyte that can be reliably detected or quantified.
- Range: The concentration span over which the method provides accurate and precise results.
- Robustness: The method's ability to remain unaffected by small, deliberate variations in parameters.

Defining the ATP at the outset provides a clear framework for method development, risk assessment, and optimization. It guides the selection of method type (e.g., HPLC, GC,

HPTLC), critical method parameters, and critical analytical attributes, ensuring that the analytical method meets regulatory expectations and supports lifecycle management.

A well-defined ATP also facilitates

- Systematic identification of Critical Quality Attributes (CQAs) for the analytical method.
- Efficient risk-based method development.
- Establishment of the Method Operable Design Region (MODR).
- Implementation of a robust control strategy to ensure consistent analytical performance.

3.1.2 Identification of Analytical CQAs[35]

Critical Quality Attributes (CQAs) in analytical methods are the physical, chemical, or performance characteristics that must be controlled to ensure the Analytical Target Profile (ATP) is consistently achieved. CQAs vary depending on the analytical technique (HPLC, GC, HPTLC, etc.) and the nature of the analyte or drug substance. Examples include resolution, retention time, peak symmetry, signal-to-noise ratio, detection wavelength, and sample stability. Identification of analytical CQAs provides the foundation for risk assessment, method optimization, and development of a robust analytical procedure.

3.1.3 Risk Assessment[36-37]

Risk assessment is a systematic, science-based process to identify factors that may impact analytical method performance. Within AQbD, risk assessment begins in the early stages of method development and continues throughout the lifecycle of the method. Tools such as Ishikawa (fishbone) diagrams, FMEA (Failure Mode and Effects Analysis), and risk ranking are commonly used to prioritize method parameters and material attributes that could affect CQAs. This process informs the design of experiments and control strategy.

3.1.4 Method Optimization using DoE[38-39]

Design of Experiments (DoE) is applied to systematically evaluate the effect of multiple analytical variables on method performance. DoE allows simultaneous assessment of factors such as mobile phase composition, pH, column type, flow rate, and temperature, thereby optimizing method conditions with fewer experiments. Techniques like factorial designs, fractional factorial designs, and response surface methodology (RSM) are commonly employed to identify optimal conditions and understand interactions among parameters.

3.1.5 Method Operable Design Region (MODR)[40-41]

The Method Operable Design Region (MODR) defines the multidimensional range of analytical method parameters within which the method consistently meets the ATP requirements. MODR is established based on DoE studies and risk assessments and ensures method robustness under routine variations. Operating within MODR provides regulatory flexibility, while operations outside this region may require additional validation or regulatory notification.

3.1.6 Control Strategy and Method Validation[44-46]

A control strategy is a systematic set of measures designed based on the nature of the analyte and the understanding gained from the Method Operable Design Region (MODR). In the context of Analytical Quality by Design (AQbD), a method control strategy is established using comprehensive statistical data obtained from Design of Experiments (DoE) and MODR studies. These data allow the correlation of method parameters with analyte attributes, ensuring that the method consistently meets the Analytical Target Profile (ATP) requirements.

The control strategy addresses potential variability in method parameters, such as reagent grade, instrument type or brand, and column selection. While the overall concept of method control is not drastically different from traditional approaches, AQbD enhances its robustness by grounding controls in experimentally derived data from CQAs, DoE, and MODR. This establishes a stronger, science-based link between the analytical method's purpose and its performance, ultimately supporting reliable and reproducible results.

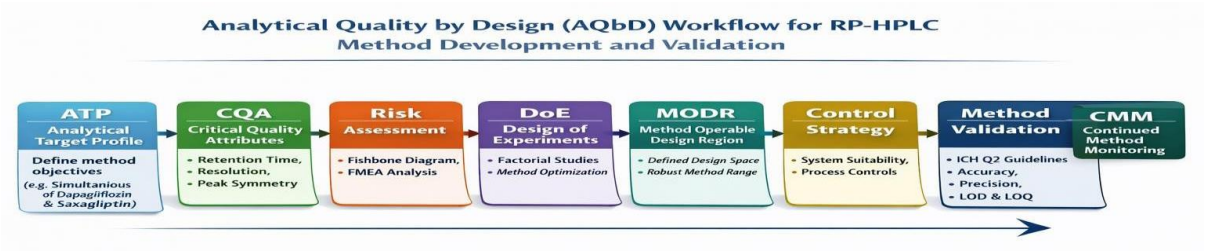
In the AQbD framework, method validation involves verifying the analytical method across a range of different batches of the active pharmaceutical ingredient (API). This approach leverages knowledge from Design of Experiments (DoE) and the Method Operable Design Region (MODR) to design validation studies that accommodate manufacturing changes without requiring complete revalidation. By integrating statistical and experimental insights, this method ensures compliance with ICH validation requirements while also providing information on factor interactions, measurement uncertainty, control strategy, and opportunities for continuous improvement. Compared to traditional validation methods, the AQbD-based approach is more resource-efficient while maintaining robust analytical quality and reliability.

3.1.7 Continuous Method Monitoring[42-43]

Lifecycle management serves as a control strategy for implementing the design space during the commercial stage of a product. Within the framework of Analytical Quality by Design (AQbD), Continuous Method Monitoring (CMM) represents the final step of the analytical method lifecycle. CMM is a systematic and ongoing process that leverages the knowledge gained during method development and the implementation of the design space. This includes the results of risk assessments, prior knowledge, statistical design considerations, and the integration of the Design Space, Method Operable Design Region (MODR), control strategy, Critical Quality Attributes (CQAs), and Analytical Target Profile (ATP).

Once an analytical method has been validated, it can be applied for routine use, while its performance is continuously monitored. CMM can be conducted using control charts, system suitability tracking, method-related investigations, and other monitoring tools. This proactive monitoring allows analysts to detect and address any out-of-trend performance before it impacts data quality.

Advantages and Recommendations: AQbD shifts analytical development from reactive troubleshooting to proactive failure prevention. The type and depth of risk assessment should be aligned with the stage of the project within the development timeline. Successful implementation of AQbD depends on proper planning, timely application of appropriate tools, and efficient execution of tasks. Applying risk assessment strategically helps prevent method failures, enhances understanding of the design space, and strengthens the overall control strategy.



4. CONCLUSION

Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of AQbD is the understanding from product development to commercial production. Scientists can easily identify the risk initially so that quality can be increased. AQbD tools are ATP, CQA, Method Optimization and Development

with DoE, MODR, and Control Strategy with Risk Assessment, Method validation and Continuous Method Monitoring (CMM), and continuous improvement. AQbD requires the right ATP and Risk Assessment and usage of right tools and performing the appropriate quantity of work within proper timelines. The use of Analytical Quality by Design (AQbD) provides a systematic, scientific, and risk-based approach for the development and optimization of analytical methods. It helps in clearly defining the Analytical Target Profile (ATP), identifying Critical Quality Attributes (CQAs), and understanding the influence of different method parameters on analytical performance. Through tools such as risk assessment and Design of Experiments (DoE), AQbD allows efficient optimization of chromatographic conditions and establishment of a Method Operable Design Region (MODR). This ensures that the analytical method remains robust, reliable, and reproducible under defined operating conditions. In addition, AQbD supports method validation and continuous monitoring in accordance with guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ensuring regulatory compliance and consistent analytical quality throughout the method lifecycle. Overall, the implementation of AQbD leads to better method understanding, improved robustness, reduced method failure, and enhanced quality assurance in pharmaceutical analysis.

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