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# A REVIEW ON RECENT STRATEGIES IN AQbD APPROACH

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**ABSTRACT**

*Recent strategies in the Analytical Quality by Design (AQbD) approach have transformed the way analytical methods are developed, optimized, and controlled in pharmaceutical and regulatory environments. AQbD integrates scientific knowledge and risk-based strategies to ensure the consistent performance and quality of analytical methods throughout their lifecycle. This article explores the latest advancements in AQbD, focusing on key strategies such as method understanding, risk assessment, and the application of experimental designs like Design of Experiments (DoE) to optimize method parameters. Emphasizing the importance of system suitability criteria, monitoring, and trending of method outputs, the article highlights how these strategies can enhance method robustness, reduce variability, and ensure product quality. Case studies from regulatory agencies, including the MHRA and British Pharmacopoeia, illustrate the practical application of AQbD concepts in the development of compendial methods, such as the Atorvastatin Assay method. By leveraging these innovative approaches, pharmaceutical industries can improve method performance, ensure compliance, and meet evolving quality standards.*

**KEYWORDS:** *Analytical Quality by Design (AQbD), Quality by Design (QbD), Critical Quality Attributes (CQAs)*

## 1. INTRODUCTION

The pharmaceutical industry is increasingly embracing innovative approaches to ensure consistent product quality, with Analytical Quality by Design (AQbD) emerging as a key strategy in this evolution. AQbD, which builds on the principles of Quality by Design (QbD), applies a science- and risk-based approach to the development, validation, and lifecycle management of analytical methods. Unlike traditional methods that rely on fixed procedures, AQbD introduces a more dynamic and flexible framework that incorporates quality into the analytical process from the start. This allows for ongoing improvement and adaptation over time, ensuring more robust and efficient methods. The need for an Analytical Quality by Design (AQbD) approach arises from the increasing complexity of pharmaceutical processes, regulatory demands, and the emphasis on maintaining high levels of product quality and patient safety. Regulatory bodies like the FDA and EMA are placing greater importance on lifecycle management, making AQbD essential for ensuring that analytical methods remain robust, reproducible, and capable of delivering accurate results under varying conditions. By emphasizing an understanding of method variability, identifying critical method parameters (CMPs), and establishing a method operable design region (MODR), AQbD helps develop methods that are both compliant with regulatory standards and resilient to variations.

## 2. HISTORY OF AQbD[16]

### 1990- Dr. JOSEPH M. JURAN

Dr. Joseph M. Juran laid the foundation for the Quality by Design (QbD) approach with the concept that "quality should be designed into a product, and most quality problems stem from how a product was designed in the first place." He emphasized that quality should be incorporated into the product during the early stages of development, ensuring that potential issues are addressed proactively rather than reactively.

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**2004-2012: ICH Published Guidelines That Outlined Qbd Approach**
**2004 ICH Q8**: Pharmaceutical product development
**2005 ICH Q9**: Quality Risk Management
**2007 ICH Q10**: Pharmaceutical Quality System
**2012 ICH Q11**: Development & manufacturing of drug substance
**2017: International Consortium For Innovation And Quality By Aqbd-Working Group:**
In 2017, the International Consortium for Innovation and Quality (IQ) AQbD working group conducted a survey of pharmaceutical companies and identified those that were not only interested in applying the QbD concept in manufacturing but also in developing analytical methods using the QbD approach.
**2018: ICH New Guideline**
In 2018 ICH proposed a new guideline on the QbD approach i.e., ICH Q14
**Q14** - Procedure Development
**2020: USP General Chapter Analytical Procedure Life Cycle Management:**
In 2020 the UNITED STATE PHARMACOPOIA (USP) published a general chapter on Analytical procedure life cycle management (1220) which explains about the application of AQbD approach.
**2021: British Pharmacopeia:**
In 2021 British Pharmacopoia published a supplementary chapter about AQbD which cantain **The Application of AQbD to Pharmacopoial Methods**
**2022: ICH Guideline:**
In 2022 ICH published a draft version of the ICH Q14 Analytical procedure development.
**2022 R2)** – Procedure Validation

## 3. BASIC TERMINOLOGY OF AQbD[16]

### 3.1 Analytical Target Profile(ATP):

The Analytical target profile is crucial concept in the ICH Q14 Guideline the specifies the conditions the pn analytical method must achieve in order to property quality a product quality attributes.

### 3.2 Critical Method Parameters (CMP) / Critical Method Variables (CMV)

A critical method/Process parameters (CMP) refers to a process variables in pharmaceutical products that influence a critical Quality attribute (CQA), As a result CMP must be monitored or controlled to ensure the drug product achieve the desired quality

### 3.3 Analytical Design Space

ICH Q8 (R2) defines the space design as the multidimensional combination and interaction of input variables (such as material attributes) and process parameters that have been shown to ensure quality operating within the design space is not considered a change.

### 3.4 Method Operable Design Region:

The Method Operable Design Region (MODR), or design space, refers to the combination of method parameter ranges (at a minimum including all critical parameters, but not limited to them) that have been evaluated and verified to meet both the Analytical Target Profile (ATP) criteria and the specific method performance criteria.

### 3.5 Critical Analytical Attribute (CAA)

The CAA is a characteristics or property whether physical, chemical, biological or microbiological that must fall within a specific limit range , or distribution to ensure the desired quality of the product .

