



A REVIEW OF QBD AS A MODERN APPROACH IN ANALYTICAL METHOD DEVELOPMENT

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Received: 01 August 2026

Revised: 16 August 2026

Accepted: 05 September 2026

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392015, India. DOI: <http://doi.org/10.5281/zenodo.23088040>,

• ABSTRACT

Instead of depending only on end-product testing, Quality by Design (QbD) is a methodical, science-based approach that stresses integrating quality into pharmaceutical processes. This idea, known as Analytical Quality by Design (AQbD) in analytical method development, aims to improve method comprehension, robustness, and reliability. Trial-and-error-based traditional analytical methods frequently result in inconsistency and variability. AQbD, on the other hand, uses an organized framework that includes defining the Analytical Target Profile (ATP), identifying Critical Quality Attributes (CQAs), and assessing Critical Method Parameters (CMPs). Design of Experiments (DoE) and risk assessment tools are used to optimize method conditions and create a Method Operable Design Region (MODR), guaranteeing reliable performance. AQbD is frequently used in methods like impurity profiling, dissolution testing, UV spectroscopy, and HPLC. Additionally, it complies with regulations set forth by agencies such as the US Food and Drug Administration and the International Council for Harmonization. All things considered, AQbD offers a reliable and effective method for creating superior analytical techniques with increased adaptability and decreased failure risk.

• **KEYWORDS:** QbD, HPLC, And QbD

• INTRODUCTION

Quality is the foremost requirement for a product to meet its intended standards.^[1]

Along with safety and efficacy, quality is one of the essential requirements for any substance to be eligible for approval as a medication.^{[7][12]} In order to guarantee that pharmaceutical systems and products operate consistently, Building the "quality" rather than just testing it has been the focus lately. Quality by Design (QbD)^[2] is based on this philosophy. According to ICH guidance Q8(R2), QbD is "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".^[1] Designing a suitable process and comprehending process performance for the intended product performance are the main goals of QbD.

Major element in the overall scheme is continuous improvement, which in turn is based on the knowledge gained during process understanding.^{[21][34]} The concept gravitates towards a 'desired state' marked with 'regulatory flexibility' focusing on scientific knowledge building, superior design, demonstration of performance, Quality Risk Assessment (QRM), Design of Experiments (DoE), Process Analytical Technology (PAT) tools, continuous improvement and learning, and life-cycle management.

Earlier several trials and errors needed for designing or building the quality in the product but after this AQbD^{[3][4]} leads to a systematic process and proper designing.

Product development heavily relies on the development and validation of analytical methods. A strong analytical technique acts as a purity check at every stage of the product development life cycle in addition to ensuring that the drug's quality is attained in accordance with the intended therapeutic application. Since the final quality control results of the finished product, together with other batch data, determine the product's release into the market, it is crucial that the analytical method used in commercial manufacturing be reliable, accurate, and time-efficient.

