# Analytical Quality-by-Design: Concept, Implementation and Challenges

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## ABSTRACT

**Background:** The quality-by-design approach stands for its hallmark of quality that is built into the method. This approach is simplified by statistical software that requires an analyst to design a set of experiments as per its critical quality attributes and critical process parameters. This reveals the optimum conditions for method development, yielding a quality method with a high degree of robustness.

**Main Text:** Analytical quality-by-design paradigmis discussed here, for analysis of pharmaceuticals. Methods can be developed and validated for the estimation of drugs in bulk and formulation using the analytical quality-by-design approach. This approach is advantageous as it allows risk assessment prior to method validation, minimizing the chances of method failure and also provides regulatory flexibility.

**Conclusion:** This review gives a clear picture about the concept and implementation of analytical quality-by-design. It also throws light on the regulatory aspectsof QbD, along with the advantages and challenges underlying it.

**Keywords:** Analytical quality-by-design (AQbD), critical process parameters (CPP), critical quality attributes (CQA), design of experiment (DoE), risk assessment, lifecycle approach.

## INTRODUCTION

The concept of Quality-by-Design (QbD) has been getting considerable importance in pharmaceutical development and analysis. QbD is a systematic approach to pharmaceutical development with planned set of goals and focusses on the knowledge of product, process, its control on the basis of scientific and quality risk management [1].The International Conference on Harmonization (ICH) has framed quality guidance document, Q8 to enlighten the paradigm of QbD in Pharmaceutical Development. In relation to analytical systems, it is termed Analytical Quality by Design or AQbD [2,3].

The main objective of quality by design paradigm in pharmaceutical industries is to promote highly robust manufacturing and analytical processes with a view to boost product quality following the six sigma principles. Six sigma technique is a crucial segment of total quality management (TQM) and strives to achieve continuous improvement of processes. QbD arrived as a major breakthrough strategy to overcome out-of-trend (OOT), out-of-specification (OOS), out-of-control (OOC) and out-of-statistical-control (OOSC) results occurring in pharmaceutical industries [4,5].

QbD is a holistic approach that encompasses developing formulations, manufacturing and analytical processes and includes product specifications, critical process parameters (CPP) and critical quality attributes (CQA) to ease ongoing quality control and final regulatory approval

of the drug [6]. These details are to be elaborated in regulatory submissions. The ICH Q8 guidelines state that the concept of QbD can be implemented to API, generics, drug products, its components including excipients, container closure system; processes like formulation, manufacturing and analytical development. It also takes into consideration the physicochemical, biological, microbiological characteristics and compatibility studies.

## THE REGULATORY PERSPECTIVE OF QbD

The US FDA has mandated QbD for generics from January 2013. The generic drug companies are expected to include Quality by Design (QbD) into their Abbreviated New Drug Applications (ANDA), as per the Quality Module 3.2.P.2 Pharmaceutical Development.

Since the concept of QbD became so successful in pharmaceutical industry, FDA has been encouraging the implementation of QbD for the formulation, manufacture and analysis of pharmaceuticals. FDA has cited many reasons for nudging the use of QbD in pharma industry: considerable product quality is attained in pharma industry by utilizing ample amounts of efforts; less emphasis is laid on manufacturing of APIs, especially on development, although considerable cost is expended on manufacturing. The impact of scale-up on final product is also not estimated correctly. The causes of manufacturing failures are not evaluated or understood. Manufacturing problems, at times, also pose drug shortages. There is enormous scope for improvements based on new technologies requiring flexible regulatory controls for the globally spread pharmaceutical industry [7, 8].

Lately, FDA has furnished elaborate documents to assist on implementation of QbD for pharmaceutical product design, understanding of processes and the entire lifecycle management. Considerable stress is laid on performing in-process quality testing for minimizing process failures.

Likewise, the European Medicines Agency (EMA) and other ICH countries also promote QbD as a technique to assure drug quality by implementing the principles of statistics, assessment and risk-management methodologies for formulation, manufacture and analysis of pharmaceuticals. Since there are less chances of method failure using the QbD technique, it can considerably save the cost of rework which might be required in case of method failure. Thus it can reduce manufacturing, analytical and regulatory expenditure. Although QbD does not amend or lessen the regulatory requirements, it does provide scope for flexible regulatory approaches. The revalidation of analytical method is not required if QbD approach is followed, since changes within the approved design space are acceptable [9].

