



Analytical method development and validation using the QbD approach: Review

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Abstract

A QbD is defined as “A systemic approach to the method development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. The QbD approach emphasizes product and process understanding with quality risk management and controls, resulting in higher assurance of product quality, regulatory flexibility, and continual improvement. The QbD method was based on the understanding and implementation of guidelines ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System. Analytical science is considered to be an integral part of pharmaceutical product development and hence go simultaneously during the entire product life cycle. Analytical QbD defined as a science and risk based paradigm for analytical method development, endeavoring for understanding the predefined objectives to control the critical method variables affecting the critical method attributes to achieve enhanced method performance, high robustness, ruggedness, and flexibility for continual improvement. The main objective of the present review article is to describe different steps involved in method development by the QbD approach for analytical method development.

KeyWords: Quality by Design (QbD), Analytical method development, Validation

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Introduction

A QbD is defined as “A systemic approach to the method development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [1].” The QbD approach emphasizes product and process understanding with quality risk management and controls, resulting in higher assurance of product quality, regulatory flexibility, and continual improvement. The QbD method was based on the understanding and implementation of guidelines ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System [2]. Analytical science is considered to be an integral part of pharmaceutical product development and hence go simultaneously during the entire product life cycle. Analytical QbD defined as a science and risk based paradigm for analytical method development, endeavoring for understanding the predefined

objectives to control the critical method variables affecting the critical method attributes to achieve enhanced method performance, high robustness, ruggedness, and flexibility for continual improvement [3, 4]. The result of analytical QbD is well known, fit for purpose, and robust method that reliably delivers the intended output over its lifecycle, similar to the process QbD [5, 6]. For QbD, HPLC methods, robustness, and ruggedness should be tested earlier in the development stage of the method to ensure the efficiency of the method over the lifetime of the product [7]. Otherwise, it can take considerable time and energy to redevelop, revalidate, and retransfer analytical methods if a non-robust or non-rugged system is adapted. The major objective of A QbD has been to identify failure modes and establish robust method operable design region or design space within meaningful system suitability criteria and continuous life cycle management.

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Quality, safety, and efficacy of pharmaceutical products have been the prime focus for regulatory agencies such as the United States food and drug administration (USFDA), and Medicines and Healthcare Products Regulatory Agency (MHRA). The recent recalls and warning letters have amplified the surmise on the quality of the drug products and resulted in a higher level of scrutiny by the regulators. Various guidelines (Q8, Q9, Q10, Q11, and Q12) have been introduced by ICH on the implementation of Quality by design (QbD) and PAT tools [8]. The quality of the pharmaceutical products can not solely be controlled by testing, instead it is expected to be built in by design. As per ICH guideline, Pharmaceutical Development Q8 (R2), "Pharmaceutical development is aimed at designing a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained during the product development give scientific understanding to define the design space, specifications, and manufacturing controls" [9]. QbD is an expectation from regulatory agencies to increase process and product understanding and thereby decreasing the risk for patients. From a manufacturer's perspective, it gives a better understanding of the product/process, and reduced regulatory burden. It gives regulatory flexibility to the regulators without sacrificing quality and to the patients, it gives increased assurance of product quality. Hence QbD implementation is a win-win-win situation for manufacturers, regulatory agencies, and patients. Analytical testing is one of the important aspects of pharmaceutical development. Having the right analytical method is vital in ensuring the quality of the drugs. Various analytical techniques are used to test the physical, chemical, and biological parameters of the subjected pharmaceutical product. Chromatographic techniques (HPLC, UHPLC, etc.) are the most widely used techniques in the pharmaceutical industry due to its advantages over the other techniques. The key challenge in front of the analytical chemist is to develop a robust and rugged analytical method with optimum separation with shorter run time. The traditional approach for analytical method development is based on 'trial and error'. In this approach analytical chemist optimizes one factor at a time by using his prior knowledge. This approach may result in getting stable method conditions but these may not be the optimal conditions. The methods developed based on a traditional approach may have robustness