### 3.6 Experimental Trials or Runs

Trials done on the new product to evaluation the effectiveness and safety of the product, services and the effect of the product is checked Ex. Clinical and preclinical trials done on new drug for people getting better way of treatment with new drug .

### 3.7 Control Stratergy

The product control strategy should be define the analytical method to be used in AQbD studies and specify the stage at which they should be applied. In other words developing ghe control strategy for the entire process from the methods initiation .

A robust control strategy is obtained during the data obtained during the method development and confirmation stages of while considering ATP criteria.

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## 4. RECENT STRATEGIES IN AQbD APPROACH:

### 4.1 GROUP 2017: INTERNATIONAL CONSORTIUM FOR INNOVATION AND QUALITY BY AQBD-WORKING

### 4.2 2020: USP GENERAL CHAPTER ANALYTICAL PROCEDURE LIFE CYCLE MANAGEMENT

### 4.3 2021: BRITISH PHARMACOPEIA - THE APPLICATION OF AQBD TO PHARMACOPOIAL METHODS

### 4.1 GROUP 2017: INTERNATIONAL CONSORTIUM FOR INNOVATION AND QUALITY BY AQBD-WORKING[7]:

Published on: April 2, 2017

Elizabeth Hewitt, Andy Rignall, Mark D. Trone, Patrick Jackson, Marion Chatfield, Mark Argentine, Qinggang Wang, Shreekant Karmarkar, Andrea M. Pless, Zeena Williams, Kimber Barnett, David Semin, Yanqun Zhao, Ariane Marolewski.

The Analytical Quality by Design Working Group (AQbD WG) of the IQ Consortium has published the results of a survey in Pharmaceutical Technology, focusing on the implementation of Analytical Quality by Design concepts by both small- and large-molecule pharmaceutical companies. The survey was distributed to IQ Consortium member companies and completed by 16 of them, including 12 large companies (with over 10,000 employees) and four smaller ones. It revealed that more than two-thirds of the companies had implemented AQbD to some extent, with larger companies being more likely to adopt AQbD concepts. The survey also explored the technical aspects of AQbD, challenges with implementation, business considerations, and regulatory experiences. Overall, the analysis of the survey responses concluded that AQbD implementation offers operational benefits, fostering continued interest and application.

More than two-thirds of the companies surveyed (69%, or 11 of the 16) had implemented AQbD in some form (Figure 1). As expected, large pharmaceutical companies had a higher implementation ratio (83%, or 10 of 12 companies) compared to smaller pharmaceutical companies (25%, or 1 of 4 companies). In other words, 91% (or 10 of the 11 companies) implementing AQbD concepts were from large companies, although these companies submitted significantly more survey responses. Among the varied responses, AQbD implementation occurred for both large and small molecules, with many companies indicating that their approaches were similar for both types.

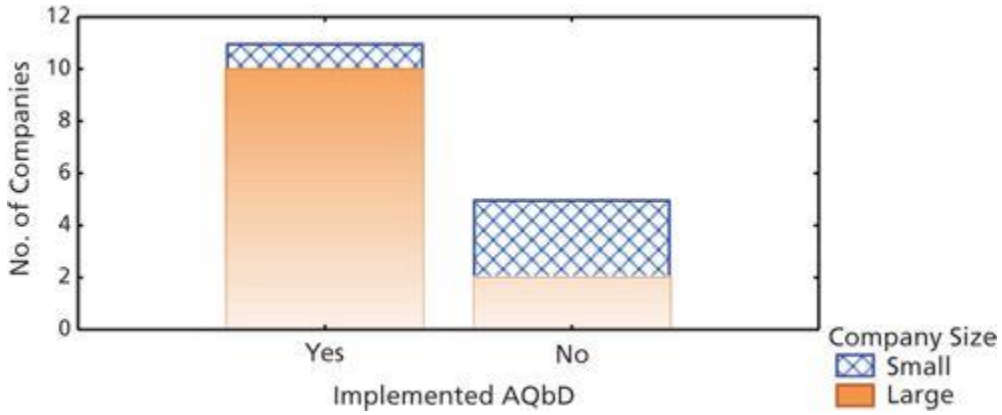


**Fig: Breakdown of all responding companies by whether they have implemented analytical quality by design (AQbD) and their size. (All figures courtesy of authors**

Companies that implemented AQbD concepts identified improved method performance as the primary business driver. Conversely, the five companies that did not integrate AQbD into their development programs cited concerns about increased costs and resource investments with minimal benefit as their main reasons.

#### 4.1.1.Technical Details And Challenges With Implementation

Among the 11 companies that have implemented AQbD concepts, respondents were nearly evenly divided between those who recently started implementation and those who have been practicing AQbD for an extended period. Of the five companies that have not implemented AQbD, three indicated they are just beginning. Notably, most companies tend to practice AQbD concepts during late-stage

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development (over 80% in Phase III) and commercialization, rather than in earlier development stages, to maximize the value of their investment efforts.

### 4.1.2.AQbD Concept In Drug Development[7]

**Table I** presents a breakdown of AQbD implementation during the drug development lifecycle for the 18 respondents. This outcome aligns with the key benefits expressed from AQbD implementation, including achieving robust methods, better validation packages, and significantly improved method knowledge during development. Although not shown in Table I, some comments regarding utilization indicate that certain companies apply subsets of AQbD tools (e.g., modeling) during earlier development stages (Phases I and II), albeit with less systematic rigor compared to later phases to enhance knowledge development.