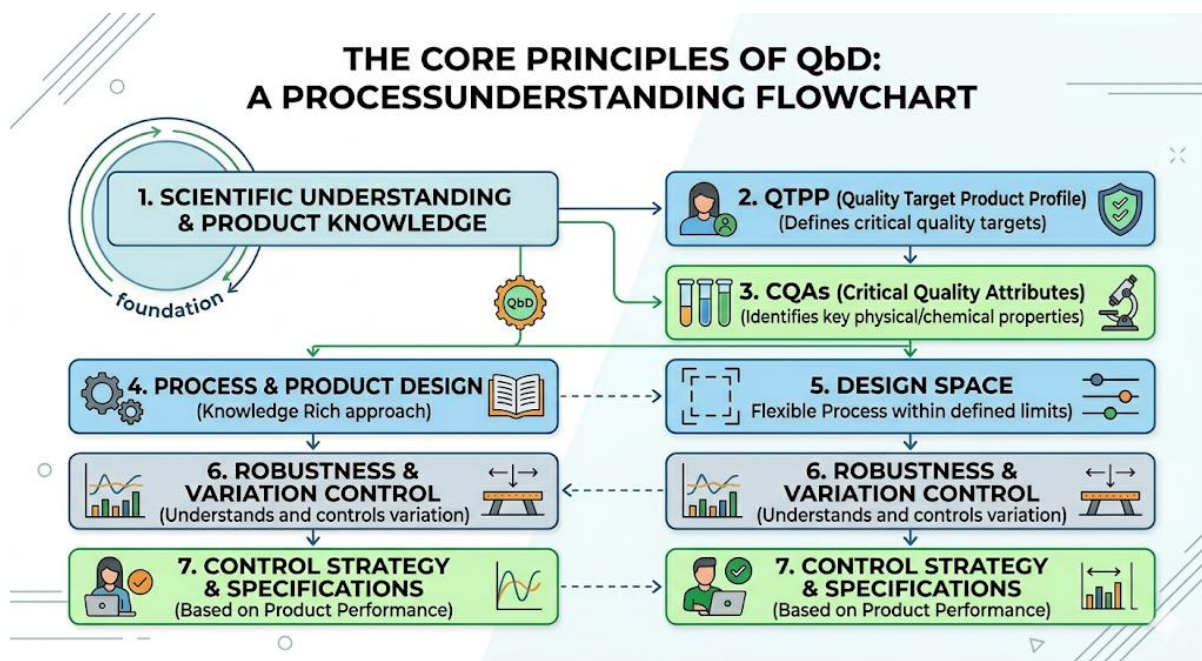


Figure 1: Core principles of QbD.

Analytical techniques^[5] are commonly employed to estimate the physical, chemical, physicochemical, and biological parameters of a material of interest. Among these, chromatographic methods such as **High-Performance Liquid Chromatography (HPLC)**, **Gas Chromatography (GC)**, **High-Performance Thin-Layer Chromatography (HPTLC)**, and **Supercritical Fluid Chromatography (SFC)** are widely used due to their significant advantages over non-chromatographic techniques.

These methods are highly robust, sensitive, and versatile, and they require relatively small sample quantities. Additionally, the incorporation of automation in these techniques minimizes human intervention, thereby reducing the chances of error and improving accuracy and reproducibility.

Table 1: Difference between Traditional approach and AQbD approach.

Parameters	Traditional approach	AQbD approach
Performance	Trial and error	Systematic
Understanding	Limited	Best
Development of method	One factor at a time	DoE
Robustness	Less robust	Highly robust
Risk assessment	Not considered	Performed
Failure chances	High	Flexible
Regulatory acceptance	Limited	High (as per ICH)
Time bound	high	less

Definition [ICH Q 8(R1)]- A methodical approach to development built on solid science and high-quality risk management that starts with predetermined goals and prioritizes product and process understanding and process control.

- **Benefits of Qbd**^[6]

QbD is a profitable business.

Get rid of batch failures

Reduce deviations and expensive investigations

Prevent issues with regulatory compliance and learning within an organization is an investment in the future.

QbD is a good science.