related issues. Another approach for analytical method development is based on quality by design. It is based on sound scientific knowledge and starts with defining the separation goals, performing the risk assessment, conducting the design of experiments, and defining the MODR and control strategy. There are no specific guidelines on QbD based analytical method development, however, there are multiple methods reported that are developed based on the QbD principle [10]. The reported analytical methods utilized QbD application for various objectives such as method development, method optimization, robustness studies, etc. There are few review articles published on Analytical Quality by design [11]. Analytical methods require development, validation and controls just as any other product and process development activities. Measurement of API, key characteristics of the drug substance/product and impurities are essential for characterization and control of the drug. Analytical methods play an important role supporting implementation of QbD in process pharmaceutical development and development and manufacturing. Analytical testing also plays prominent role in pharmaceutical development, risk assessment, process monitoring and control and continuous quality assessment throughout the product. QbD is well-established in development and manufacture of pharmaceutical drug substance and drug product and is discussed in ICH Q8, Q9 and Q2. The same QbD approach can be applied to analytical procedures as per ICH Q2. In addition, there is now a technique to definitively link the data to its intended use. These are exciting times for testing laboratories and the users of the data they produce. The knowledge obtained during development helps to justify the establishment of a design space, process control strategy and set point within the (regulatory approved) design space. Materials made within the design space will produce an acceptable product, and changes within the design space are regulatory acceptable. QbD approach suggests looking into the quality of analytical process during the development stage itself. It says that quality should be built into the process design rather than testing into final results of analytical process. Analytical method development and validation are key elements of any pharmaceutical development program. An HPLC analysis method is developed to identify, quantify or purifying compounds of interest. This technical brief will focus on



development and validation activities as applied to drug products. Effective method development ensures that laboratory resources are optimized, while methods meet the objectives required at each stage of drug development. Method validation, required by regulatory agencies at certain stages of the drug approval process, is defined as the “process of demonstrating that analytical procedures are suitable for their intended use” [12-14]. Chromatographic method development can be time consuming and subjective process. As companies accelerate drug development programs and candidate compounds move through this process, fast and robust HPLC method development becomes increasingly important. Most method development is done using a manual, one-factor-at-a-time (OFAT) process where the approach is to vary one system parameter at a time and examine the resultant performance. This procedure is continued until no further improvement is obtained, at which time another parameter is selected for study. These separations are often sub-

optimal in terms of resolution, tailing, retention time and lack robustness. This can be particularly problematic when preparative chromatography is required to purify milligram to gram amounts of product, as compounds that appear to be well resolved at the analytical scale, may no longer separate efficiently when scaled up, necessitating either further method development or additional product purification steps. This process can be improved by applying a Quality-by-Design (QbD) strategy that develops analytical LC methods to meet performance requirements using sound statistical experimentation principles that accurately quantify system behavior and then scale these up for preparative separations.

Analytical Quality By Design (Aqbd)

Analytical Quality by Design (AQbD) is a systematic approach to design the methods that start with defining the separation goals and target method.