**Table I: Analytical quality-by-design (AQbD) concept implementation during drug development process by respondent.**

| Response | Phase I | Phase II | Phase III | Post-Approval |
|---|---|---|---|---|
| 1 | | | X | |
| 2 | | | X | |
| 3 | | X | X | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | X | X | X |
| 8 | X | X | X | X |
| 9 | X | X | | |
| 10 | X | X | X | |
| 11 | | | X | X |
| 12 | | | X | |
| 13 | | X | X | X |
| 14 | | | X | |
| 15 | | X | X | |
| 16 | | | | |
| 17 | | | X | |
| 18 | X | | | |
| Total: | 4 | 7 | 12 | 4 |

**Table : Analytical quality-by-design (AQbD) concept implementation during drug development process by respondent.**

### 4.1.3 AQbD Concept In Drug Product Method

The survey clearly indicated that the primary focus for implementing AQbD concepts is on drug substance and drug product methods, with much lower application to the testing of other materials (Table II). Interestingly, and perhaps not surprisingly, respondents have applied AQbD concepts almost equally to chromatographic and non-chromatographic methods, while clearly not applying these concepts to compendial methods.

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Table II: Method types to which analytical quality-by-design concepts have been applied.

| Type of methods | Percentage of respondents |
|---|---|
| Drug product methods | 100 |
| API methods | 93 |
| Non-chromatographic methods | 57 |
| Only chromatographic methods | 47 |
| Methods for API starting materials | 33 |
| Process intermediate methods | 30 |
| In process monitoring methods | 22 |
| Compendial methods | 14 |

**Table : Method Types To Which Analytical Quality-By-Design Concepts Have Been Applied.**

Eight respondents reported that developing robust methods saved time, while six respondents disagreed. Although a multivariate AQbD-based approach was perceived to require more time and additional resources for lifecycle management of methods, it was believed that the resulting methods were more robust, leading to fewer issues encountered during routine use.

The majority of survey companies leveraged commonality among methods to enhance efficiencies in AQbD implementation. They utilized generic risk assessments based on method types, such as templates for reversed phase-high-performance liquid chromatography (RP-HPLC) assay methods, and standardized method development approaches, including standard chromatographic column screens. To address the increased resource demands of method development, 13 out of 15 respondents implemented various software packages like Fusion AE, DryLab, ChromSword, and ACD/AutoChrom. Respondents applied statistics (92%) and experimental design (100%) to improve AQbD efficiency, consistent with numerous literature examples promoting robust method development under AQbD. The simple design of experiments (DoE) approach was the most widely used tool for robustness testing, and 64% of companies employed modeling and simulation tools for AQbD applications. However, most respondents did not use any additional approaches beyond these tools to address the potential rise in resource demands for AQbD implementation.

Six of the 16 companies reported having departmental guidelines or standard operating procedures (SOPs) for implementing AQbD concepts, representing about half of those that have adopted AQbD. Comments indicated that some groups felt specific guidance on QbD implementation was unnecessary, with some responses noting that QbD aspects of analytical work were documented directly within work packages (e.g., method development or validation) rather than as separate entities.

**4.1.4.Summary Of The Survey**

In summary, results from a 34-question survey indicate that the majority of responding companies have adopted AQbD concepts over the past decade, with about half of the companies just beginning their implementation. A key driver for adopting AQbD principles has been the development of more robust analytical methods, alongside the use of various tools that enhance experimental design and modeling, demonstrating a commitment to this goal. Moreover, the greatest value from implementation is found during the late development stages and commercialization phases for optimal return on investment. These survey results align with an informal AQbD adoption survey conducted in November 2015, which involved representatives from approximately 25 biopharmaceutical companies, including small-molecule, large-molecule, and vaccine-related organizations. During that meeting, there was clear interest in advanced discussions of AQbD principles, with more robust analytical methods and enhanced regulatory flexibility (averaging 4.7 out of 5, with 5 being the highest rating) identified as drivers for developing AQbD case studies to further the conversation on the topic.

**4.2. 2020: USP GENERAL CHAPTER (1220) ANALYTICAL PROCEDURE LIFE CYCLE MANAGEMENT[1]:**

**According to the USP GC (1220) AQbD called as** A systematic approach to development of that begins with predefined objectives and emphasizes product and process understanding and process control,based on sound science and quality risk management. (USP) GC (1220).

