ANALYTICAL QUALITY BY DESIGN

Abstract

Analytical development is considered as an integral part of the pharmaceutical product life-cycle, where establishment of an effective, cost-effective, robust, sensitive, and specific analytical methods are always required for analysis of drug(s), degradation product(s), and impurities in dosage forms. As analytical method development involves a series of factors that are critically responsible for attributing variability in the method performance; thus implication of systematic analytical development practices such as quality by design (QbD) is very useful for optimizing the method performance. Analytical QbD has demonstrated high fruition for reducing the variability, attaining high robustness and performance throughout the product life-cycle including method development, validation, and transfer stages. It has huge applicability in the analysis of pharmaceutical substance using for various types of procedures such as spectrophotometry, liquid chromatography, gas chromatography, nondestructive techniques, and many more. The present chapter aims to provide an introductory review on analytical QbD, and various applications in the development of analytical methods.

Keywords: Analytical development, pharmaceutical product life-cycle, analysis of drug(s), degradation product(s), and impurities

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I. INTRODUCTION

The International Conference on Harmonization (ICH) defines "QbD as a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to gain product and process understanding and ultimately process control". Principles of QbD can be implemented in development of analytical procedure. QbD transforms into AQbD, i.e. Analytical quality-by-design. The product designed to meet patients need and intended product performance, QbD is systematic approach to development of product or development of analytical test method. Degree of regulatory flexibility is expected with high level of scientific knowledge generated during development.

The AQbD process includes, define analytical target profile (ATP), identification of critical quality attributes (CQA), initial risk assessment, chromatographic development, Design of experiments (DoE), Method operable design region (MODR), final risk assessment with control strategy, method validation and life cycle management like continuous method monitoring**.**

II. ANALYTICAL QUALITY BY DESIGN

AQbD is a systematic approach used in the pharmaceutical industry to ensure the quality and reliability of analytical methods and procedures throughout the product lifecycle. It is a concept derived from the broader Quality by Design (QbD) principles, which aim to build quality into the product development process.

Analytical Quality-by-Design The AQbD evolvement in the pharmaceutical industry has been seen from its wide implementation. The global regulatory community already understands the importance and ICH proposed new regulatory guideline "Q14 Analytical procedure development" and this guideline will be released soon for public opinion. Up to now most of analytical procedures were based on one factor at a time (OFAT). In OFAT, one parameter alone is adjusted and other factors were kept constant. This practice gives narrow robust behavior of test procedure. Therefore, usual OFAT has high risk in analytical method failure. It may require a revalidation or partial method validation program. AQbD application in method development 3 stress the organized way of development through unassailable decision-making. Important benefits of AQbD are highly robust methods, which endure long-term usage by quality control laboratories with reduced chance of failure. More scientific knowledge will be gained in complex method development (such as UPLC, HPLC, LC–MS/MS etc.). Since many parameters need to be optimized in analytical method development, DoE supports to achieve the goal. Hence it is encouragement to implement the DoE with risk assessment tools, the analytical chemists to ride over critical peak separation during method development. This research assesses AQbD technique using the statistical DoE to demonstrate the strength of analytical tools for estimating the drugs and impurities in their formulations using RP-HPLC methods.

1. Outline of important benefits of implementing AQbD

- Ensures quality of results of analytical method through risk assessment
- Reduces the variations in critical quality attributes
- No OOS or OOT results

- Strengthen the understand of analysis of drug substances and drug product
- No revalidation within design space
- Easy method transfer
- Lifecycle approach.

III. IMPORTANCE OF AQBD

The importance of Analytical Quality by Design (AQbD) lies in its ability to enhance the quality, reliability, and efficiency of analytical methods throughout their lifecycle. Following are reasons which make AQbD important:

1. **Science-based Approach:** AQbD promotes a science-based approach to method development, optimization, and control. It emphasizes understanding the fundamental relationships between critical method parameters (CMPs), critical quality attributes (CQAs), and method performance. By applying scientific principles and statistical tools, AQbD helps develop a deep understanding of the analytical method, leading to more robust and reliable results.

2. **Risk Mitigation:** AQbD incorporates risk assessment techniques to identify and manage potential risks associated with analytical methods. By systematically evaluating and controlling CMPs, sample matrix effects, instrument variability, and other factors, AQbD helps mitigate risks that can impact method performance and result accuracy. This proactive risk management approach enhances data integrity and supports regulatory compliance

3. **Enhanced Method Performance:** AQbD facilitates the optimization of analytical methods by considering multiple factors simultaneously. Design of Experiments (DoE) allows for efficient exploration of the design space and identification of the optimal combination of CMPs. By optimizing method conditions and reducing sources of variability, AQbD improves method performance, including accuracy, precision, selectivity, sensitivity, and robustness.

4. **Increased Efficiency and Productivity:** AQbD streamlines method development and optimization by providing a systematic and structured approach. It helps in identifying critical factors and optimizing their settings, reducing the number of experiments required, and avoiding trial-and-error approaches. The use of statistical tools and modeling techniques enables efficient data analysis and decision-making, saving time and resources.

5. **Better Understanding of Analytical Methods:** AQbD encourages a deeper understanding of analytical methods and their underlying principles. By focusing on the relationship between CMPs and CQAs, scientists gain insights into the method's limitations, sources of variability, and potential failure modes. This understanding enables more effective troubleshooting, method transfer, and method lifecycle management.

6. **Regulatory Compliance:** AQbD aligns with regulatory expectations and requirements for method development, validation, and control. It emphasizes a thorough and systematic approach to method optimization, validation, and ongoing monitoring. AQbD provides a

transparent and well-documented process that supports regulatory submissions, inspections, and compliance with current Good Manufacturing Practices (cGMP) and other quality standards.

7. **Continuous Improvement:** AQbD promotes a culture of continuous improvement in analytical laboratories. By implementing AQbD principles, laboratories can continuously monitor and assess method performance, identify areas for optimization, and proactively address potential issues. This leads to a cycle of learning and improvement, ensuring that methods evolve and remain effective over time.

Overall, AQbD is important for achieving reliable, robust, and efficient analytical methods. It brings together scientific principles, risk assessment, statistical techniques, and quality control to optimize method performance, enhance data integrity, and support regulatory compliance. By adopting AQbD, analytical laboratories can improve the quality of their analytical results, increase productivity, and drive continuous improvement in their operations.

