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A Review on Application of Quality by Design Concept to Analytical Method Development

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ABSTRACT

Quality is a heart of the pharmaceutical industry. The ICH Q8-Q11 is described the concepts of Analytical Quality by design (QbD) for drug and related substance. The ICH Q8 is Pharmaceutical Development, ICH Q9 is Quality Risk Management, and ICH Q10 is Pharmaceutical Quality Systems is the ICH guidelines gives the complete procedure for applying analytical QbD process. QbD technique particularly used for developing the analytical method for selected drugs to identifying and quantifying the active content and minimizing source of variability. The applications of multivariate statistical techniques for the optimization of chromatographic and Spectroscopic systems. The surface response methodologies, central composite design, Doehlert matrix, and Box– Behnken design systems. for QbD. A very useful component of QbD is the understanding of factors and their interaction effects by a desired set of experiments. For the purpose of QbD for HPLC methods, robustness and ruggedness should be verified early in the method development stage to ensure method performance over the lifetime of the product. Quality by design principles are applied to build in a more scientific and risk based multi-factorial approach to the development and validation of analytical methods using HPLC and spectroscopic technique

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INTRODUCTION

Analytical methods play an important role supporting the implementation of QbD in process Pharma cuticle development and development and manufacturing. Analytical testing also plays the prominent role in Pharmaceutical development, risk assessment, process monitoring and control and continuous quality assessment throughout the product. Quality by design (QbD) is well established in development and manufacture of pharmaceutical drug substance and drug product and is discussed in ICH Q8, [1] Q9 and Q2. The same QbD approach can continuous quality 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 regulatorily acceptable. Quality by Design 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. QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management‖. In alignment with the approach proposed in the draft FDA guidance for process validation, a three-stage approach can the to method validation.[2]

Stage1. Method Design: Define method requirements and conditions and identify critical controls.

Stage2. Method Qualification: Confirm that the method is capable of meeting its design intent. Stage3. Continued Method Verification: Gain ongoing assurance to ensure that the method remains in a state of control during routine use. A critical function of Stage 1 is the design of an Analytical Target Profile (ATP) for the method. To design the ATP, it is necessary to determine the characteristics that will be indicators of method performance for its intended use. These are selected from the performance characteristics described in ICH Q2 as per the traditional approach. Instead of being applied in a tick box manner, they are

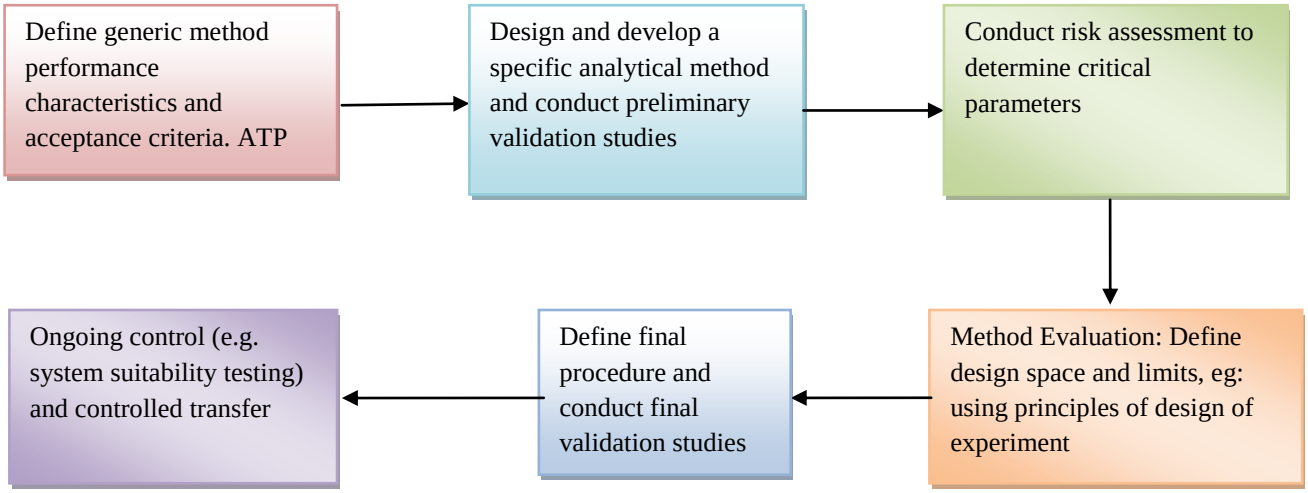

Fig. 1-QbD workflow

Investigated by a risk assessment exercise as described in ICH Q9 in combination with carefully designed development studies to identify the critical method and sources of variation. Variables are then investigated by robustness and ruggedness experiments to understand the functional relationship between method input variables and each of the method performance characteristics and the results are compared to the desired outcome defined in the ATP. From this, one can identify a set of operational method controls. Also, having evaluated the critical method parameters and gained a better understanding of the method through structured experimentation.[3] Addition to validating the method characteristics as per regulatory guidance, verifying the accuracy and precision provides additional understanding of the method‘s measurement uncertainty and confirms conformance to the previously defined method performance requirements (ATP). This can be accomplished through a joint accuracy and precision.

Analytical Quality by Design (AQbD) as per ICH, QbD is defined as “A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.” Equivalent to process QbD, the outcome of AQbD is well understood and fit for intended purpose with robustness throughout the lifecycle. AQbD life cycle has different tools such as ATP (Analytical Target Profile), CQA [5, 6], Risk Assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy and Risk

Assessment, AQbD Method Validation, andContinuousMethodMonitoring.Figure2 represents the AQbD life cycle with each tool.