Improved choices for development

Technical staff empowerment

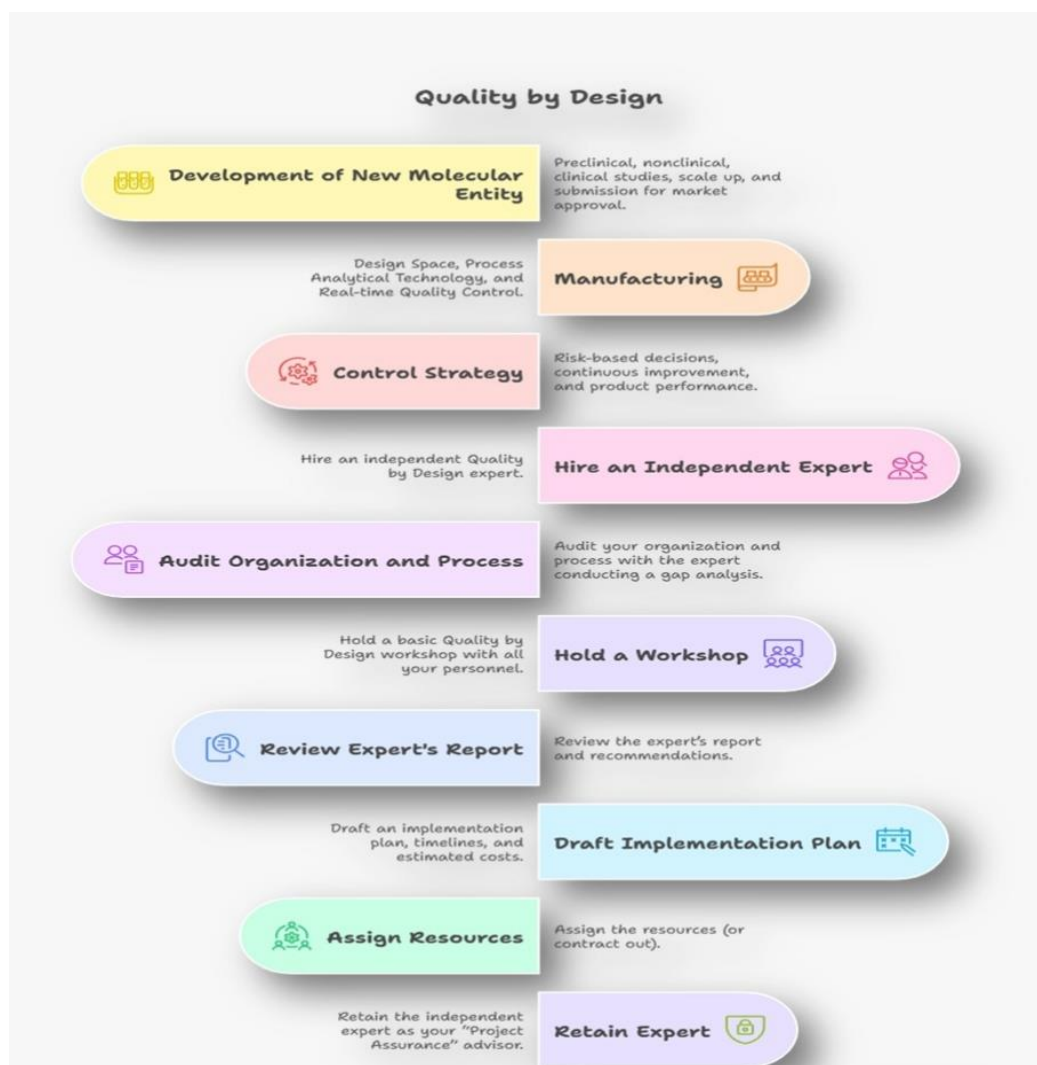


Figure 2: Start up plan for QbD.^[7]

AQbD ensures analytical method quality through systematic design and thorough understanding, instead of relying only on performance testing.

Increased method adaptability enhances AQbD-based method development by minimizing the likelihood of unexpected errors and out-of-specification (OOS) results during long-term routine application of the method. Consequently, this reduces the need for post-approval changes, making the method more cost-effective and improving the reliability and validity of analytical results.

AQbD^[9] approach emphasizes systematic method development by critically assessing potential risks of method failure and evaluating both the main and interaction effects of method parameters. This enables the identification of a method's operable design region (method operable design space) and ensures optimal performance. As a result, a deeper understanding of the method's operational behaviour is achieved during development, which greatly facilitates successful method validation and transfer. Furthermore, AQbD offers opportunities for enhanced regulatory flexibility.



Figure 3: Enhancing Pharmaceutical Quality.

Quality by design (QbD ^[10] in the production process can be linked to a number of notions connected to similar concepts in developing analytical approaches. The analytical target profile (ATP), which describes the aim of the experiment, is the first step in analytical QbD (AQbD). The crucial method parameters (CMPs), which are based on comprehensive study and evaluation of risk approaches, are then thoroughly examined to emphasize the significance of completely understanding the analytical system. The design space (DS) is the multidimensional area of the CMPs' successful operating ranges that generates the desired values for the critical method attributes (CMAs).

- **Elements of AQbD**^{[13][14][15]}

- 1) ATP

- The analytical target profile (ATP) was used to specify the method performance, and analytical methods were created utilizing the quality by design process. The initial step in QbD is to create an analytical target profile parallel to QTPP. It describes the goal of the process for creating analytical techniques and links the results to QTPP.^[20] An approach's requirements and measurement levels are described in the ATP.

The ATP specifies particular standards for measurement and criteria. This entails deciding on a target analyte for analytical procedures, picking a suitable analysis technique (such as ion chromatography, HPTLC, GC, or HPLC), and defining method specifications, such as the impurity profile.^[27]

2. CQA (Critical quality Attributes) -Key quality characteristics of drug/Product^[17]

- CQA, the second stage of AQbD, involves methodology and defines physical, chemical, and biological characteristics within suitable bounds for the intended product quality.^{[1][20]} It also involves product parameters and characteristics.
- Eg in HPLC – resolution time, retention time, peak area, peak symmetry^[27]

3. CMP (Critical Method Parameters)

- They are the method variables that can significantly affect the performance of an analytical method.^{[3][22]} Eg in HPLC – flow rate, pH, injection volume, mobile phase composition^[37]

4. DoE

- For increasingly complex levels of response surface design, the analyst's primary objective is to develop a method's design space utilizing DoE results from response modeling.^{[4][19]}
- A multiresponse surface plot, which displays overlapped contour plots for each response according to factors and interactions, is used to describe space. The design space is the area within the trial area where the approach is deemed robust and all CMA standards are met. The method operable design region, or MODR, is a design area that clearly illustrates how an analytical process works.
- For instance, try to determine the ideal circumstances for creating an HPLC technique. To find the crucial elements, such as mobile phase composition, flow rate, and column

temperature, first perform a screening or factorial experiment. The best settings for each factor can then be determined using a response surface-designed experiment.