Table 1: Conventional method development Vs AQbD

Parameter	**Conventional method development**	**AQbD**
Approach to the method development	Factual	Systematic
Assurance of product quality	Final testing	Built into the method/product
Issues in regular QC analysis	Out of specification or Out of trend	No such issues.
Specifications setting	Previous knowledge	Analytical target profile
Flexibility to regulatory submission	Fixed and modification not allowed	Flexible within operable design region.
Benefit for implementation	Narrow	Robust and no revalidation

IV. LIFE CYCLE OF AQBD

AQbD is broad life-cycle approach to method development that uses DoE, quality risk management tools and statistics but is not limited to statistics and effectively identifies the critical method parameters and their subsequent effect on method performance. Defined critical method parameters are captured as controlled strategy and design space of the method to minimize the method related issues during implementation.

- The method is designed to meet predefined requirements and performance.
- To consistently meet critical method quality attributes.
- The impact of different materials and method parameters in quality of analytical method has identified by risk assessment tools.
- The process of performing the analysis is assessed and allowed for consistent quality over a period.

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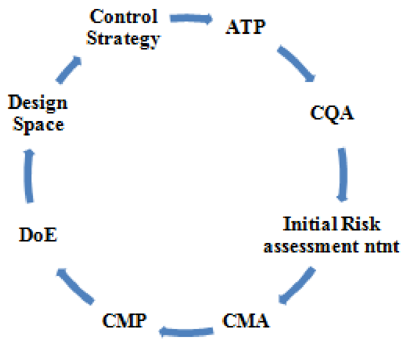
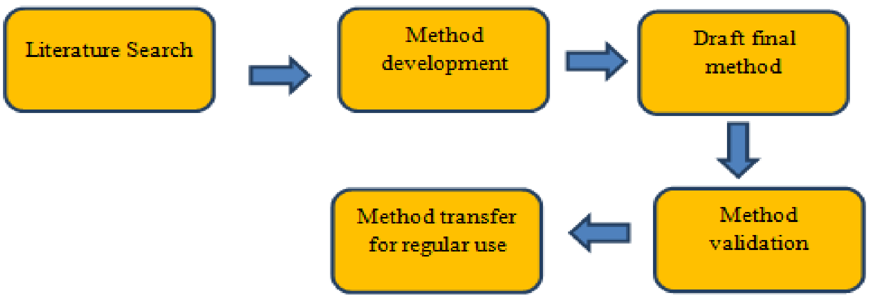
- Critical sources of analytical method variability are identified and suitably controlled by DoE experimentation.
- Developing of appropriate control strategies and captured in the analytical testing procedures along with design space of the method.

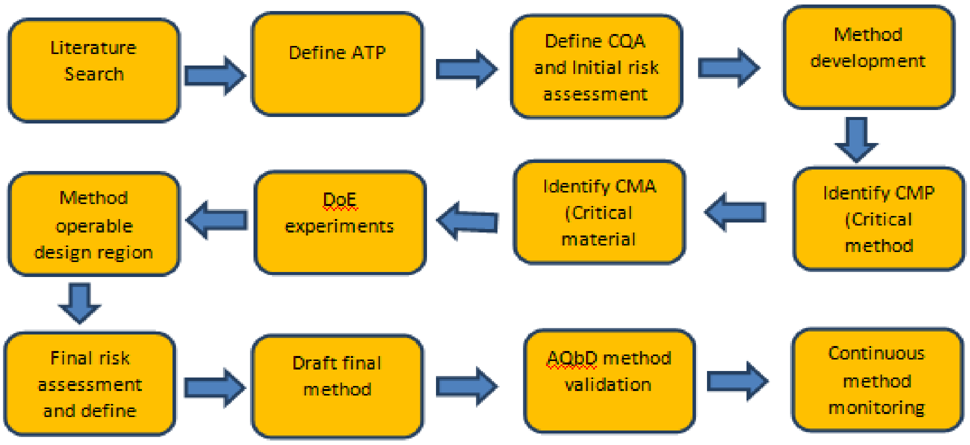
Life Cycle of AQbD



Conventional Method Development and Validation Process



AQbD method development and validation process



The main goal of AQbD is to understand and control the sources of variability in analytical methods, thereby ensuring the accuracy, precision, and robustness of the data generated. It involves a proactive and science-based approach that focuses on method development, optimization, and validation, with an emphasis on risk assessment and management.

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V. ANALYTICAL QUALITY BY DESIGN INCLUDE

1. **Analytical Target Profile (ATP):** This defines the analytical requirements and performance criteria for a specific measurement. It includes factors such as accuracy, precision, detection limits, and measurement range.
2. **Risk Assessment:** This involves identifying and evaluating potential sources of variability and uncertainty in the analytical method. Risk assessment tools, such as Failure Mode and Effect Analysis (FMEA) or Fishbone diagrams, are often used to identify critical process parameters (CPPs) and critical method attributes (CMAs).
3. **Design of Experiments (DoE):** DoE is used to systematically evaluate the effects of different factors (e.g., method parameters, sample characteristics) on the analytical method's performance. By varying these factors and analyzing the results, optimal method conditions can be identified and the robustness of the method can be assessed.
4. **Method Control Strategy:** This involves establishing appropriate controls and specifications for critical method parameters and attributes. It includes setting acceptance criteria, defining system suitability requirements, and establishing appropriate calibration and maintenance procedures.
5. **Method Validation:** AQbD encourages a more comprehensive approach to method validation, taking into account the range of operating conditions and sample characteristics that the method may encounter during routine use. The validation process should address all critical method attributes and ensure that the method is fit for its intended purpose.
6. **Continuous Improvement:** AQbD promotes an ongoing process of monitoring, analyzing, and improving the analytical method. This involves periodic method performance reviews, data trending analysis, and implementation of corrective and preventive actions when necessary.

By implementing Analytical Quality by Design principles, pharmaceutical companies can enhance the reliability and robustness of their analytical methods, leading to more accurate and consistent data. It also supports regulatory compliance and facilitates the development of more efficient and effective analytical processes.