The principles of QbD are explained elaborately in the following ICH quality guidelines –

- ICH Q8 Pharmaceutical Development (scientific and risk-based approach)
- ICHQ9 Quality Risk Management(risk assessment)
- ICH Q10 Pharmaceutical Quality System (lifecycle approach)

Analytical testing of pharmaceuticals plays a vital role in the application of AQbD principles. The requirements of FDA can be met by the inclusion of QbD principles for updating the manufacturing and analytical processes. Therefore, the application of AQbD principles for analytical method development needs to be encouraged for elevated product-process quality.

As regards to inspections for analytical QbD method, the design, testing, and monitoring activities that showcase robustness and consistency should be focused. The FDA inspection will evaluate how effectively process design is implemented and whether scientific, risk-based, lifecycle approaches are applied successfully during analysis. Inspections would further evaluate overall quality, process improvements, change control procedures and deviation management.

## BENEFITS OF QbD

QbD presents several benefits for the pharmaceutical industry. The Quality by Design approach entitles pharmaceutical products to constantly meet its target specifications. It identifies, explains and controls the sources of variability affecting a process, avoiding further rework. It targets to build quality into a drug product from the very first step on the basis of knowledge of drug quality attributes and manufacturing process [10]. For example, characteristics like identity, strength, purity etc. may represent quality.

The technique is significant in that incorporating the QbD approach in regulatory submissions assures minimum complications during review. More perfection can lead to faster approval. Thanks to the adjustments within the approved design space, which omits further submissions to the regulatory authorities and creates a robustness domain for the process [11].

Other benefits of QbD include lesser problems during manufacturing, and the addition of advanced innovated technology that improves analytical process as well.

As regards to analysis, QbD reduces number of experimental runs in method development and validation. It promotes continuous improvement in the manufacturing and analytical processes, following the lifecycle approach for a product. This typically allows continuous verification of the process by real-time release testing and thus reduces testing of the finished products. The risk-based control strategy ensures preventive action for drug product quality [12].

## JUXTAPOSITION OF OFAT AND AQbD APPROACHES

The one-factor-at-a-time (OFAT) is the traditional way of analytical method development by experimentation of a single factor at a time. Now diving deep, one needs to clearly understand the differences between the OFAT and AQbD approaches in analytical method development [13, 14] refer table 1.

**Table 1. Differences between OFAT and AQbD approaches**

| Sr. No./Parameters | OFAT Approach | AQbD Approach |
|---|---|---|
| 1. Meaning | Optimization of only One Factor At-a-Time (OFAT) is performed and response evaluated. | Multiple factors are varied at-a-time and response is evaluated. |
| 2. Robustness of the analytical method | Robustness is narrow for process parameters used in analytical method development. | Yields highly robust method. |
| 3. Risk of method failure | High risk of method failure. | Low risk of method failure. |
| 4. Need for revalidation protocol | Revalidation protocol is often needed after method transfer or alternate method. | Revalidation protocol not needed. |
| 5. Cost effectiveness of method | Increases cost of the method due to method failure and revalidation. | Yields a cost effective method. |
| 6. Risk assessment | Not performed. | Forms a significant element of AQbD approach. |
| 7. Continuous Improvement | Not much scope | Greater scope |
| 8. Quality | Lower than that achieved by AQbD. | Higher quality of product/processes is achieved. |

## IMPLEMENTATION OF ANALYTICAL QbD

Analytical QbD begins with setting goals or analytical target profile (ATP) as per the intended use of the method. It requires a control strategy that encompasses identification, control of critical quality attributes (CQA), the critical process parameters (CPP) which have an impact on the CQAs, risk assessment, design plan by selection of appropriate design of experiment (DoE) and identification of design space/method operable design region (MODR). Refer table

2. It also includes regulation of analytical processes, operating conditions, monitoring specifications, method validation and a lifecycle approach [15].

