



A Review on Analytical Quality by Design

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ABSTRACT

Quality-by-design (QbD) is 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. The concept of QbD can be extended to analytical methods. The emphasis of AQbD approach is on understanding of the operation and the variables affecting Analytical Methods employed in product development and hence creating an extensive knowledge repository. The variables which affect the output are identified and subjected to thorough risk assessment employing various tools and techniques discussed in the article, after which the variables are optimized. The final method is validated and a control strategy is put in place. Additionally, global harmonization of QbD terms and explicit guidelines on implementation of the QbD approach in all fields of product development including Analytical Techniques is necessary to streamline the path towards embracing this unique and effective approach.

Keywords: Quality, Quality by Design, Analytical QbD, MODR.

INTRODUCTION

Quality-by-design (Qbd) has become an important paradigm in the pharmaceutical industry it was introduced by the US Food and Drug Administration. Quality is one of the fundamental criteria in addition to safety and efficacy for any entity to be qualified and approved as a drug. For ensuring consistency of performance of pharmaceutical products and systems, the recent emphasis has been on building the "quality" rather than merely testing it. This philosophy forms the basis of Quality by Design (Qbd). ICH guidance Q8 (R2) describes QbD as, "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" As per Janet Woodcock (2004), "Means that product and process

performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches." QbD is all about designing an appropriate process and understanding process performance for the desired product performance. Major element in the overall scheme is continuous improvement, which in turn is based on the knowledge gained during process understanding. 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. Figure 1 pictorially depicts the building of a QbD-based progression.¹⁻⁵

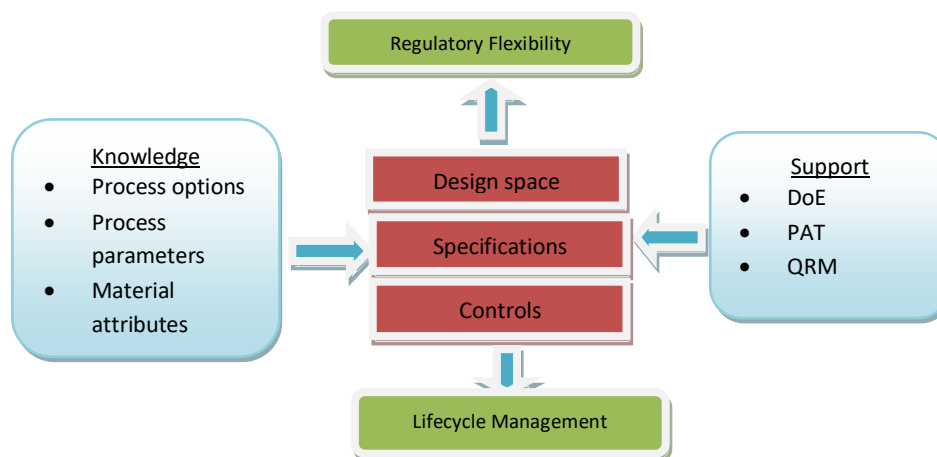


Figure 1: Building blocks of Quality by Design (QbD);

Key terms: QRM: Quality Risk Management; DoE: Design of Experiments; PAT: Process Analytical Technology

Table 1: Difference between Conventional approach and Qbd approach

Conventional approach	QBD approach
Quality assured by testing and inspection	Quality is built into the product and process by design and scientific approach
Includes only data for submission	Submission with product knowledge and process understanding
Specifications are based on batch history	Specifications are based on product performance requirements
Process is frozen, discourages changes	Flexible process with design space, allows continuous improvement
Focuses on reproducibility ignores variation	Focuses on robustness which understands control variation

Benefits of QBD:⁶⁻⁸

- Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples.
- Reduction in variability in analytical attributes for improving the method robustness.
- Eliminate batch failures.
- Minimize deviations and costly investigations.
- Avoid regulatory compliance problems.
- QbD is good Science.
- Better development decisions.
- Empowerment of technical staff.
- Smooth process of method transfer to the production level.