VI. ANALYTICAL TARGET PROFILE (ATP)

The Analytical Target Profile (ATP) is a key component of the Analytical Quality by Design (AQbD) approach in pharmaceutical analysis. It is a systematic way of defining the desired performance characteristics and requirements for an analytical method or procedure.
The ATP provides a clear and concise description of the analytical method's intended purpose, including the target measurement parameters and the acceptable range of performance criteria. It serves as a communication tool between different stakeholders involved in the method development, optimization, and validation processes.

1. The ATP have following Components

- **Target Analyte**: It specifies the substance or analyte to be measured by the analytical method. This could be an active pharmaceutical ingredient (API), impurity, degradation product, or any other relevant component.

- **Measurement Parameters:** The ATP defines the specific parameters to be measured for the target analyte. This may include quantitative attributes such as concentration, purity, or assay potency, as well as qualitative attributes like identification or impurity profiling.
- **Performance Criteria:** The ATP establishes the acceptable range or limits for each measurement parameter. These criteria are usually based on regulatory requirements, pharmacopeial standards, or specific project needs. Performance criteria may include accuracy, precision, linearity, detection limits, quantification limits, robustness, and selectivity, among others.
- **Sample Matrix:** The ATP specifies the type of sample matrix or formulation in which the analytical method will be applied. Different matrices may have varying characteristics that can influence the performance of the method, such as complexity, interferences, and stability.
- **Method Attributes**: The ATP identifies any specific attributes or characteristics that the method should possess to fulfill its intended purpose. This could include factors like speed, simplicity, ruggedness, or compatibility with certain equipment or instruments.

By clearly defining the ATP, the method development team can have a shared understanding of the desired analytical performance. This helps guide the selection of appropriate method parameters, experimental design, and optimization strategies. Additionally, the ATP serves as a reference for method validation, allowing the evaluation of the method's performance against the predefined criteria.

Analytical Target Profile facilitates a systematic and risk-based approach to method development, ensuring that the analytical method is fit for its intended purpose and meets the required quality standards.

2. Example of an Analytical Target Profile (ATP) for a Hypothetical Assay

- **Analyte**: Drug X
- **Matrix:** Serum
- **Measurement Technique:** High Performance Liquid Chromatography (HPLC)
- Analytical Target Profile (ATP) for Drug X Assay:
- Target Measurement Range:
- **Lower Limit:** 5 ng/mL
- **Upper Limit:** 500 ng/mL
- **Accuracy:**
- Target Accuracy: ±10% of the true value
- **Precision:**
- **Intra-day Precision:** ≤ 5% relative standard deviation (RSD)
- Inter-day Precision: ≤ 10% RSD
- **Specificity:**
- The assay should be specific to Drug X and should not cross-react with any known impurities or closely related compounds.
- **Sensitivity:**
  Limit of Detection (LOD): ≤ 2 ng/mL
  Limit of Quantification (LOQ): ≤ 5 ng/mL

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- **Robustness:** The method should demonstrate robustness to small variations in key parameters, such as mobile phase composition, pH, column temperature, and flow rate.
- **Sample Stability:** The assay should demonstrate stability of the analyte in the serum matrix over a specified storage period and under relevant storage conditions.
- **Sample Throughput:** The method should be capable of analyzing a minimum of 50 samples per day with a reasonable turnaround time.
- **Method Suitability:** The method should be suitable for routine analysis in terms of ease of use, simplicity, and cost-effectiveness.
- **Data Integrity:** The method should produce reliable and reproducible data, with appropriate data handling and reporting procedures in place to ensure data integrity.

The ATP serves as a benchmark and defines the desired performance characteristics for the analytical method. It provides guidance during method development, optimization, and validation to ensure that the method meets the specified requirements for accuracy, precision, sensitivity, specificity, and other critical attributes. The ATP helps align the expectations of the method users and stakeholders and serves as a reference for assessing method performance and suitability.

VII. RISK ASSESSMENT

Risk assessment is a science-based, which is used in quality risk management process. It can identify criticality in the material attributes and method parameters. Risk assessment can be performed from initial stage of method development to life cycle of the project. Risk assessment is an integral part of the AQbD process.

1. **Overview of relative Risk ranking system:** Low Risk Broadly acceptable risk. No further investigation is needed. Medium Risk is acceptable. Further investigation may be needed in order to reduce the risk. High Risk is unacceptable. Further investigation is needed to reduce the risk.Risk assessment is a systematic process of identifying, analyzing, and evaluating potential risks or hazards associated with a system, process, or activity. In the context of Analytical Quality by Design (AQbD), risk assessment is an essential component used to identify and evaluate potential sources of variability and uncertainty in analytical methods. It helps to prioritize critical process parameters (CPPs) and critical method attributes (CMAs) that significantly impact the method's performance and reliability. The goal is to understand and control these risks to ensure accurate and consistent analytical results. Following are the steps involved in the risk assessment process:

- **Hazard Identification**: This step involves identifying potential risks or hazards associated with the analytical method. It includes considering factors such as method complexity, sample characteristics, instrument limitations, and potential sources of error or variability.

- **Risk Analysis**: Once the hazards are identified, a qualitative or quantitative analysis is conducted to assess the severity and likelihood of each risk. Severity refers to the potential impact of the risk on the method's performance or the quality of results. Likelihood assesses the probability of the risk occurrence.

- **Risk Evaluation:** The identified risks are evaluated based on the severity and likelihood analysis. This step helps prioritize risks by determining their significance and determining which ones require further attention and mitigation.

- **Risk Control:** In this step, strategies and measures are developed to mitigate or control the identified risks. This may involve process optimization, method modifications, improved instrumentation, enhanced training, or the implementation of appropriate quality control measures. The aim is to reduce the likelihood or impact of the identified risks.

- **Risk Communication:** Effective communication of risks and their control measures is crucial to ensure that all stakeholders understand and take appropriate actions. This includes sharing risk assessment findings, discussing mitigation strategies, and promoting awareness of potential limitations and uncertainties in the analytical method.

- **Risk Review:** Risk assessment is an ongoing process, and periodic reviews should be conducted to reassess identified risks, evaluate the effectiveness of control measures, and identify new risks that may arise due to changes in the system, process, or regulatory requirements.

- By conducting a systematic risk assessment, analytical laboratories can identify and address potential sources of variability and uncertainty in their methods. This helps to improve method robustness, accuracy, and reliability, leading to consistent and high-quality analytical results. Additionally, risk assessment supports compliance with regulatory requirements and enhances overall laboratory quality management systems.