**Table.2: List of some analytical target profiles (ATPs), critical quality attributes (CQAs) and critical process parameters (CPPs)**

| ATPs (Goals) | CQAs | CPPs |
|---|---|---|
| Quantitative analysis of API | Short analysis time | Flow rate |
| Analysis of degradation products | Good peak symmetry | Detection wavelength |
| Estimation of finished product | Increased number of theoretical plates | Type of column |
| Impurity profiling | Retention time | Column temperature |
| Stability studies | Resolution | Ratio of mobile phase |
| Dissolution profiling | Area | pH of mobile phase |

## RISK ASSESSMENT

Risk Assessment is also an important step in the entire QbD process. It helps in evaluating the amount of risk that could be taken safely without affecting the quality of product and process. Risks involved in process, equipment, input materials etc. should be evaluated. As QbD facilitates the lifecycle approach for a process or product, the assessment of risks aids in prolonging the life of the process or product, without further need of regulatory approvals if the modifications performed are in the boundaries of approved design space.

Risk assessment typically involves identification, analysis and evaluation of risk. This is followed by controlling the risk by reducing it, establishing safe limits for risk acceptance and reviewing the risk. At each step, the risk should be communicated properly to the concerned persons, so that timely actions are taken if the risk is unacceptable [16].

## THE FISHBONE/ISHIKAWA DIAGRAM

The fishbone/Ishikawa diagram shows the causes and effect relationship of various variables that can have an impact on quality. The independent variables influence the dependent variables and provide an estimate of the potential risks involved [17] Refer figure 1.

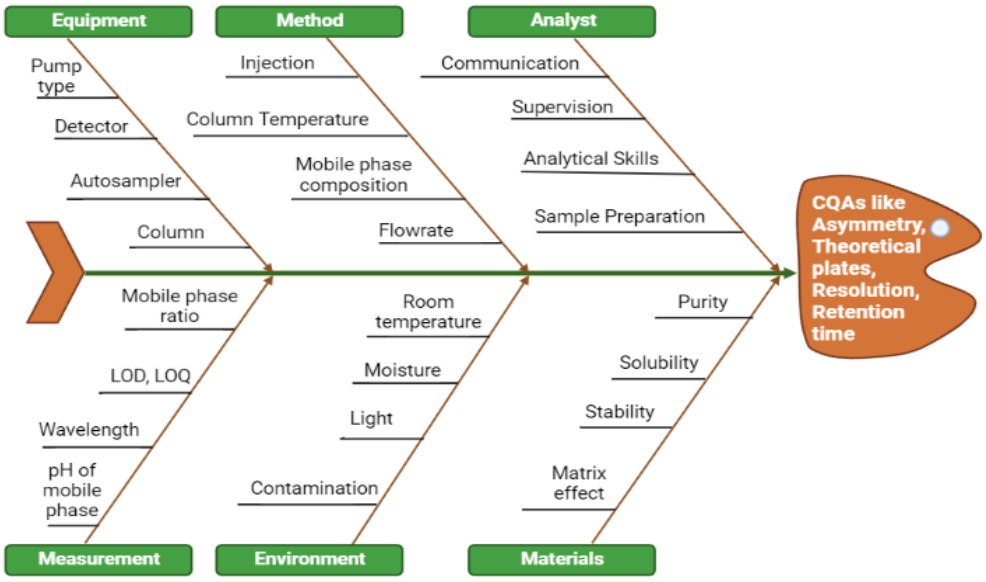
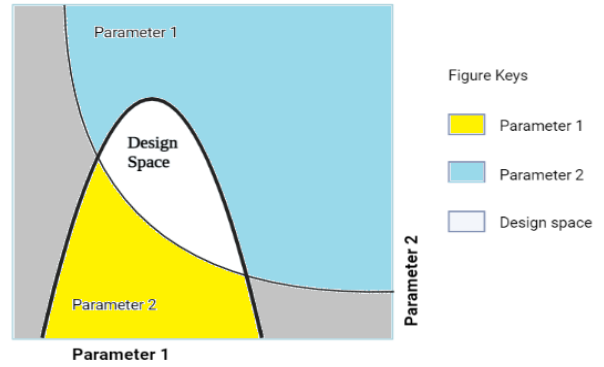



**Fig. 1 The fishbone (Ishikawa) diagram for risk assessment depicting association of several parameters on CQAs. The diagram shows various parameters related to the**