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**4.2.1. According To The Usp Gc The History Of AQbD Is**
**2004-2012 ICH guidelines outline AQbD concepts:**
2004: Q8 Pharmaceutical development
2005: Q9 Quality risk managment
2007: Q10 Pharmaceutical quality system
2012: Q11 Development and Manufacture of Drug Substance

**2013 Stimuli Article**
PF 39(5) Lifecycle Management of Analytical Procedures

**2016 Stimuli Article**
PF 42(2) Fitness for Use PF 42(5) ATP PF 42(5) Analytical control strategy

**2014-2017 ICH Q12**
Pharmaceutical Product Lifecycle Management

**2018 –** Q14/Q2(R2) Working Group

**2020 –**BP/MHRA Consultation response application of AQbD concepts to pharmacopoeial standards
**1ST SEP 2020 –** USP GC published in PF46(5)

**2021 –** BP Supplementary chapter proposed
**1ST DEC 2021 –** USP GC became online in USP-NF
**MARCH 2022 –** Public Consultation **ICH Q14** draft guideline Procedure Development
**ICH Q2(R2)** draft guideline Procedure Validation
**1ST MAY 2022 –** USP GC become official

**4.2.2.According To USP GC The Q14 Guideline Contains[9]:**

| Q14 – Procedure Development | Q2 (R2) – Procedure Validation |
|---|---|
| Minimal vs enhanced approaches | Selection of analytical procedure validation experiments and criteria |
| Analytical target profile | Considerations for multivariate procedures |
| Knowledge management | Specificity/selectivity |
| Risk management | Validation of the reportable range |
| Robustness | Validation of lower range limits |
| Analytical procedure control strategy | Accuracy and precision |
| Evaluation of change management | |
| Multivariate analytical procedures | |
| Real-time release testing | |

**4.2.3.Topics Covered In USP GC[1]**

**4.2.3.1.Analytical Target Profile (ATP)**
ATP is a predefined objective that stimulates the performance requirments for the analytical procedure ,

**It Include**
Definition of analyte
Description of analytical matrix
Range

Used to measure the value and source of errors
1. **Bias -** How close the measurement is, on average, to the true value that is being measured (systematic error)
2. **Precision -** how much the measurement will vary randomly under routine use; (random error)

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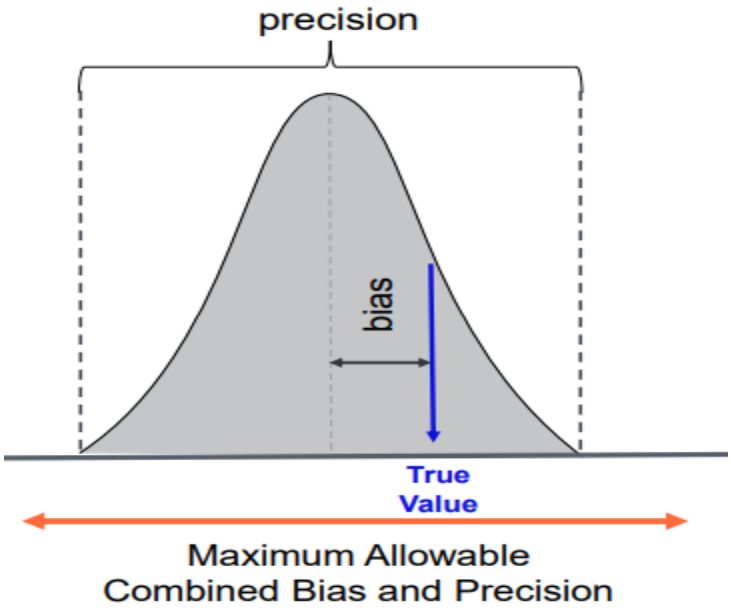


**Fig. Analytical Target Profile (Atp)**

**4.2.3.2. Quality Risk Management (QRM)**[22]

A systematic process for the assessment, control, communication, and review of risks to the quality of the reportable value throughout the lifecycle of the analytical procedure.

Quality risk management supports a practical and scientific approach to decision-making (ICH Q9).

**Quality Risk Management Methodologies**

Flowchart,
Process Mapping,
Cause And Effect Diagrams,
Failure Mode Effects Analysis (FMEA),
Failure Mode Effects And Criticality Analysis (FMECA) etc.

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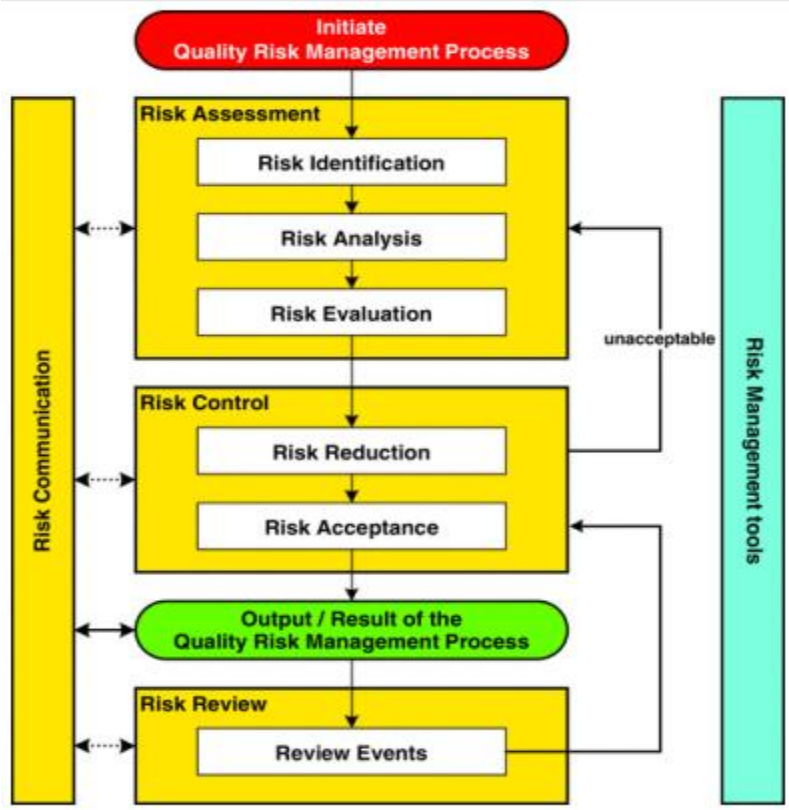


**Fig. Overview of a typical QRM process (ICH Q9).**

**4.2.3.3. Method Operable Design Region (MODR):**
MODR is a multidimensional combination and interaction of procedure parameters, where all combinations of study factors have been demonstrated to:
– Provide acceptable mean performance
– Provide acceptable robustness
– Ensure the ATP is fulfilled.