2. Risk Assessment Parameters

Critical Quality Attributes (CQAs) [22-24]

Critical Quality Attributes (CQAs) are the measurable physical, chemical, biological, or microbiological characteristics of a product or process that directly impact its quality and performance. CQAs are determined based on the intended use of the product and the expectations of the patient or end-user. They are essential in ensuring the safety, efficacy, and quality of pharmaceuticals, biologics, medical devices, and other regulated products.

3. CQAs includes following

- **Definition:** CQAs are specific attributes or characteristics of a product that are critical for ensuring its desired quality and performance. They are typically identified through scientific knowledge, prior experience, and risk assessment. CQAs can include parameters related to the product's identity, strength, purity, stability, dissolution, potency, content uniformity, particle size distribution, microbiological contamination, and other relevant aspects.

- **Relationship to patient safety and efficacy:** CQAs directly impact the safety and efficacy of a product. They are linked to the product's intended therapeutic effect, its ability to meet patient needs, and its potential to cause harm if not controlled within acceptable lim-

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its. CQAs should be identified and controlled throughout the product's lifecycle, from development to manufacturing and beyond.

- **Determination and control**: CQAs are identified through a combination of scientific understanding, regulatory requirements, and patient needs. They are established based on a comprehensive understanding of the product's critical quality attributes, their impact on safety and efficacy, and the available analytical methods for their measurement and control. Once identified, CQAs are monitored and controlled throughout the manufacturing process to ensure product quality and consistency.

- **Relationship to Critical Process Parameters (CPPs):** CQAs are often influenced by Critical Process Parameters (CPPs), which are the key variables or parameters of a manufacturing process that need to be controlled within defined limits to ensure product quality. Understanding the relationship between CPPs and CQAs is crucial for process optimization and control. By controlling the CPPs, manufacturers can achieve the desired CQAs consistently.

- **Analytical methods and specifications:** CQAs are typically measured using validated analytical methods that are specific, accurate, precise, and reliable. Specifications are established for each CQA to define acceptable limits or ranges. These specifications are often based on regulatory guidelines, pharmacopoeial standards, and product-specific requirements.

- **Control strategy and risk assessment**: CQAs are an integral part of the control strategy for a product. The control strategy outlines the measures, procedures, and tests that ensure the product meets the defined CQAs. Risk assessment is performed to identify the potential risks to CQAs and develop appropriate control measures.

- **Impact on regulatory compliance**: CQAs play a critical role in regulatory compliance. Regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), require manufacturers to identify and control CQAs as part of their quality systems. Demonstrating control over CQAs is essential for product approval, regulatory submissions, and compliance with Good Manufacturing Practices (GMP) guidelines.

- By identifying and controlling CQAs, manufacturers can ensure the quality, safety, and efficacy of their products. CQAs serve as the foundation for quality control, process optimization, and continuous improvement throughout the product's lifecycle.

4. Following are some examples of critical quality attributes (CQAs) for analytical methods

- **Accuracy**: The closeness of the measured value to the true or reference value. It indicates the method's ability to provide results that are free from systematic or constant errors.

- **Precision**: The degree of agreement among repeated measurements of the same sample. It measures the random or indeterminate variation in the results and reflects the method's reproducibility and repeatability.

- **Selectivity/Specificity:** The ability of the method to differentiate and measure the analyte of interest accurately in the presence of potential interferents or impurities. It ensures that the method responds selectively to the analyte without interference from other components.

- **Sensitivity**: The ability of the method to detect and measure small changes in the analyte concentration. It relates to the lowest level of analyte that can be reliably quantified (limit of quantification) and the lowest level that can be detected but not necessarily quantified (limit of detection).

- **Linearity:** The ability of the method to provide a proportional response over a defined concentration range. It assesses whether the method exhibits a linear relationship between the analyte concentration and the measured response.

- **Robustness**: The method's ability to remain unaffected by small, deliberate variations in operating parameters such as temperature, pH, flow rate, or sample preparation conditions. It ensures that the method is reliable and reproducible under different experimental conditions.

- **Ruggedness**: The ability of the method to withstand and deliver reliable results when used by different analysts, on different instruments, or in different laboratories. It assesses the method's performance under varied operational conditions and personnel.

- **Stability:** The ability of the method to maintain consistent performance over time, including the stability of calibration standards, reagents, and sample matrices. It ensures that the method remains reliable during extended periods of use.

- **Repeatability/Reproducibility**: Repeatability refers to the precision obtained when the same analyst performs the same method under similar conditions. Reproducibility refers to the precision obtained when the method is performed by different analysts or in different laboratories. Both measures reflect the method's reliability and consistency.

- **Sample Throughput**: The capacity of the method to handle a specified number of samples within a defined time frame. It assesses the method's efficiency and practicality for routine analysis.

These are just a few examples of CQAs that are commonly considered in analytical methods. The specific CQAs relevant to a particular method may vary depending on the analyte, matrix, intended use, and regulatory requirements. It's important to identify and prioritize the CQAs based on the specific needs of the analytical method and its intended application.

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5. **Critical Method Parameter (CMPs)** : Critical Method Parameters (CMPs) are the key variables, factors, or conditions that significantly influence the performance, reliability, and quality of an analytical method. These parameters need to be carefully controlled within predefined limits to ensure accurate, precise, and reproducible analytical results. CMPs are essential for maintaining the validity and robustness of the method throughout its lifecycle.

   Following are the important points to understand about Critical Method Parameters

- **Identification:** The selection of CMPs is based on a thorough understanding of the analytical method and the factors that can affect its performance. CMPs are identified through a combination of scientific knowledge, method development studies, and risk assessment. They may include factors related to sample preparation, instrument settings, chromatographic conditions, reagents, and calibration standards.

- **Impact on Method Performance**: CMPs have a direct and significant impact on the performance of the analytical method. Variations or deviations in CMPs can lead to changes in the analytical results, affecting accuracy, precision, specificity, sensitivity, linearity, and other critical method attributes. By controlling CMPs, laboratories can ensure the method consistently produces reliable and valid results.