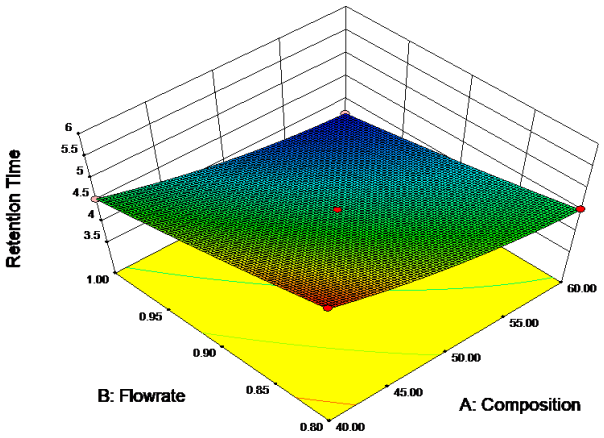
**analyst, method, equipment, measurement, environment and materials which can impact the critical quality attributes.**

## DESIGN SPACE AND 3D SURFACE PLOTS

Design space/method operable design region (MODR) implies the range in which the analytical method is operated. It involves association of various input parameters and quality attributes. This is the robustness domain of the method. Establishing a design space shows product-process understanding and provides manufacturing, analytical and regulatory flexibility. It is also called method operable design region (MODR) in analysis. From the regulatory perspective, the MODR/design space offers freedom for adjustment in a validated method, within the approved region only and is not considered a change. This avoids the extra work involved in revalidation of the method. Thus, MODR provides greater flexibility for the method during routine analysis [18]. MODR can be identified from 3D surface plots of desirability using mathematical models. Refer figures 2(a) and 2(b).




**(a)**




**(b)**

**Fig. 2(a) Design space/MODR for two parameters. The unshaded overlapping portion represents the design space. (b) Three dimensional (3D) surface plot for MODR concept, from predicted values of 3 input parameters: composition of mobile phase, flowrate and wavelength with retention time as output response.**

## DESIGN OF EXPERIMENTS (DoE)

Of late, there is an inclination towards the use of design of experiment (DoE) based approach in analytical method development. Literature reveals that it demonstrates a comprehensive understanding of the important analytical parameters affecting the method performance, potential risks and their interaction effects. It includes optimization of the method by evaluation of the most suitable technique through response surface methods. Thus, it reflects upon the MODR and proposes risk control methods for continual improvement. The DoE approach is

now-a-days widely used for generating effective and economic analytical methods for determination of drugs in bulk and formulations [19]. DoE is a systematic, structured and statistical plan of experiment that gives the relationship between input (independent X) variables and output responses (dependent y variables). Therefore, it is one of the most crucial aspects of analytical QbD.

## CHOICE OF EXPERIMENTAL DESIGN

Selection of experimental design should be based on different aspects like the aim of the experiment, number of input factors, their interactions, statistical significance and efficiency of each design. For better comprehension of the DoE methods, they are classified into two types: i) screening designs and ii) optimization designs [20]. Refer table 3.

## SCREENING DESIGNS

They allow one to assess multiple input factors with less number of experiments. Screening designs are frequently used in the initial step of DoE, to identify the most critical input factors and discard the insignificant ones. Pareto charts are bar graphs, which aid in the screening of significant input factors by representing the main and interaction effects of input factors. Screening designs commonly used areas follows –

- Two-level full factorial designs,
- Fractionate factorial designs and
- Placket-Burman designs.

## OPTIMIZATION DESIGNS

Screening designs present the limitation of allowing models with only 1$^{st}$ order, linear response, since they possess only 2 levels for each input factor. Optimization designs permit mimicking 2$^{nd}$ order, quadratic response surface. However, since they require large number of trials, few input factors are studied. Commonly used optimization designs that enable designing complex response surfaces are -

- Three-level full factorial designs,
- Central composite designs (CCD) and
- Box-Behnken designs (BBD).