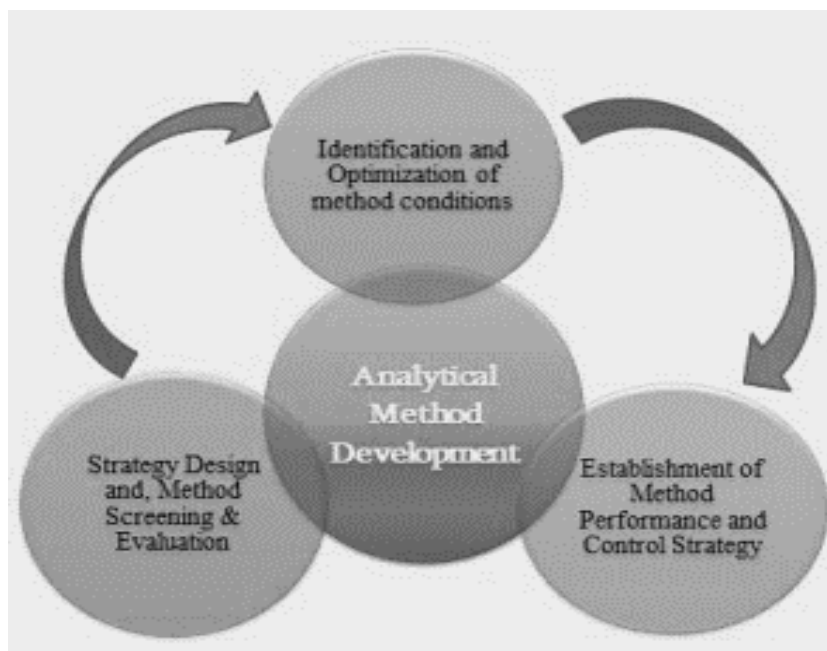


Figure 1: AQbD overview (Analytical)

Understanding of method parameters and controls, based on sound science and quality risk management are the key focus areas in AQbD. AQbD is also an integral part of the product development control strategy along with other parameters such as process parameters, material attributes, equipment operating conditions, in-process controls, and finished product specifications. Regulatory agencies do not define

any specific process of AQbD, however, a parallel approach can be drawn based on product QbD e.g. Quality target product profile (QTTP) can be inferred as Quality target method profile (QTMP), CQA can be interpreted as critical quality attributes such as tailing factor, the resolution between adjacent peaks, and plate count, etc. Design space can be called method operable design range (MODR) [15, 16]. In AQbD, critical method



parameters (CMP) are defined based on the technique involved and the method intent. Risk assessment is done based on prior knowledge, to shortlist the CMPs. Design of Experiment (DoE) is used to optimize the CMPs. DoE helps in understanding the interactions among the input variables and their effect on selected responses. AQbD paradigm is a preferred and recommended strategy to be followed in analytical method development to attain regulatory flexibility and to reduce Out of specification (OOS) and Out of trend (OOT) results.

Elements of AQbD

Critical Quality Attributes (CQA)

CQAs are the parameters which influence the method performance and can impact the results. CQAs are selected based on the techniques used (e.g. High performance liquid chromatography, and Gas chromatography) and the method intent (e.g. Assay, impurity estimation, drug release determination). Tailing factor, plate counts, % relative standard deviation of replicate injections of

the reference standard, and extraction efficiency (% recovery) are the CQAs for the assay determination method. In addition to these CQAs, the resolution between adjacent peaks could be an additional CQA for the impurity estimation method.

Quality target method profile (QTMP)

The quality target method profile is the target profile of CQAs, which is decided based on the intended use of the method and regulatory requirements. Pharmaceutical products are analyzed to ensure that the product meets its intended performance. Product performance comprises of drug safety and efficacy. To assess the drug efficacy, usually, pharmaceutical products are tested for assay and drug release. Similarly for safety assessment, impurities are estimated in pharmaceutical products. Hence while developing the analytical method, the most common goals are assay estimation, determination of drug release, and quantification of impurities in pharmaceutical products. A typical example of QTMP for the different methods is given in Table-1.