- **Control and Monitoring**: CMPs must be tightly controlled and monitored throughout the method's lifecycle. Well-defined standard operating procedures (SOPs) and control measures are established to ensure that CMPs remain within specified limits. Regular monitoring and verification of CMPs are performed during routine testing to ensure method performance and to detect any deviations.

- **Relationship to Critical Quality Attributes (CQAs)**: CMPs are closely related to Critical Quality Attributes (CQAs) of the product being analyzed. CQAs represent the key quality characteristics of the product, and the analytical method is designed to measure these attributes accurately. By controlling CMPs, the analytical method ensures that the CQAs are accurately measured and meet the predefined acceptance criteria.

- **Validation and Verification**: During method development and validation, the impact of CMPs on method performance is thoroughly evaluated. Validation experiments are conducted to demonstrate that the method is suitable for its intended purpose and that it can consistently produce accurate and reliable results. Ongoing verification of CMPs is performed during routine use to ensure method performance remains within acceptable limits.

- **Criticality Ranking:** Not all method parameters are equally critical to the method's performance. Criticality ranking helps prioritize and focus efforts on controlling the most influential parameters. Factors with a higher impact on method performance are considered more critical and receive greater attention during method development, validation, and routine use.

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- **Flexibility and Robustness**: While CMPs must be controlled within specific limits, some level of method flexibility and robustness is also desirable. Robust methods can tolerate small variations in CMPs without significantly affecting results. Flexibility allows analysts to adjust certain parameters within acceptable ranges without the need for extensive revalidation.

- By identifying and controlling Critical Method Parameters, analytical laboratories can ensure the reliability and validity of their analytical methods. This contributes to the overall quality of analytical data and supports regulatory compliance for various industries, such as pharmaceuticals, biotechnology, food and beverages, and environmental monitoring.

6. Critical Material Attributes (CMAs) [26-27]

Critical Material Attributes (CMAs) refer to the key characteristics or properties of raw materials, intermediates, or components that can significantly impact the quality, safety, and performance of a product. CMAs play a crucial role in ensuring the consistency and reliability of the manufacturing process and the final product. They are identified based on scientific knowledge, risk assessment, and the intended use of the material.

Critical Material Attributes: Includes

- **Definition:** CMAs are specific properties or characteristics of a material that have a direct impact on the quality, safety, efficacy, or performance of the product. CMAs can include attributes such as chemical composition, physical properties (e.g., particle size, shape, density), purity, stability, solubility, moisture content, microbial load, and other relevant factors.

- **Influence on Product Quality**: CMAs have a direct influence on product quality and performance. Variations or deviations in CMAs can result in variations in the product's characteristics, affecting its identity, strength, purity, stability, and other critical quality attributes. It is essential to control CMAs within predefined specifications to ensure consistent product quality.

- **Material Control Strategy**: CMAs are an integral part of the material control strategy within a quality management system. The control strategy outlines the measures, procedures, and tests used to ensure that materials meet the defined CMA specifications. It may include supplier qualification, material testing, incoming material inspection, sampling plans, and release criteria.

- **Material Characterization**: The characterization of materials involves the systematic assessment and understanding of their CMAs. This process includes analytical testing, physical measurements, and other relevant analyses to determine the material's attributes. Material characterization provides valuable information for assessing material suitability and establishing appropriate specifications.

- **Risk Assessment and Control:** CMAs are identified and controlled based on a risk-based approach. Risk assessment techniques, such as Failure Mode and Effects Analysis

(FMEA) or Hazard Analysis and Critical Control Points (HACCP), help identify and evaluate the potential risks associated with CMAs. Appropriate control measures, such as tighter specifications, supplier qualification programs, or additional testing, are implemented to mitigate these risks.

- **Supplier Qualification and Management**: CMAs can be influenced by factors such as raw material sourcing, manufacturing processes, and storage conditions. Supplier qualification and management programs play a vital role in ensuring the consistency and reliability of materials. Suppliers are evaluated based on their ability to meet defined CMA specifications, provide consistent quality, and adhere to good manufacturing practices.

- **Change Control and Impact Assessment:** Any changes related to CMAs, such as changes in raw material suppliers, manufacturing processes, or specifications, should be managed through a formal change control process. The impact of these changes on the product's quality, safety, and efficacy is assessed, and appropriate actions, including revalidation or requalification, are taken to ensure continued control over CMAs.
  By identifying, controlling, and monitoring Critical Material Attributes, manufacturers can ensure the consistency and reliability of their products. This helps to mitigate risks, meet regulatory requirements, and deliver high-quality products that meet the needs and expectations of patients and consumers.

VIII. DESIGN OF EXPERIMENTS (DoE)

Design of Experiments (DoE) is a systematic approach used to plan, conduct, and analyze experiments in order to understand and optimize complex systems or processes. DoE allows for the efficient gathering of information, identification of critical factors, and evaluation of their effects on the system or process under investigation.

1. The main objectives of DoE:

- **Efficient Data Collection:** DoE helps in designing experiments in a way that maximizes the information obtained from a minimum number of experiments. By systematically varying and controlling the factors of interest, DoE allows for the collection of data that can be analyzed to understand the relationship between the factors and the response variables.

- **Identification of Critical Factors**: DoE helps in identifying the factors that have a significant impact on the system or process performance. By analyzing the experimental data, it becomes possible to determine which factors are most influential and should be given more attention and control.

- **Evaluation of Factor Interactions:** DoE allows for the evaluation of interactions between different factors. Interactions occur when the combined effect of two or more factors differs from the sum of their individual effects. Understanding and quantifying these interactions is crucial for optimizing the system or process.

- **Optimization of System or Process Performance**: By using DoE, it is possible to find the optimal settings or conditions for the factors that will result in the best performance of the system or process. This optimization can be done based on desired response variables or by minimizing variability or other performance criteria.

2. There are various types of experimental designs that can be used in DoE, including

- **Full Factorial Design**: In this design, all possible combinations of the factor levels are tested. It provides a complete understanding of the factor effects and interactions but may require a large number of experiments.

- **Fractional Factorial Design**: This design allows for the testing of only a subset of the possible combinations of factor levels. It reduces the number of experiments required but provides an estimate of the main effects and a subset of the interactions.

- **Response Surface Design**: This design focuses on finding the optimal settings for the factors by fitting a mathematical model to the experimental data. It allows for the exploration of the factor space and the identification of the optimal conditions.