Historical background

Quality by design has been seen as a new paradigm in the pharmaceutical industry, QbD is not that new. The history is given in the Table 2.⁹⁻¹¹

Table 2: History of QBD

Year	Activities
1950	Operation windows
1970	QBD created by Joseph M Juran
Sep 2002	QBD concept integrated by USFDA in cGMP
Sep 2004	USFDA release final report in "Pharmaceutical cGMP"
Sep 2004	USFDA Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
Nov 2009	ICH: Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
Jun 2008	ICH: Q10 Pharmaceutical Quality System

KEY ASPECTS OF ANALYTICAL QBD**Analytical target profile**

Analytical Target Profile (ATP) is analogous to Quality Target Product Profile (QTPP) element in QbD. ATP is way for method development and has been mentioned in the ICH Q8 R(2) guidelines. It describes the method requirements which are expected to be measured. Recently PhRMA and EFPIA defined ATP as: "ATP is a

statement that defines the method's purpose which is used to drive method selection, design, and development activities".¹²

General ATP for analytical procedures is as follows:¹³⁻¹⁴

- a) target analytes selection (API and impurities),
- b) Technique selection (HPLC, GC, HPTLC, Ion Chromatography, chiral HPLC, etc.),
- c) Method requirements selection (assay or impurity profile or residual solvents).

Critical Quality Attributes and risk assessment**CQA (Critical Quality Attributes)**

CQA for analytical methods includes method attributes and method parameters. Each analytical technique has different CQA. HPLC (UV or RID) CQA are mobile phase buffer, pH, diluent, column selection, organic modifier, and elution method. GC methods CQA are gas flow, oven temperature and program, injection temperature, sample diluent, and concentration. HPTLC methods CQA are TLC plate, mobile phase, injection concentration and volume, plate development time, color development reagent, and detection method. Nature of impurities and DS can define the CQA for analytical method development such as solubility, pH value, charged functional groups, polarity, boiling point, and solution stability. Table 3 represents the common ATPs and CQA for an HPLC method.

Risk Assessment

Upon identification of the technique, AQbD focuses on detailed risk assessment of the factors of possible variability in the method, such as analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. Traditional method development was based on testing the method after transfer whereas Analytical QbD necessitates the risk assessment step before method transfer and throughout the product life cycle.

Risk assessment strategy as specified in the ICHQ9 guideline: "it is systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle".¹⁵ This step is imperative in order to reach a confidence level that the method is reliable.

According to ICH Q9, risk assessment can be done in three steps viz., risk identification, risk analysis and risk



evaluation.¹⁶ Fig 2: describes different steps involved in Risk Assessment. The terminologies used in the diagram are discussed as follows.

Table 3: Represents the common ATPs and CQA for an HPLC method.

Sr. No.	Analytical Target Profile (ATP)	CQA with Risk Assessment		
		Low	Medium	High
1.	Number of analyte (API and impurities)			✓
2.	Separation of all analytes			✓
3.	Mobile Phase (buffer and organic modifier)			✓
4.	Elution method (gradient or isocratic)			✓
5.	Sample concentration			✓
6.	Sample diluent			✓
7.	Sample solution stability		✓	
8.	Sample preparation process (dilution process and sonication time, etc.)		✓	
9.	Filter or centrifuge		✓	
10.	Impurity specification limits			✓
11.	Column type (Stationary phase and Dimensions)			✓
12.	Detection category (UV/RID/ELSD)		✓	
13.	RRT, RRF establishment		✓	
14.	Flow rate	✓		
15.	Injection volume	✓		
16.	Column oven temperature		✓	
17.	Runtime		✓	
18.	System suitability parameters selection with Limits		✓	
19.	LOD and LOQ concentrations establishment			✓
20.	Impurities calculation method establishment			✓
21.	Recovery establishment			✓

The first step that is Risk Identification is extremely important to identify and prioritize potential risks. These risks could be method of operation of instrument, characteristics of reagent, cycle time etc. It is generally advisable to determine a contingent method incase the primary method fails. Flow charts and check lists are utilized to identify risk factors. Second step in the process is Risk Analysis. Tools which are employed in this step include Ishikawa Fishbone Diagram and the CNX approach. Cause and Effect diagram or the Ishikawa Fishbone diagram compartmentalizes the risks into different categories depending on their source. The other tool is the CNX approach where C indicates the high risk factors, N represents the potential noise factors and X is the factors which are to be experimented upon. According to this approach the risk factors are classified into the following categories:

- I. **High Risk Factors** – e.g. Sample preparation methodology. These are to be fixed during the Method Development process.
- II. **Noise Factors:** These are subject to an MSA study. Done through staggered cross nested study design and variability plots. These factors are subjected to robustness testing.
- III. **Experimental Factors:** e.g. Instrumentation and operation methods. Subjected to ruggedness testing and acceptable range is identified. The third step is Risk Evaluation which is done through Failure mode and effects analysis (FMEA) and the Matrix designs.¹⁸

Control Strategy

A planned set of control(s) for all possible variation(s) assures that ATP requirement would be met during analytical method transfer as well as routine use. This can be attained with continuous monitoring of CMAs or system suitability parameters. Control strategy is not always a one-time exercise that is performed only during method development, but it can get changed with different stages of method lifecycle.¹⁹

Lifecycle Management

Even after going through all the elements of QbD for a particular analytical method, method validation, verification and transfer are the key exercises that ensure fitness of the method for its intended use. Combining together, this is termed as '*lifecycle management of analytical procedure*', which starts with establishment of ATP and continues till the method is in use. The resultant confirmation with respect to ATP is the main focus for performance qualification, e.g., precision study on the site of routine use. Continual verification involves activities, which provide the assurance that the method is under control throughout its lifecycle.