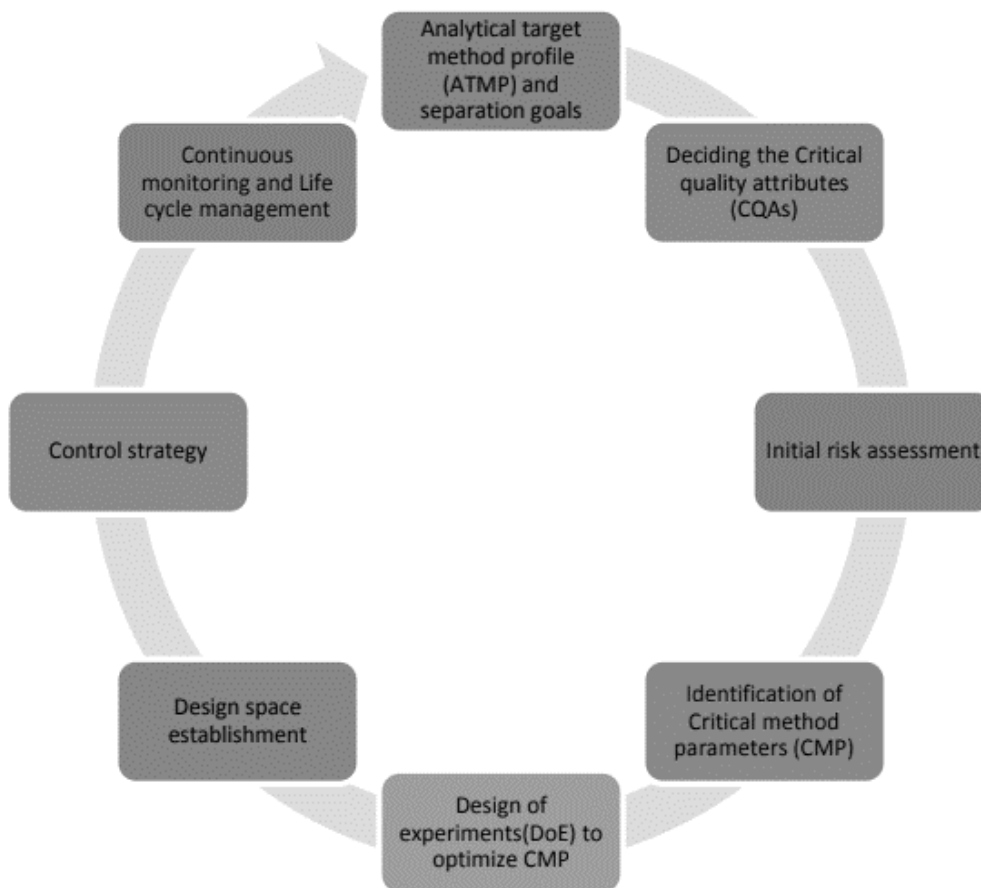


Figure 2: Analytical Quality by design (AQbD) elements



Table 1: Quality target method profile

Test	Critical quality attribute	Regulatory Requirement	Quality target method profile
Assay method	Tailing Factor %RSD1 Plate Counts Recovery Run time	NMT 2.0 NMT 2.0 NLT 2000 97.0% to 103.0% -	NMT 1.5 NMT 2.0 NLT 4000 97.0 % to 103.0 % <10 Minutes
Drug release method	Tailing Factor %RSD1 Plate Counts Recovery Run time	NMT 2.0 NMT 2.0 NLT 2000 95.0% to 105.0% -	NMT 1.5 NMT 2.0 NLT 4000 95.0 % to 105.0 % <7 Minutes
Impurity estimation method	Tailing Factor %RSD1 Plate Counts Resolution Recovery Run time	NMT 1.5 NMT 10.0 NLT 2000 NLT 1.5 97.0% to 103.0% -	NMT 1.5 NMT 10.0 NLT 4000 NLT 2.0 97.0 % to 103.0 % <30 Minutes

% Relative standard deviation of peak area from five replicate injections of reference standard.