- **Taguchi design**: This design is often used for robust parameter design, where the goal is to find factor settings that are insensitive to sources of variability or noise. It involves testing a limited number of factor combinations and employs orthogonal arrays to reduce the number of experiments required.

The primary goal of DoE is to efficiently gather relevant information, identify critical factors or variables, and understand their effects on the system or process under investigation. By systematically varying and controlling these factors, DoE helps in optimizing and improving the performance, reliability, and robustness of analytical methods.

Following are important steps involved in the DoE process

- **Problem Definition and Objective Setting:** The first step is to clearly define the problem or objective of the experiment. This involves identifying the response or output variables to be measured and improved, as well as the critical factors or inputs that may influence the system or process.

- **Factor Selection and Level Determination**: In this step, the factors to be investigated are selected, and the specific levels or settings for each factor are determined. Factors can be categorical (e.g., different instruments or reagents) or continuous (e.g., temperature, pH), and they can have different levels or ranges to be explored.

- **Experimental Design**: Experimental design involves creating a plan or layout for conducting the experiments. There are various types of designs, such as full factorial, fractional factorial, response surface, or Taguchi designs, depending on the number of factors, levels, and available resources. The design should ensure an adequate exploration of the factor space while minimizing the number of experiments needed.

- **Data Collection and Analysis**: The experiments are conducted based on the designed plan, and data is collected for each combination of factor settings. Statistical analysis techniques, such as analysis of variance (ANOVA), regression analysis, or optimization algorithms, are applied to analyze the data and understand the relationships between factors and responses. This analysis helps in identifying significant factors, interactions, and optimal factor settings.

- **Model Development and Optimization**: Based on the data analysis, mathematical or empirical models are developed to describe the relationship between the factors and the responses. These models can be used for further optimization and prediction of responses under different conditions. Techniques like response surface methodology (RSM) or mixture designs can be employed for model development and optimization.

- **Validation and Implementation**: The developed models and optimized conditions are validated using additional experiments or data sets to ensure their accuracy and reliability. Once validated, the optimized conditions can be implemented in routine operations, and appropriate control strategies can be established.

By employing DoE, analytical scientists can efficiently explore and understand the effects of critical factors on analytical methods. This helps in identifying optimal method conditions, improving method robustness, and enhancing method performance and reliability. Moreover, DoE enables a scientific and data-driven approach to method development and optimization, reducing the reliance on trial-and-error approaches.

3. Method Operable Design Region (MODR)

Method Operable Design Region (MODR) is a concept used in the Analytical Quality by Design (AQbD) approach to define the acceptable range or design space for critical method parameters (CMPs) in an analytical method. It is an important aspect of method development and optimization.

The MODR represents the range of values within which the CMPs can be varied while still ensuring that the method provides reliable and valid results. It defines the operating conditions under which the method will consistently meet its performance requirements and produce accurate and precise analytical results.

Method Operable Design Region (MODR) include

- **Definition:** The MODR is a multidimensional space that encompasses the acceptable ranges or limits for the critical method parameters. These parameters may include factors such as mobile phase composition, column temperature, flow rate, injection volume, pH, and other relevant variables that influence method performance.

- **Determination:** The MODR is established through a systematic approach, including experimental design, data analysis, and statistical modeling. It involves conducting a series of experiments to evaluate the impact of the CMPs on method performance and identifying the ranges within which the method consistently meets predefined acceptance criteria.

- **Risk-based approach**: The MODR is determined based on a risk-based approach, considering factors such as critical quality attributes (CQAs) of the analyte, regulatory requirements, method robustness, and the intended use of the method. Risk assessment techniques, such as Design of Experiments (DoE) and Quality Risk Management (QRM), can be employed to identify and evaluate critical factors and their acceptable ranges.

- **Optimization and trade-offs**: The MODR allows for the optimization of the method by identifying the most favorable combination of CMPs that provides the desired analytical performance. It also helps in understanding potential trade-offs between different parameters and their impact on method robustness and reliability.

- **Control strategy:** The MODR forms an integral part of the control strategy for the analytical method. It guides the selection and control of critical method parameters during routine operation. By ensuring that the CMPs are maintained within the defined MODR, the method's performance and reliability can be assured.

- **Flexibility and adaptability**: The MODR provides some flexibility within its defined limits, allowing for minor adjustments of the critical method parameters without the need for extensive revalidation. This flexibility facilitates method transfer between laboratories or instruments while maintaining the method's performance.

It is important to note that the establishment of the MODR is typically part of the method development and optimization process. Once established, it serves as a guide for routine method operation, monitoring, and control. Monitoring and periodic verification of the CMPs within the MODR are necessary to ensure ongoing method performance and compliance with quality requirements.

Overall, the MODR is a tool used in the AQbD approach to define the acceptable range of critical method parameters and ensure reliable and robust analytical methods. It provides a scientific and systematic approach to method development, optimization, and control, leading to enhanced method performance and quality assurance.

IX. METHOD CONTROL STRATEGY

Method Control Strategy refers to a set of procedures, controls, and specifications implemented to ensure the ongoing performance, reliability, and compliance of an analytical method throughout its lifecycle. It is an essential component of the Analytical Quality by Design (AQbD) approach and is crucial for maintaining the quality and accuracy of analytical results.

The Method Control Strategy involves the following Key Elements

- **Critical Method Parameters (CMPs):** CMPs are the key parameters or variables that significantly influence the performance and reliability of the analytical method. These parameters are identified through risk assessment and design of experiments. The Method Control Strategy defines the acceptable ranges or limits for each CMP that ensure the method's accuracy, precision, and robustness.

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- **System Suitability**: System suitability tests are performed to evaluate the performance of the entire analytical system, including instruments, reagents, and sample preparation procedures. The Method Control Strategy specifies the criteria and acceptance limits for system suitability parameters, such as resolution, peak shape, retention time, and signal-to-noise ratio. Regular monitoring of system suitability ensures that the method is functioning within the defined control limits.

- **Calibration and Standardization**: The Method Control Strategy includes procedures for instrument calibration, standardization of reference materials, and calibration verification. It defines the frequency, techniques, and acceptance criteria for calibrating instruments and establishing traceability to reference standards. Regular calibration and verification activities ensure the accuracy and reliability of measurement results.