Figure 4: Steps in AQB method development:^{[8][13]}

• **Tools used in QBD**^{[11][12]}

A) Design of experiments^{[17][18][19]}

1. Completely randomized design

2. Randomized Block Design

a) Latin square

b) Graeco Latin Square

c) Hyper Graeco latin square

3. Full factorial designs
 - a) Two – level full factorial designs
 - b) Full factorial example
 - c) Blocking of full factorial designs
4. Fractional factorial designs
 - a) $A2^{3-1}$ half fractional design
 - b) How to construct a design
 - c) Confounding
 - d) design resolution
 - e) Use of fractional factorial design
 - f) Screening designs
 - g) Fractional factorial designs summary tables
- 5) plackett – Burman designs
- 6) Response surface (second – order) designs
 - a) Central Composite design
 - b) Box Benkehnker designs ^[19]
 - c) Response surface design comparison
 - d) Blocking a response surface design
- 7) Adding centre points

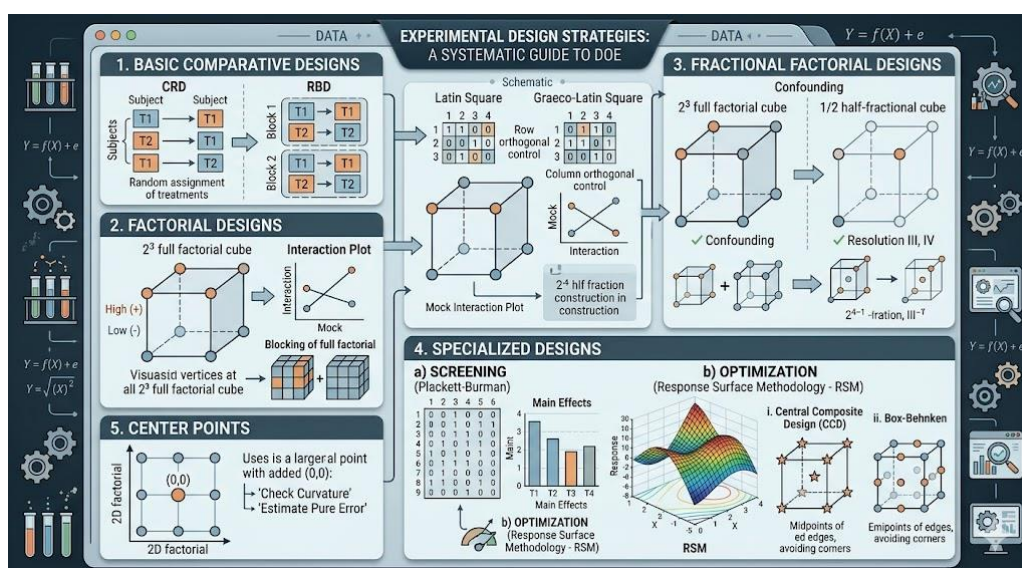


Figure 5: Design Of experiments

B) Risk Assessment

Analytical QbD assesses the analyst approach, instrument configuration, assessment factors, material characteristics, preparations, and surrounding conditions.^[22] risk associated with CQA variability. The ICH Q9 recommendations for improvement describe the methodical evaluation of risks plan for quality control, interactions, and product lifecycle review. Risk identification, analysis, and evaluation comprise risks, Risk assessment include locating and ranking possible hazards, such as cycle duration, reagent properties, and instrument operation techniques. In the event of a primary failure, a contingent approach is recommended^{[35][37]} Checklists and flow charts are used to describe risk variables. Using Fishbone diagrams or Ishikawa, which classify risks into high-risk, noise, and experimental aspects is much useful.

Identifying and ranking possible hazards, such as cycle duration, reagent properties, and instrument operation techniques, is the initial stage of risk analysis. Establishing a backup plan is essential in case the main approach fails. The second stage of risk analysis is risk evaluation, which uses the Fishbone diagram—also known as the Ishikawa approach—to classify risk elements into high-risk.^[22,24]



Figure 6: Risk Assessment.

Relative ranking, failure mode and effects analysis (FMEA/FMECA), and failure mode effects and criticality analysis are examples of semiquantitative methods for risk rating.