Table 2: Categorization of Critical method parameters (CMP)

Sr. No	Category of CMP	CMP
1	Material attributes	Make and grade of reagents used for analysis e.g. buffers and ion pair reagents used in mobile phase preparation Quality of reference standard e.g. purity of standard HPLC columns of various lots Type of glassware used for analysis e.g. amber coloured or clear Type of filters used for sample filtration
2	Instrument related aspects	Dimensions and stationary phase of HPLC column Different HPLC detectors e.g. UV/PDA Make of HPLC e.g. Agilent, Waters HPLC system configuration e.g. diameter of tubing and size of injector loop
3	Instrument operating parameters	Column flow, column oven temperature, gradient program, detection wavelength, detector sampling rate, needle wash after injection
4	Method parameter	pH of buffer, concentration of buffer, organic modifier in mobile phase, diluent for sample preparation, sonication time

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Table 3: Critical Method parameters for HPLC, GC and TLC methods

Critical Method parameters			
Sr. No.	HPLC Method	GC Method	TLC Method
1	HPLC Column (dimensions, stationary phase, make, ageing)	GC Column (dimensions, stationary phase, make, ageing)	TLC plate stationary phase and coating thickness
2	Column Flow	Column Flow	Development distance
3	Column oven temperature	Column oven temperature	Temperature of solvent mixture (mobile phase)
4	Buffer for mobile phase	Carrier gas e.g. Hydrogen, Nitrogen	Composition of solvent mixture
5	Buffer concentration	Split flow	pH of solvent mixture



6	Concentration of additives (ion pair etc.)	Oven temperature program	Volume of sample solution spotted
7	pH of mobile phase buffer	Injector temperature	Size and shape of spot
8	Mobile phase gradient	Detector temperature	Drying time and conditions of TLC plate
9	Organic modifier in mobile phase	Type of injector liner	Technique used for visualizing the spot e.g. by spraying reagent, detection under UV light

Critical method parameters (CMP) and Risk assessment

Critical method parameters are the sensitivities associated with the analytical method. CMP has a cause-effect relationship with CQA and can impact the defined CQAs. CMP can be categorized into multiple categories such as material attributes, instrument-related CMP, operating parameters of instrument, and other method parameters. An example of typical CMPs of a HPLC method is given in Table-2. Critical method parameters (CMP) can be classified based on the technique also (High-performance liquid chromatography, Gas chromatography, and Thin layer chromatography, etc.). For a HPLC method, pH of the mobile phase, organic modifier in the mobile phase, and column oven temperature are the critical method parameters whereas for a Gas chromatography (GC) method, injector temperature, detector temperature, type of carrier gas, and split ratio could be the critical method parameters. Categorization of CMP based on technique is given in Table-3. For a HPLC method, the column aging (CMP) can impact the tailing factor and plate counts (CQA). Similarly, during sample preparation, sonication time (CMP) has an impact on drug extraction efficiency (CQA). After finalization of CMP and CQA, risk assessment is performed based on prior knowledge to shortlist the CMPs for further evaluation through Design of experiments (DoE).

Design of Experiments (DoE)

Design of experiments (DoE) is a series of tests, in which changes are made to input factors so that the causes for significant changes in the output responses can be identified. DoE is a statistics optimization tool, which helps in achieving a predictive knowledge of a complex, multivariable process with the fewest trails possible.

Selection of input variables and responses

Based on initial risk assessment, CMPs are shortlisted and are subjected to the Design of experiments (DoE) for further optimization. CMPs are input variables (factors) in DoE and could be qualitative or quantitative in nature. Qualitative variables are different columns, the grade of the buffer, and ion pair reagent for the mobile phase. Quantitative variables are column flow rate, column oven temperature, and concentration of organic modifier in the mobile phase, etc. After the selection of input variables, responses are finalized. Critical quality attributes (CQA) are the responses in DoE. Again, the response could be quantitative or qualitative in nature. A qualitative response could be acceptable/not acceptable (1/0) e.g. when the impact of the grade of buffer in the mobile phase on the interference at the retention time of analyte peak, is studied, the response would be either Yes or No. Quantitative responses are resolution between adjacent peaks, tailing factor, recovery of drug from the sample matrix, etc. The selection of levels for the input variables is the next step in DoE. Levels are selected based on the normal operating ranges (NOR) of the selected variables e.g. for column flow rate in HPLC, NOR is $\pm 2\%$, hence the levels selected for DoE for column flow rate should be broader than $\pm 2\%$ (e.g. $\pm 10\%$) from the centre point. Usually, 3 levels (including center point) are selected for DoE.