- **Quality Control Samples**: The use of quality control (QC) samples is an integral part of the Method Control Strategy. QC samples, prepared with known concentrations or properties, are analyzed alongside test samples to monitor method performance. The strategy specifies the types of QC samples to be used (e.g., blank, low, medium, high), their frequency of analysis, and the acceptance criteria for their results. Deviations from the defined control limits trigger investigations and corrective actions.

- **Data Integrity and Documentation**: The Method Control Strategy emphasizes the importance of maintaining data integrity and ensuring proper documentation. It defines protocols for data collection, recording, storage, and retention. The strategy may include procedures for electronic records and signatures, data backups, and version control. Adherence to data integrity and documentation practices ensures the reliability and traceability of analytical data.

- **Change Control and Continual Improvement**: The Method Control Strategy includes procedures for managing changes to the analytical method. It defines the requirements for evaluating and implementing changes, such as method modifications, instrument upgrades, or new reagents. The strategy ensures that any changes are properly evaluated, validated, and communicated to stakeholders. Furthermore, it encourages continual improvement by promoting data analysis, trend monitoring, and implementation of corrective and preventive actions.

The Method Control Strategy is developed based on the understanding gained from method development, validation, and ongoing performance monitoring. It serves as a roadmap to ensure the consistent application of the method, control of critical parameters, and compliance with regulatory requirements. By implementing an effective Method Control Strategy, analytical laboratories can maintain the quality and reliability of their analytical methods, ultimately ensuring accurate and reliable results.

X. METHOD VALIDATION AQbD

Method validation is an essential part of the Analytical Quality by Design (AQbD) approach. It is the process of demonstrating that an analytical method is suitable for its intended purpose and provides reliable and accurate results. Method validation ensures that the method meets predefined criteria and is fit for its intended use throughout its lifecycle.

When applying AQbD principles to method validation, the following key aspects are considered:

- **Analytical Target Profile (ATP):** The ATP, defined as part of AQbD, outlines the performance criteria and requirements for the analytical method. During method validation, the method's performance is assessed against the ATP to ensure it meets the predefined criteria for accuracy, precision, specificity, sensitivity, linearity, and other relevant attributes.

- **Risk Assessment**: A risk assessment is conducted to identify and evaluate potential sources of variability and uncertainty that could impact the method's performance. The identified risks, such as critical method parameters (CMPs) and critical method attributes (CMAs), are considered during method validation. The validation plan focuses on assessing and controlling these critical factors to mitigate potential risks.

- **Design of Experiments** (DoE): DoE techniques may be utilized during method validation to systematically evaluate the effects of various factors on the method's performance. By varying the CMPs and CMAs within a design space, DoE helps to understand and optimize the method's robustness and performance.

- **Protocol Development**: The validation protocol is developed based on the ATP, risk assessment, and DoE outcomes. It includes detailed procedures, acceptance criteria, and statistical analysis plans for the validation experiments. The protocol defines the validation parameters, experimental design, number of replicates, and sample types to be used.

- **Validation Experiments**: The validation experiments are conducted following the predefined protocol. The method's performance is evaluated by assessing its accuracy, precision, linearity, limit of detection (LOD), limit of quantitation (LOQ), specificity, and robustness. Different validation parameters, such as recovery studies, ruggedness assessments, and matrix effect evaluations, may be included based on the method's characteristics and intended use.

- **Data Analysis**: The data generated during validation experiments is analyzed using appropriate statistical methods. This includes determining mean values, standard deviations, regression analysis, and evaluating the results against the predefined acceptance criteria. The statistical analysis helps to assess the method's reliability, suitability, and compliance with the ATP.

- **Documentation and Reporting**: Method validation activities and results are documented in a validation report. The report includes a summary of the validation approach, validation parameters, experimental details, data analysis, and conclusions. It serves as a comprehensive record of the validation

- In process and is used for regulatory compliance and internal quality control purposes.
  By integrating AQbD principles into method validation, pharmaceutical companies can enhance the reliability, accuracy, and robustness of their analytical methods. AQbD ensures a proactive and risk-based approach, focusing on critical factors and performance

criteria. This ultimately leads to the development and validation of methods that are more reliable, consistent, and fit for their intended purpose.

- **Analytical Quality by Design Validation**

Analytical Quality by Design (AQbD) validation refers to the process of demonstrating that an analytical method developed using the AQbD principles is suitable for its intended purpose and consistently provides accurate, precise, and reliable results. AQbD validation aims to ensure that the method meets predefined acceptance criteria and regulatory requirements.

- **Following are Point regarding the AQbD Validation**

- **Method Performance Verification**: AQbD validation begins with the verification of the method's performance characteristics, such as accuracy, precision, linearity, specificity, limit of detection, and limit of quantification. This is typically done using a series of validation experiments, including testing of appropriate standards, spiked samples, or reference materials.

- **Design of Experiments (DoE):** AQbD validation often involves the use of DoE principles to systematically evaluate the impact of critical method parameters (CMPs) and their interactions on method performance. DoE allows for efficient and comprehensive method optimization and validation by considering multiple factors simultaneously.

- **Validation Protocol:** A validation protocol is developed, outlining the validation approach, acceptance criteria, experimental design, and data analysis procedures. The protocol describes the validation experiments to be conducted, the number of replicates, and the statistical methods to be used for evaluating method performance.

- **Robustness Evaluation:** AQbD validation includes the assessment of method robustness, which refers to the method's ability to remain unaffected by small, deliberate variations in method parameters. Robustness studies help identify the criticality of CMPs and evaluate the method's tolerance to minor changes in operating conditions.

- **System Suitability Testing**: System suitability tests are performed as part of AQbD validation to ensure that the analytical system, including equipment, reagents, and other components, is suitable and properly calibrated for the method. These tests verify that the system is capable of generating reliable and reproducible results.

- **Method Transfer and Comparability**: If the method is intended for use in multiple laboratories or instruments, method transfer studies may be conducted as part of the validation process. These studies evaluate the method's performance when transferred between different systems to ensure consistency and comparability of results.

- **Documentation and Reporting**: AQbD validation requires comprehensive documentation of all validation activities, including protocols, raw data, data analysis, and validation reports. The validation report summarizes the validation results, discusses any deviations

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or issues encountered during the validation process, and provides a conclusion regarding the suitability and reliability of the method.