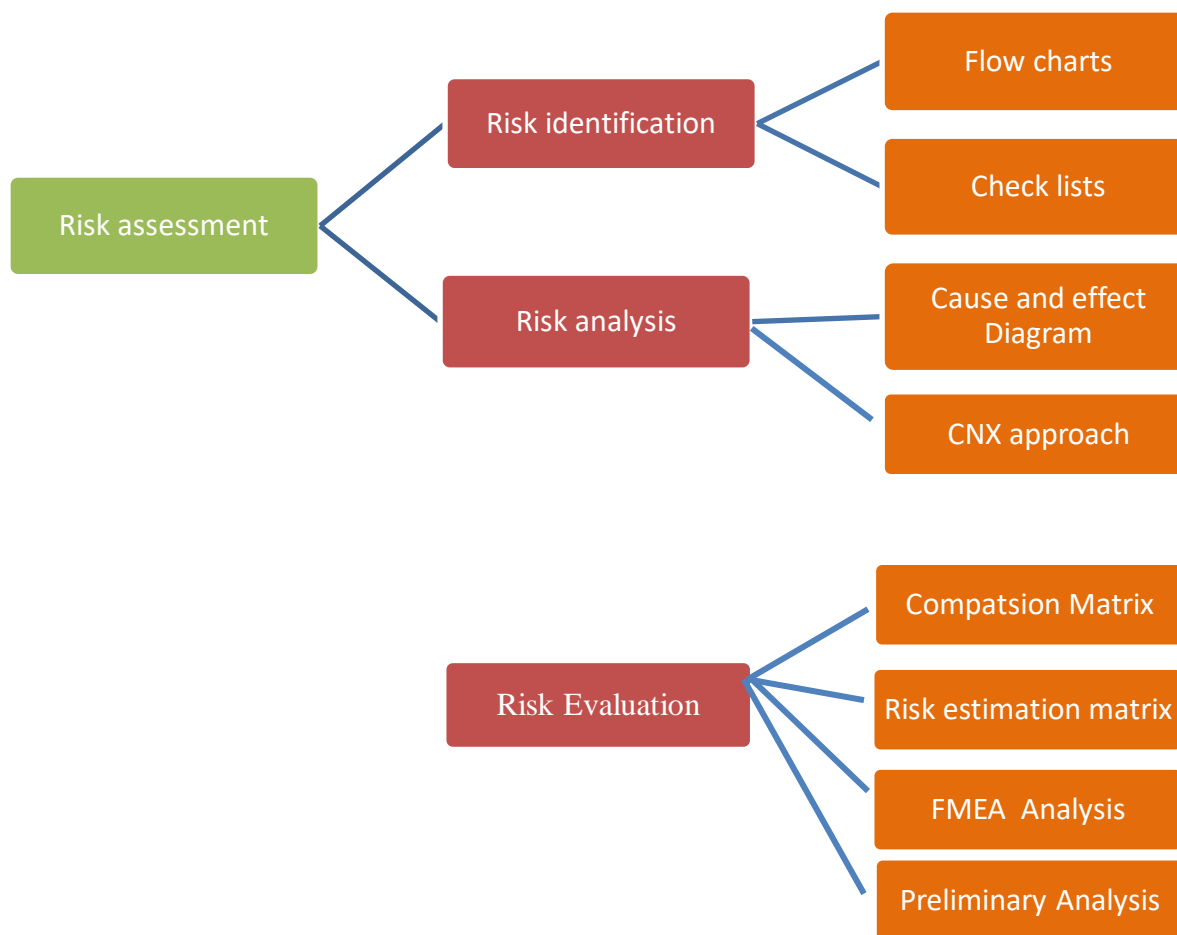


Fig 2: A sequence of steps involved in Risk Assessment and the various tools involved in the process as mentioned in ICH Q9 Guidelines.

Tools of QBD:²⁰

Design of Experiments

In accordance with the requirement of ICHQ8 guidelines, regarding “design space” in product development, method operable design region (MODR) can also be established in method development phase, which could serve as a source for robust and cost effective method. MODR is the operating range for the critical method input variable (similar to CQAs) that produces results which consistently meet the goals set out in the ATP. MODR permits the flexibility in various input method parameters to provide the expected method performance criteria and method response without resubmission to FDA. It is based on a science, risk based and multivariate approach to evaluate effects of various factors on method performance. FDA has suggested conducting MODR together with method validation as most recommended. Once this is defined, appropriate method controls can be put in place and method validation can be carried out. There are many analytical works which have been reported using experimental design based on factorial or fractional factorial design or response surface methodology. But those works were limited to the development of mathematical models to correlate input variables (X_n) and output responses (Y_n). The

implementation of DoE in method development phase requires a huge understanding in selection of input variables and output response. DoE in AQbD approach includes the following.

a) **Screening**

In screening, qualitative input variables can be screened out. It identifies the various critical method parameters (CMP) to be considered in the optimization experiments. In addition, it also works as a semi optimization tool to indicate the required levels of CMA for an optimization experiments. The various tool and selection approaches are shown in Table 4. The screening experiments should conclude the segregation of CMP that need to be either controlled or subjected to DOE techniques in MODR optimization.

b) **Optimization**

In this stage, quantitative measures for critical method in variables (i.e., CMP) either from screening or directly from risk assessment can be incorporated. It provides a base for scientific understanding of relation between quantities of input variables (CMP) and output response which will show considerable effect on method performance and ATP.

c) Selection of DOE Tools

During the optimization, many approaches can be used to derive a mathematical relationship (model). The decision on selection of tool for DoE has to be made based on the number of input variables, knowledge on controlled parameters, and scientific understanding between result and variable (if any). Statistical knowledge is prime importance to interpret the interaction and contribution of variables (X_n) in method responses (Y_n), serving as a tool to select the variables at optimum levels. For example, if the effect of all input variables and their

interactions are to be measured, factorial design can be applied then it can be considered and optimized with RSM (response surface methodology). Taguchi method can be used with lower number of experimental runs compared to factorial designs (say, 50%, 25%, etc.) but the interactions confounded need to be resolved. Where large numbers of input variables are to be studied without interaction effects, Plackett- Burman methods can be used. A typical selection of techniques is shown in Table 4.

Table 4: Selection of DOE tools in analytical quality by design.

Design	Number of variables and usage	Advantage	Disadvantage
Full factorial design	Optimization/ 2-5 variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables
Fractional factorial design or Taguchi methods	Optimization/ and screening variables	Requiring lower number of experimental runs	Resolving cofounding effects of interactions is a difficult job
Plackett- Burman Method	Screening or identifying vital few factors from large number of variables	Requiring very few runs for large number of variables	It does not reveal interaction effect
Pseudo- Monte Carlo sampling (pseudorandom sampling) method	Quantitative risk analysis/ optimization	Behavior and changes to the model can be investigated with great ease and speed. This is preferred where exact calculation is possible	For nonconvex design spaces, this method of sampling can be more difficult to employ. Random numbers that can be produced from a random number generating algorithm
Full factorial Design	Optimization/ 2-5 Variables	Identifying the main and interaction effect without any confounding	Experimental runs increase with increase in number of variables