Selection of design

The selection of design is an important aspect of DoE and is made based on the purpose of DoE. Screening DoE is used to find out the most critical variables among multiple variables. More variables can be studied by using this category of designs and only the main effects can be understood e.g. fractional factorial and Plackett-burman design. Advanced screening designs are used to study the main effects and interactions among variables e.g. Full factorial design. Optimization designs are used



to optimize critical variables e.g. Full factorial, Box Behanken, and central composite designs.

Method validation

A finalized analytical method can be taken for method validation. Analytical method validation is performed based on ICH guidelines on Analytical method validation to demonstrate that the developed analytical method fits for the purpose. Specificity, precision, accuracy, linearity, ruggedness, robustness, ranges, and limit of detection/limit of quantitation are the parameters, usually performed during method validation. Method validation parameters are selected based on method intent e.g. for testing for the impurities-limit test, specificity and detection limit are adequate whereas, in case of testing for the impurity-quantitative test, all the above-listed parameters are required. For the assay estimation method, detection limit and quantitation limit tests are not required. After successful validation, the analytical method can be implemented for regular analysis of Pharmaceutical products.

Continuous monitoring and life cycle management

After successful method validation, the analytical method is implemented in the quality control lab for routine testing. During this process, certain challenges may arise due to differences in the operating environment, the model of instruments, etc. These challenges need to be looked very carefully and accordingly, adjustments should be made in method conditions within a method operable design range. It is also expected that the analytical method may need some changes or improvements during the product life cycle due to continuous improvement, unplanned deviations, and operating in a different environment. As a part of continuous improvement, the performance of the analytical method is monitored by doing a trending of incidents, out of specification (OOS), and out of trend (OOT) occurred during a specified time. Based on the trending, if a trend emerges which indicates a specific concern in the analytical method, it is relooked and necessary improvements are done. If the improvements/changes are within the defined method operable range, it will not call for any additional method validation but when changes are beyond the MODR, these need to be validated appropriately. Sometimes based on the outcome of the investigation of out of trend or out

of specification, the identified root cause is related to the analytical method. In such cases, necessary precautions are added in the standard testing procedure to prevent the reoccurrence of a similar incident.

Key Benefits Of Qbd In Analytical Method Development

The key benefits of method development by using Analytical Quality by design approach are given below

- ✓ A systematic approach to method development.
- ✓ It is helpful in building insights into the critical attributes of the analytical method.
- ✓ DoE reduces the number of experiments to reach optimal conditions.
- ✓ Ensures the method robustness by design.
- ✓ It helps in reducing the Out of specification (OOS) and Out of trend (OOT) results during analysis
- ✓ It reduces the costly and time consuming investigations.
- ✓ It helps in eliminating batch failures due to analytical method variations.
- ✓ Avoid deficiencies from regulatory agencies.
- ✓ Adjustments within "Design Space" are not considered a change in method.
- ✓ It helps in gaining regulatory flexibility.
- ✓ Enhanced assurance on quality.

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Conclusion

As numerous factors, such as instrument settings, sample characteristics, method parameters, and calibration model selection, have a substantial impact on the method results, it is crucial to apply the QbD principle to analytical methods. Implementing QbD offers the chance to achieve regulatory flexibility but necessitates a high degree of robustness, product quality, and analytical method development due to the fact that the chromatographic technique is the most widely used analytical tool in pharmaceutical quality control and the number of variables involved are almost equivalent to those involved in formulation and development protocols for dosage form. Analytical method transfers in QbD are possible and will allow for better, more effective, and continual method upgrades going forward.

Conflict Of Interest

None. Declared by Author.



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