- **Continued Method Performance Verification:** After validation, ongoing monitoring and periodic verification of method performance within the validated design space is necessary to ensure that the method remains reliable and robust over time. This may involve routine system suitability testing, proficiency testing, or method performance monitoring based on established quality control procedures.

AQbD validation provides a structured approach to method validation, focusing on understanding and controlling critical method parameters to ensure reliable and accurate analytical results. By integrating AQbD principles into the validation process, analytical laboratories can enhance the quality and robustness of their methods, leading to improved regulatory compliance, product quality, and patient safety.

XI. CONTINUOUS IMPROVEMENT AQbD

Continuous improvement is a fundamental principle of the Analytical Quality by Design (AQbD) approach. It emphasizes the ongoing assessment, optimization, and enhancement of analytical methods and processes to achieve and maintain a high level of quality and performance.

1. In the context of AQbD, continuous improvement involves the following main elements:

- **Data Analysis and Monitoring:**Continuous improvement relies on the systematic analysis of data generated from routine analytical activities. By monitoring key performance indicators (KPIs), trends, and patterns in the data, laboratories can identify areas for improvement and potential sources of variability or inefficiency. Statistical tools and techniques, such as control charts, capability analysis, and trend analysis, can be employed to analyze the data effectively.

- **Root Cause Analysis**: When issues or deviations are identified through data analysis, a thorough root cause analysis is performed to determine the underlying factors causing the problem. This involves investigating the contributing factors, such as method parameters, equipment performance, operator practices, or sample characteristics. By identifying the root causes, appropriate corrective and preventive actions can be implemented to address the underlying issues and prevent recurrence.

- **Risk-Based Decision Making:** Continuous improvement in AQbD is driven by a risk-based approach. Risks and potential sources of variability are identified, assessed, and prioritized based on their impact on method performance and patient safety. This enables laboratories to allocate resources effectively and focus improvement efforts on areas that have the greatest impact on quality, reliability, and regulatory compliance.

- **Process Optimization**: Continuous improvement involves optimizing analytical processes to enhance efficiency, reduce variability, and improve overall performance. This may involve modifying method parameters, optimizing instrument settings, streamlining sample preparation steps, or implementing automation where appropriate. Design of Experiments (DoE) techniques can be employed to systematically explore and optimize process parameters to achieve desired outcomes.

- **Change Management**: Continuous improvement often requires changes in analytical methods, equipment, or procedures. Effective change management practices are crucial to ensure that changes are properly evaluated, validated, documented, and communicated to relevant stakeholders. Change control procedures help prevent unintended consequences and ensure that changes are implemented in a controlled and compliant manner.

- **Training and Competency Development**: Continuous improvement is supported by ongoing training and competency development programs for laboratory personnel. Training ensures that analysts are equipped with the necessary knowledge, skills, and understanding of AQbD principles and quality management practices. It also helps foster a culture of continuous learning and improvement within the organization.

- **Collaboration and Knowledge Sharing**: Continuous improvement benefits from collaboration and knowledge sharing among different stakeholders, including scientists, analysts, quality professionals, and regulatory experts. Sharing best practices, lessons learned, and success stories across the organization helps drive improvement initiatives and promotes a culture of continuous improvement.

By embracing continuous improvement within the AQbD framework, laboratories can systematically enhance their analytical methods, processes, and overall quality management systems. This leads to increased efficiency, reliability, and compliance, ultimately benefiting patient safety and product quality.

XII. APPLICATION OF ANALYTICAL QUALITY BY DESIGN

Analytical Quality by Design (AQbD) is a systematic and scientific approach that can be applied across various stages of the analytical method lifecycle to ensure the quality, reliability, and robustness of analytical methods.

Following are some important applications of AQbD in analytical laboratories

1. **Method Development**: AQbD principles can be applied during the method development phase to systematically design and optimize analytical methods. By considering critical method parameters (CMPs) and their impact on method performance, scientists can identify the key factors influencing the method and establish a solid foundation for method optimization.

2. **Risk Assessment:** AQbD incorporates risk assessment techniques to identify and evaluate potential risks associated with the analytical method. This includes assessing the impact of CMPs on critical quality attributes (CQAs) of the analyte and considering factors such as instrument variability, sample matrix effects, and method robustness. The results of risk assessment help prioritize efforts and resources for method development, validation, and routine operation.

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3. **Design of Experiments (DoE):** AQbD employs DoE principles to efficiently and comprehensively evaluate the impact of multiple factors on method performance. DoE allows scientists to study interactions between CMPs and systematically identify the optimal settings for these parameters. This approach helps reduce the number of experiments required and provides a scientific basis for method optimization.

4. **Method Validation:** AQbD principles can be applied during the validation of analytical methods. By considering the design space established during method development, scientists can define appropriate validation protocols, acceptance criteria, and statistical approaches. AQbD validation ensures that the method is fit for its intended purpose and consistently provides accurate, precise, and reliable results.

5. **Control Strategy:** AQbD facilitates the development of a comprehensive control strategy for analytical methods. This includes establishing appropriate specifications for CMPs, defining system suitability criteria, implementing robust quality control procedures, and monitoring method performance using statistical process control tools. The control strategy ensures ongoing control and monitoring of method performance throughout its lifecycle.

6. **Continuous Improvement:** AQbD supports the concept of continuous improvement in analytical laboratories. By systematically collecting and analyzing data, laboratories can identify opportunities for optimization, process enhancements, and risk mitigation. The use of statistical tools and quality control charts helps in detecting trends, deviations, and potential issues, allowing for proactive actions and process improvements.

7. **Method Transfer and Lifecycle Management:** AQbD principles can be applied during method transfer between laboratories or instruments. The systematic understanding of CMPs and the establishment of a validated design space facilitate successful method transfer, ensuring that the method remains reliable and robust across different settings. AQbD also promotes the periodic review and reassessment of analytical methods to ensure their continued fitness for purpose throughout their lifecycle.

By applying AQbD principles, analytical laboratories can enhance method development, validation, and routine operation, leading to improved analytical performance, increased efficiency, and enhanced regulatory compliance. AQbD fosters a proactive and science-based approach to analytical quality, ultimately resulting in reliable and accurate analytical results.

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