**4.3 2021: BRITISH PHARMACOPEIA - THE APPLICATION OF AQBD TO PHARMACOPOIAL METHODS[25]:**
This chapter is intended to serve as selective guidance for applying Analytical Quality by Design principles to pharmacopoeial procedures and throughout the entire Analytical Method Lifecycle, rather than as a mandatory requirement. The British Pharmacopoeia, along with its expert working party, will expand and revise this guidance as both internal and external knowledge advances and as further international standards are developed.

**4.3.1. Application Of Analytical Quality By Design To Pharmacopoeial Methods:**

**4.3.1.1. Background**

The development and control of an analytical method throughout the product lifecycle is a crucial part of the overall product control strategy. This control is founded on key concepts collectively known as 'Analytical Quality by Design (AQbD)'. The MHRA and British Pharmacopoeia have investigated the practical application of these concepts to a pharmacopoeial assay procedure, and they are using insights from this studyfootnote text{footnote}footnote to inform individual finished product monographs on a scientific and risk-based approach. This Supplementary Chapter outlines the principles and offers practical guidance for implementing AQbD principles in pharmacopoeial procedures. The chapter covers:

- A discussion of Quality Risk Management (QRM)
    - Risk identification tools: Ishikawa/Fishbone
    - Risk analysis tools: FMEA
    - Risk evaluation and control

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•Establishment of method understanding
  o Systematic method development and evaluation
  o Experimental design
  o Statistical approaches to support experimental design

Supplementary Chapter SC I, titled 'Basis of Pharmacopoeial Requirements,' provides an overview of the use, application, and necessity of pharmacopoeial procedures. The methods outlined in the Pharmacopoeia are designed to be robust, as they are used by analysts across a wide range of laboratories, sometimes only occasionally. The General Notices of the British Pharmacopoeia allow for alternative methods if they are known to yield results of equivalent accuracy. For instance, a manufacturer may opt to use their own optimized method. However, in cases of doubt or dispute, only the pharmacopoeial methods are deemed authoritative. The concepts presented in this supplementary chapter can support the development of both robust pharmacopoeial methods and alternative methods used by manufacturers, as well as their application throughout the product lifecycle to ensure the quality of a specific drug substance or its pharmaceutical preparation.

Analytical Quality by Design is an evolving field within analytical science, and this supplementary guidance chapter will be updated in future editions of the BP to include additional guidance on applying these concepts to pharmacopoeial methods and their role throughout the Analytical Method Lifecycle.

**4.3.1.2.Application To The British Pharmacopoeia:**

Analytical method performance—and thus the results produced by an analytical method—is generally subject to variability during routine use. It is therefore essential to understand how variability in method parameters (e.g., temperature, solvent composition, etc., for an HPLC method) can influence the results, as well as to consider the impact of typical changes in method conditions that may arise over time and across different laboratories (e.g., instrument type/design, reagent quality, sample shakers, analyst training, etc.).

Pharmacopoeial methods are designed to be applicable to a wide variety of available formulations, often requiring a review of data and laboratory evaluation of submitted, registered methods to confirm their suitability for pharmacopoeial use. This process involves applying quality risk management principles and tools to target the investigation on the method's most critical aspects, thereby maximizing the knowledge gained from laboratory work.

The case study conducted by the MHRA and the BP applied a stepwise process to explore how AQbD principles can be effectively implemented in pharmacopoeial procedures. The goal of this work was to demonstrate that AQbD can be used to develop robust, fit-for-purpose methods within the BP. The case study highlighted the value of applying these principles to an assay procedure, and the BP is continuing to apply and further investigate the insights gained across a range of pharmacopoeial procedures.

**4.3.1.3.Quality Risk Management For Analytical Procedures[22]:**

Building method understanding begins during method development and continues through formal validation (in line with conventional ICH Q2: Method Validation), as well as verification, method transfer exercises, and routine use, including for pharmacopoeial methods. Traditionally, the BP has applied risk management principles to guide the laboratory evaluation of analytical methods, and the outcomes of the AQbD case study have been used to enhance this process.

Pharmacopoeia users may not have prior knowledge of a given method beyond what is provided in the pharmacopoeia. This section summarizes the application of quality risk management tools, such as risk assessments, to analytical methods in the pharmacopoeia.