**Table 3. Advantages, limitations, number of experiments, levels and factors for various experimental methods.**

| **Screening Methods** | | | | | |
|---|---|---|---|---|---|
| **Experimental Methods** | **Advantages** | **Limitations** | **No. of Experiments** | **Levels** | **Factors** |
| 1. Plackett-Burman | Requires very few trials for large number of input factors. | It does not reflect interaction effects. | N | 2 | < N-1 |
| 2. Fractionate factorial | Most widely used for screening as they allow evaluation of large number of input factors with a less trials. | Main effects one input variable may be distorted due to interaction effects of other input variables. Thus these designs may not be suitable for assessing the interactions among factors. | $2^{(k-p)}$ | 2 | k > 4 |

| | | | | | |
|---|---|---|---|---|---|
| 3. Two-level full factorial | Most powerful, assesses the main and interaction effects clearly. | Require a large number of experiments with increase in the number of factors. | $2^k$ | 2 | 2 < k < 5 |
| **Optimization Methods** | | | | | |
| 4. Box-Behnken Design | Permits estimation of the paameters of the quadratic model, building of sequential designs, detection of lack of fit of the model. | Only second-order model is possible, since it consists of only 3 levels for each factor. | 2k (k-1) + C | 3 | 3 < k < 5 |
| 5. Central composite design | It is traditional fractional factorial design. Thus, it has all the advantages of fractional factorial design. Since it consists of 5 levels for each factor, it is possible to test upto fourth-order model. | Less efficient as compared to BBD. | $2^k$ + 2k + C | 5 | 2 < k< 5 |
| 6. Three level factorial | Models possible curvature in the response function. Permits assessment of a quadratic relationship between the response and factors. | Expensive when the factor number is higher than 2. Less efficient as compared to BBD. | $3^k$ | 3 | 2 < k < 3 |

where k = number of input factors for experiments, p = number of generators chosen to fractionate the design, C = number of central points.

**Table 4. Examples of DoE applications in analytical QbD**

| Sr. No. | Experimental design | Independent variables (Xs) | Dependent variables (Ys) | Reference |
|---|---|---|---|---|
| 1 | Central composite design (CCD) | Acetonitrile to water, pH of buffer | Retention time, theoretical plates, peak asymmetry | Patel et al. 2021 [10] |
| 2 | Two-level factorial | flow rate, column temperature, oraganic concentration, gradient program | Resolution | B. Jayagopal, S. Murugesh. 2020 [21] |
| 3 | Box Behnken Design (BBD) | Flow rate, organic phase-% methanol, buffer pH | Retention time, tailing factor, theoretical plates | Yeram et al. 2019 [22] |
| 4 | Fractional Factorial Design | ratio of organic modifier, flow rate, column temperature, type of acid, concentration of acid, % TEA | Run time, tailing factor, theoretical plates, capacity factor, ecoscale, EAT score | Megahed et al. 2021 [23] |

| | | | | |
|---|---|---|---|---|
| 5 | Box Behnken Design (BBD) | ratio of organic modifier, flow rate, and column temperature. | Run time, tailing factor, theoretical plates, capacity factor, ecoscale, EAT score | Megahed et al. 2021 [23] |
| 6 | Box Behnken Design (BBD) | Buffer concentration, pH, volume of buffer | relative fluorescence intensity | S. M. Megahed, A. A. Habib, S. F. Hammad et al. 2021 [24] |

**Table 5. Some applications of QbD to various analytical methods**

| Method | Purpose | Reference |
|---|---|---|
| Chromatography: HPLC | Simultaneous estimation of drugs | Gupta et al. 2023 [25] |
| HPLC | Bioanalytical method development and stability studies | Pant et al, 2023 [26] |
| UPLC | Simultaneous estimation of drugs | Kannaiah et al, 2023 [27] |
| HPTLC | Estimation of drug in formulation | Bodas et al., 2023 [28] |
| Hyphenated technique: LC-MS/MS | Quantification of drugs and impurities | Rocha et al. 2023 [29] |
| Capillary electrophoresis | Quantitative analysis of compounds | Zhang et al, 2023 [30] |
| Karl Fischer titration | Determination of moisture content in tablets | Patel et al, 2023 [31] |
| Dissolution | Study effect on tablet dissolution | Mesut et al, 2023 [32] |

## STATISTICAL INTERPRETATION BY ANOVA

QbD requires statistical software for computing the results of the method and gives the best suited conditions for analysis. Analysis of variance (ANOVA) can be applied for selecting the experimental model. ANOVA provides significance of the experimental response. ANOVA is a test used to determine if there is a statistically significant variation between two or more groups by assessing the differences of mean using a variance. There are two common types of ANOVA tests, one-way and two-way (factorial) ANOVA. One-way ANOVA has one type of independent variable and a normally distributed continuous dependent variable. A two-way ANOVA differs from one-way in having two or more types of independent variables only.