d) Method Operable Design Region (MODR) and Surface Plots

A model contour plot (2D plot) for MODR concept is shown in Figure 3(a). The contour plot is a 2D response plot representing the impact of pH (x -axis) and % aqueous phase (y -axis) on retention time of analyte, whilst factors like flow rate and other instrument configurations are controlled. Numbers like -1, -2, +1, and +2 in both axes represent the coded level of variables used in DOE plan. This contour is suitable for the response if it is nonlinear and the relationship between input variable and method response is having more curvature effect. Then MODR can be selected from contours using mathematic models. The predicted value of method response can be verified by using actual experimental run as a part of model validation. There is another surface model that can be obtained by means of simulation that provides the change of response with respect to variables, which is more suitable for linear relationship Figure 3(b).

e) Model Validation

Prior to the choice from contour or graph, the predicted values for the targeted method response have to be validated by actual experimental run. Then regression analysis has to be carried out to validate the model statistically.

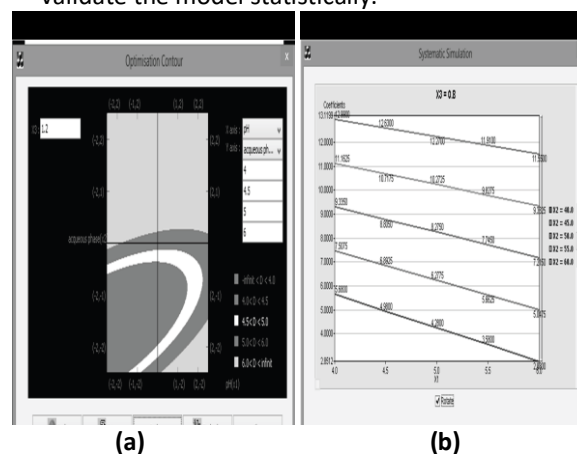


Figure 3: (a) Contour plot for MODR (retention time as method response). The above graph shows the different

shade for different region for retention time at different levels -2, -1, 0, +1, and +2. **(b)** Systematic simulation graph for retention time (*y*-axis) as method response at constant X3 (0.8 mL/min as flow rate) with change in pH (X1-*x*-axis).

Process analytical technology

For the effective implementation of process analytical technology (PAT) system, parallel development of analytical QbD is highly recommended. PAT is based on two major components: (a) understanding of the scientific and engineering principles involved manufacturing process; (b) identification of the variables which affect product quality. According to the FDA draft guidance, “the desired state of pharmaceutical manufacturing is that product quality and performance are ensured through the design of effective and efficient manufacturing processes” in which continuous and real time quality assurance was recommended. Once the properties of the drug product components are understood, the processing variables that control the relevant properties must be identified. Identification of these variables necessarily requires a multivariate approach. Now, pharmaceutical industries are in progress of establishing specific process understanding and design process analytical control strategies to make PAT approach more effective tool.

Risk Management Methodology²¹

Quality Risk Management is defined as “A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle”. Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data. The early list of potential parameters can be fairly broad, but can be modified and prioritized by additional studies (e.g., through a combination of design of experiments, mechanistic models). Once the considerable parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools and/ or internal procedures such as,

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)

- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering

Applications of Quality By Design²²⁻²³

➤ Application to Analytical QBD

- Development of a robust method.
- Understand, reduce and control sources of variability.
- Applicable throughout the life cycle of the method.
- Regulatory flexibility Movements within “Analytical Design Space” are not considered a change in method.

➤ Application to Industry:

- Ensures better design of products with less problems in manufacturing.
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation.
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny.
- Allows for possible reduction in overall costs of manufacturing –less waste.
- Ensures less hassle during review –reduced deficiencies –quicker approvals.
- Improves interaction with FDA –deal on a science level instead of on a process level.
- Allows for continuous improvements in products and manufacturing process.

CONCLUSION

QbD has gain importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. The main reason behind adoption of QbD is the regulatory requirements. Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of A QbD is the understanding from product development to commercial production. AQbD tools are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation, and continuous improvement. A QbD requires the right ATP and risk assessment and usage of right tools and performing the appropriate quantity of work within proper time lines. There needs to be steadfast commitment on the part of the pharmaceutical industry for this approach to succeed.



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