- **Quality Risk Management**

Before 2006, risk management principles were not as widely applied in the pharmaceutical industry as they were in other business areas. This changed with the publication of ICH Q9, which encouraged the industry to adopt risk assessment processes to support the manufacturing, development, and distribution of pharmaceutical products throughout the product lifecycle. One area where risk management approaches are now extensively applied is in developing robust control strategies for manufacturing processes. Similarly, risk management principles can be used to establish control strategies for analytical methods. By adopting a risk-based approach, controls for analytical methods can be focused on parameters most likely to affect the reliability of analytical results.

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- **Risk Analysis**

Risk analysis involves estimating the risk associated with each variable identified in the previous step. It considers both the likelihood of variation (probability) and the potential impact of that variation on the reportable result (severity). A variety of tools and approaches can be used to facilitate the risk analysis process (see ICH Q9 appendices for a range of examples).

- **Risk Evaluation And Control:**

Once the risk associated with each input variable is understood, an evaluation of the required controls is performed. These controls should focus on the variables most likely to impact the reportable result and, ideally, eliminate the probability of variation. This is the first step in building an analytical control strategy for a method (see section 5.1). When using an FMEA approach, this involves identifying steps to reduce the probability score, thereby lowering the overall risk. After implementing these steps, the risk score should be reassessed with the controls in place.

If the probability of variation cannot be significantly reduced, consideration should be given to detecting the variation before the reportable result is generated. For example, if batch-to-batch variation in chromatographic packing material cannot be eliminated, a resolution check may be introduced to detect any potential impact on the accuracy of the result (see section 5.2 for trending concepts). Ideally, "system suitability" tests should always be included to mitigate known risks, rather than merely satisfying a standard method template.

**4.3.1.4. Establishing Method Understanding:**

The effectiveness of a risk assessment, and ultimately the analytical control strategy for a given method, depends on the level of understanding of how method parameters relate to the method output, i.e., the result. Section 4 outlines approaches that can be adopted throughout the product lifecycle to ensure a thorough understanding of the method.

The MHRA and British Pharmacopoeia case study on Atorvastatin Tablets illustrates how the Pharmacopoeia may apply AQbD concepts when evaluating a method's suitability for compendial use. It is not expected that all of these concepts will be used in assessing the method's suitability.

- **Systematic Method Development And Evaluation:**

Experimental studies are conducted to support risk assessments by evaluating the impact of method parameters and environmental factors on method performance. These studies typically serve two main purposes:

- The Influences of deliberate variations in procedure-related method parameters (solvent strength, pH, sample concentration, etc.)
- The Influences of 'noise' factors (analyst, column batch etc.) which typically cannot be, or are preferred not to be controlled are evaluated.

When investigating deliberate variations in procedure-related method parameters, multifactor empirical modeling (e.g., Design of Experiments, or DoE) is generally preferred over one-factor-at-a-time (OFAT) experiments, although OFAT may be suitable in some cases. Mechanistic modeling, or a combination of mechanistic and empirical modeling, can also be used to reduce the experimental burden if shown to be appropriate. In addition to assessing the impact of method changes on the results, other key method attributes (such as resolution, sensitivity, accuracy, etc.) can be considered to understand method performance and optimize conditions.

The British Pharmacopoeia's case study employed several experimental designs, using multifactor approaches to assess the effects of various chromatographic, sample preparation, and stability factors with minimal injections (see Section 4.2). The case study also examined 'noise' factors; however, as this involved multiple product suppliers—which is primarily relevant for pharmacopeial applications—a more typical non-pharmacopeial example of studying 'noise' factors is provided in Section 4.2. By necessity, the case study explored these concepts in depth, though it would not be appropriate or effective to universally apply these concepts to all methods.

- **Utilising Method Development Tools And Statistical Analysis**

Analytical method parameters are factors related to the method's operation, specified either within a continuous range or at specific, controllable levels. The use of fractional factorial designs (or DoEs) for experimentation to develop general-purpose (linear) models, which describe the effects of changes in these parameters, is outlined below. These models are typically used to identify and/or confirm a setpoint and ranges for analytical method parameters to ensure robustness. While it is possible to define a broader operating region for method operation, this is not usually done.

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EPRA International Journal of Research and Development (IJRD)
Volume: 9 | Issue: 11 | November 2024 - Peer Reviewed Journal

In the practical application of AQbD to the pharmacopoeial assay procedure, DoEs were conducted to investigate sample extraction, chromatography, and solution stability. Figure 3 illustrates a two-level fractional factorial design used to examine four mobile phase factors. A full two-level factorial design includes all combinations of chosen low and high levels for the parameters, represented by the cube's corners. A fractional factorial design, however, uses a subset (or fraction) of points, represented by the solid circles in this example. This half-fraction design uses 8 out of the 16 possible combinations ($2^4$) of low and high levels for the four factors. Additionally, center points—midpoints between low and high levels and often the planned setpoint for the method—are used to estimate variability under consistent conditions and to evaluate whether a linear model in the parameters is suitable. Fractional factorial designs are highly efficient due to hidden replication (each factorial point includes replication at a parameter level, unlike OFAT experiments, which use only one level). Running all factorial combinations is unnecessary, as an adequate model is typically obtained by considering the effects of single factors or interactions between two factors.