Different types of risk assessment instruments in ICH Q9 are listed, such as failure mode and effect analysis (FMEA), comparison matrix (CM), risk estimation matrix (REM), hazard operability analysis (HAZOP), and hazard analysis critical control points (HACCP). The most used techniques in product development are FMEA and REM. REM employs distinct

risk categories, such as low, medium, and high-risk ratings based on their severity and occurrence, whereas FMEA uses a scale of 1 to 10 for risk ranking based on severity, occurrence, and detectability.

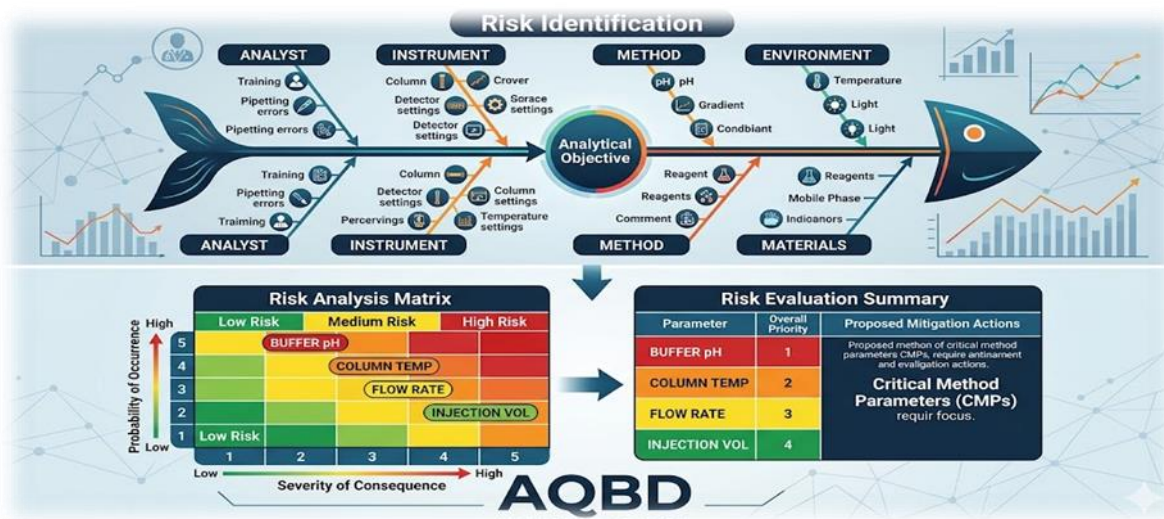


Figure 7: Detailed Information Regarding Risk Assessment.

CASE STUDY^{[26][37]}

Objective- to create a solid and dependable RP-HPLC method that uses the AQbD approach to estimate a drug (eg. paracetamol)

1) Define ATP

What the method should accomplish is defined by the ATP.

Precise measurement of medication

High definition (>2.0)

%RSD <2%

Retention time <10 mins

2) Risk Assessment

We have to use here fishbone diagram or FMEA and to find potential risk factors.

Rate of flow, temperature of the column, wavelength of detection are regarded as critical method parameters.

3) Scouting of method

Column – C18 or C8 Mobile phase

C18 mostly preferred

Mobile phase: Methanol: Water

Detection: UV

4) Design of Experiments^{[19][37]}

Central Composite design was applied.

Table 2: Variables and Critical Material Attributes.

Variables	CMAs
% organic phase	Retention time
Flow rate	Resolution
Column temperature	Peak symmetry

5. Design Space / MODR

Here in this design space all the CMAs meet acceptance criteria

Eg-If Methanol: 60-70%, Flow rate :0.9-1.1ml/min, Temperature: 25-30 °C

This range is of MODR

If the resolution is >2 and $\%RSD <2$ It means method is robust

MODR is the multidimensional region of method parameters where the method meets predefined performance criteria.

It reduces method failure and improves robustness.

6. Method Validation^{[17][31]}

Validation performed as per ICH guidelines:

Linearity: $R^2 > 0.999$

Accuracy: 98-102%

Precision: $\%RSD <2\%$

Robustness: Confirmed within design space

7. Lifecycle management

Method continuously monitored and ensures regulatory flexibility.

• Applications:



Figure 8: AQbD applications.^{[11][23][27]}

• CONCLUSION

Quality by Design (QbD) is a modern, systematic, and science-based approach for analytical method development that emphasizes understanding of method variables and their impact on performance.^{[3][34]} By applying principles such as risk assessment, design of experiments (DoE), and establishment of a design space, QbD ensures robust, reliable, and reproducible analytical methods. This approach enhances method quality, reduces variability, and supports regulatory compliance. Overall, QbD plays a crucial role in improving efficiency and lifecycle management of analytical methods, making it an essential strategy in the pharmaceutical industry.

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