ANOVA can be interpreted by using the F-value, which is the variance caused by treatment (varying the level of input factors)/variance due to random probability. The ANOVA F-value can indicate significant variation between the levels of the independent factors, in case $p < 0.05$. Thus, a higher F-value means that the treatment variables are significant and these can be included in the regression model, whereas if $p > 0.05$, such treatment variables are insignificant and should not be included in the regression model.

Another statistical determinant is the coefficient of determination ($R^2$), which is the amount of the variance in the output response that is predicted from the input variables. The coefficient of determination ($R^2$) is used to evaluate adjustment of regression models. The adjusted $R^2$ ($R^2$-adj) is a modification of $R^2$ used for adjustments in the terms of regression model. The $R^2$-adj value increases when a new term enhances the regression model; whereas, its value decreases when the term does not show improvement in the regression model. The predictive $R^2$ ($R^2$-

pred) predicts responses for new observations. The $R^2$ is always greater than $R^2$-adj and $R^2$-pred [33].

## AQbD LIFECYCLE MANAGEMENT

The umbrella of AQbD lifecycle management covers method monitoring and method improvement on a continuous basis. This serves as a regulation strategy for application of design space/MODR. One of the best features of AQbD approach is that, it permits setting of priorities and flexibility of movement in the robustness domain, which we call method operable design region (MODR). Since the AQbD technique, establishes working limits for the processes, it minimizes errors and subsequent corrective measures which would otherwise result in wastage of valuable resources, time and efforts. The continuous method monitoring (CMM) encourages knowledge sharing throughout the creation and execution of design space. This evaluates the results of risk assessments, control strategy, statistical parameters and the interaction of several factors like CPP, CQA, MODR, ATP. Method validation is a critical step after method development; the successful completion of which, allows the method to be used for routine analysis. Now, the method can be tracked for its performance. The whole system of AQbD lifecycle management safeguards against any deviations from specifications by predicting and identifying them [34].

## AQbD CHALLENGES

Just as every coin has two sides, the bundle of QbD does come with its set of challenges for the technical scientists and the regulatory bodies, abreast the benefits it unlocks. It requires a sound understanding and agreement on its concepts and terminology. It is important to sort out the relevant data required in applications. In the designing of experiments, the cost increases with the triple level complete factorial designs (in case factor number is greater than 2). The approach requires tremendous training of analysts in industries for getting expertise in its working, as well as education of regulatory agencies regarding the concept of QbD. The pharmaceutical industries should be able to manage how to efficiently work with legacy products in line with those addressed for QbD. Moreover, guidelines are needed regarding documentation of knowledge acquired during the implementation of QbD to analytical method. It also requires an agreement with the regulatory bodies or a post-market management plan. There should be a proper collaboration and co-ordination among inspectors, compliance and review. Lastly, steps need to be devised for implementing the QbD strategy worldwide [35].

## CONCLUSION

The AQbD technique has been a path-breaking advancement in the area of analytical research and promotes minimization of potential failures rather than responsive troubleshooting. The AQbD is a very rational and scientific approach to the development of analytical methods which is based on the application of QbD tools with ‘quality enhancement’ as the ultimate goal. One of the major advantages offered by AQbD approach is that it gives scope for risk assessment during the processes and thereby prevents the chances of method failure. Additionally, it encourages critical thinking, offers flexible regulatory approaches and is backed by sound statistical data. A key feature is the high degree of robustness imparted to the processes. Analytical methods are vital in the development and manufacture of a finished product. The analytical methods applying the QbD principles are not only economic but also time saving owing to the reduction of experimental work.

The combination of proper control strategy, choice of AQbD tools, continuous method monitoring and adopting the lifecycle concept leads to the success of AQbD paradigm. The faster the pharmaceutical industries equip themselves for implementing the AQbD principles globally, the sooner they would reap the benefits offered by this promising technique.

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