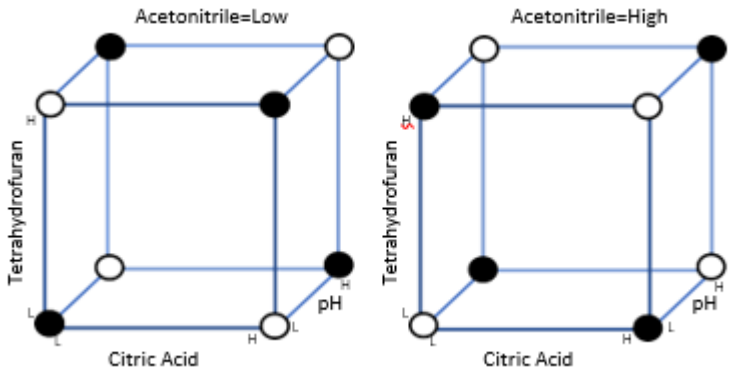


**Fig. Utilising Method Development Tools And Statistical Analysis**

- **Assessment Of Variation In Method Operating Conditions**

The variations in method operating conditions considered here are typical changes that can occur over time and across different laboratories, such as differences in instrument type, reagent quality, sample shakers, and analyst training. These variations, referred to as "noise factors," are not specified or controlled as method parameters. Studies are designed to challenge the method and assess the long-term effects of these noise factors on precision. Noise factors that significantly impact precision can be identified and further investigated to improve and control the method where feasible. Unlike designs that assess the effects of analytical method parameters, which mainly evaluate continuous factors, these studies focus on discrete, uncontrolled factors in the method description, such as the analyst. Conducting such a study during method transfer is often advantageous, as it combines both activities, conserves resources, and provides additional challenge by utilizing two laboratories.

Figure presents an example study in which the design should be selected based on the risk assessment and practical considerations. The factors and levels used are displayed at the bottom of the plot. In such a design, factors may be either "crossed" or "nested." In this example, the analyst, HPLC, and column (col) are nested within the lab, meaning each analyst is assigned to only one site. Prep is nested within each combination of analyst, HPLC, and column, with two injections performed for each prep. However, the analyst, HPLC, and column factors are crossed with one another, as each analyst uses more than one HPLC instrument. It is preferable to include a sufficient number of levels for all factors in the design (not only for preps and injections) to enable the effects or variations associated with each factor to emerge during the study, while recognizing practical constraints.

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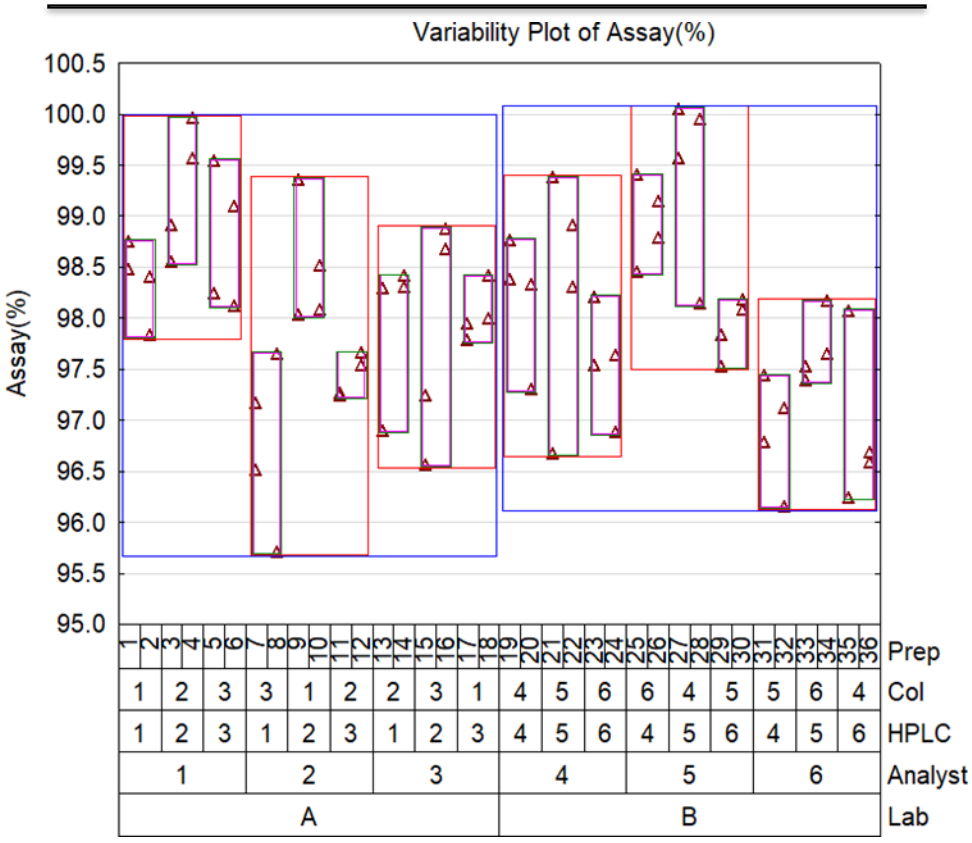


**Fig. Assessment of Variation In Method Operating Conditions**

**4.3.1.5.The Analytical Control Strategy And Its Role In Ongoing Monitoring Of Method Performance[25]:**

- **Analytical Control Strategy**

According to ICH Q10, a control strategy is a planned set of controls based on product and process understanding to ensure process performance and product quality. These controls may include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the methods and frequency of monitoring and control associated with them.

Sections 3 and 4 outline the concepts that can be adopted to develop an analytical control strategy based on a deep understanding of the method and product. The MHRA case study confirmed that the appropriate control strategy for the atorvastatin tablets assay method was to follow system suitability criteria, specifically ensuring a minimum resolution between a critical pair (Atorvastatin and a closely eluting related substance)

The chromatographic conditions and permissible adjustments outlined in Appendix III, Chromatographic Separation Techniques, complement the analytical control strategy developed according to the processes described in this supplementary chapter for a pharmacopoeial method.

- **Ongoing Monitoring Of Methods**

Monitoring the results of analytical methods provides valuable insights into process capability. An additional strategy for identifying areas of risk and alerting users to potential issues before method failure is trending a range of different method outputs. Monitoring can alert users to trends and help take corrective action in advance. There are various ways to conduct monitoring, including trending results, control sample outcomes, and performance attributes such as the retention time of specific analytes, peak shape of principal peaks, and more. Additionally, monitoring measurements of reference or standard materials analyzed repeatedly over time can also be useful.

Figure  presents a simple model of additional parameters that may need to be trended throughout the lifetime of a method, or in this case, for an individual column. The figure shows an inverse relationship between the resolution of a critical pair and the peak shape of

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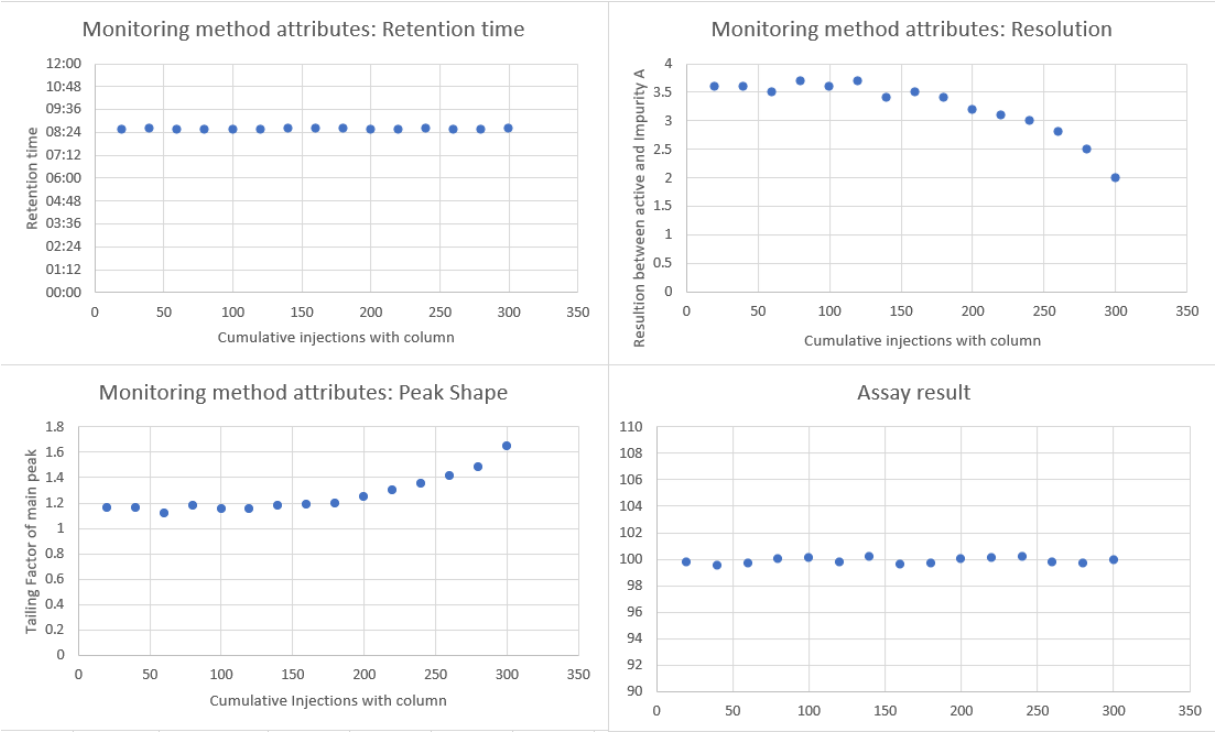
the active. In this example, an increase in peak tailing leads to a loss in separation between the drug substance and a major impurity. While the Assay value remains unaffected, the resolution is approaching a failure of the system suitability criteria, as is the peak shape.




## 5. CONCLUSION

In conclusion, recent strategies in the Analytical Quality by Design (AQbD) approach represent a significant evolution in the development and optimization of analytical methods. By integrating risk-based thinking, method understanding, and advanced experimental designs such as Design of Experiments (DoE), AQbD provides a structured framework to enhance the robustness, reliability, and performance of analytical methods. The implementation of system suitability criteria, the continuous monitoring and trending of method parameters, and the identification of potential risks contribute to maintaining high-quality standards throughout the product lifecycle. Regulatory case studies, such as those from the MHRA and British Pharmacopoeia, demonstrate the practical applications of AQbD in ensuring that methods not only meet but exceed compliance requirements. Moving forward, the adoption of AQbD principles will continue to drive improvements in analytical method development, reducing variability and enhancing product quality while supporting the evolving demands of the pharmaceutical industry.

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