Scientific QbD Approach for Synthesis and Analysis. ICHQ11 has explained the QbD approach for API synthetic process development but there is no specific discussion on AQbD. However, it is recommended to implement QbD approach in analytical method development termed as AQbD. These two scientific approaches (QbD and AQbD) can be progressed in equal time. Figure 2 represents the necessary steps in API synthesis and analytical development with QbD implementation. This simultaneous implementation produces a high-quality product. It may give better input for initiation of process analytical technology (PAT). The expression of tools in QbD and AQbD is different for synthetic development and analytical development. Both QbD and AQbD tools are presented inTable1.

Fig. 2: A QbD tools and life cycle.

Table1: QbD tools for synthetic development and analytical development.

Steps	Synthetic development (QbD)	Analytical development (AQbD)
1.	QTPP identification	ATP(Analytical Target Profile) identification
2.	CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
3.	Define product design space	Method Optimization and development with DO
4.	Control Strategy with Risk Assessment	Control Strategy with Risk assessment
5.	Process validation	AQbD Method Validation
6.	Continuous process monitoring	Continuous Method Monitoring

Regulatory Aspect of Analytical QbD:

In August 2002, with the introduction of 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach', by USFDA the concept of Quality by Design and continuous improvement was introduced in the pharmaceutical industry. In 2005, USFDA insisted CMC documents be submitted in QbD format. QbD concepts are well defined in ICH guidelines Q8 (R1): Pharmaceutical development, Q9: quality risk management, and Q10: pharmaceutical quality system. ICH Q8 (R2) guidelines do not discuss analytical method development in correlation with design space; however it is understood that the concept can be applied to analytical design space and continuous improvement in method robustness and understanding [7] In present days, analytical method failure is becoming more common especially during method transfer as well as in quality control departments. It is presumed to be due to the exception is given for robustness test compliance by ICH Q2 guidelines. The latest rise in the Quality Control warning letter issued by the FDA to pharmaceutical companies highlights the need for the development of more reliable (robust and rugged) analytical techniques. Therefore, QbD applied to analytical methods is the only way forward. ICH Q10 includes an analytical method as a part of the control strategy. There were few conferences, during late 2013 and early 2014, insisting on the implementation of the existing QbD concept to analytical method development [9] Critical analytical factors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. Analytical

Technical group (ATG) and European Federation of Pharmaceutical Industries and Association (EFPIA) have given clear ideas about parallel implementation of QbD to analytical method.

Implementation of QbD

A framework for applying QbD to analytical methods

QbD can be applied equally to processes and analytical. It displays how QbD for methods, analytical methods are driven by the overall process.

Method performance requirements (Design intent)

Fundamental to any method development is being clear about the design intent of the method (i.e., the criteria that must be met). Method-performance criteria and method-operational intent are two important aspects of this design intent.[8]

Method performance criteria

These criteria are driven by an understanding of the process monitoring and control requirements; that is, the process critical quality attributes (CQAs) and specification limits. CQAs are identified, through a thorough understanding of those characteristics of a drug substance or a drug product that may need to be controlled to ensure the safety or efficacy of a product. For methods measuring these CQAs, criteria, such as the following, would need to be met.

- Precision—the need for method variability to be a small proportion of the specification,
- Selectivity—being clear on which impurities actually need to be monitored at each step in a process and ensuring adequate discrimination between them.
- Sensitivity-ensuring the method is sufficiently sensitive relative to the specification limit.[9]

PAT methods often meet the criteria above in a different way from traditional end-point testing methods such as high-performance liquid chromatography (HPLC). Selectivity, for example, may be achieved through a multivariate model as opposed to the resolution between

adjacent peaks in an HPLC method. For these methods, precision could be demonstrated by checking the predictive validity of the model.

Method operational intent

These criteria address the aspects of the method that are required to facilitate ease of use in routine operation (e.g., analysis time, acceptable solvents, available equipment). Opportunities for the implementation of improved or new technology also may be identified. These criteria can be generated by performing an analysis of the voice of the customer (VoC) (i.e., the aspects of a method that are considered important for the quality control laboratories within manufacturing where the commercial methods will be operated).[10]

Method development (design selection)

Fundamental to design selection is the method-development phase. To develop a QbD method, the method performance criteria must be understood as well as the desired operational intent that the eventual end user would wish to see in the method.

Application of QbD in analytical methods of measurement

QbD does not necessarily mean less analytical testing ‘rather, it means the right analysis at the right time and is based on science and risk assessment. Implementation of QbD helps to develop the rugged and robust method which helps to comply with ICH guideline hence for that reason pharmaceutical industries are adopting this concept of QbD. Factors which improve robustness are taken into consideration for the development of the analytical method in QbD environment. This approach facilitates continuous improvement in the method. Parallel opportunities of application of QbD to analytical method as that of the manufacturing process are available in the literature. It suggests that approaches like target profile, design space, and risk assessment are applicable to the analytical method also. Though it is not adopted by all pharmaceutical industries it has future perspective because it may become mandatory by regulatory bodies. Voluntary adoption of this concept by industries is possible because of its various benefits, and ease of compliance with regulatory authorities. Pharmaceutical Research and Manufacturers of America (PhRMA), Analytical Technical Group (ATG) and European Federation of Pharmaceutical Industries and Association (EF-PIA) have given clear ideas about parallel implementation of QbD to analytical method. QbD can be applied for various analytical method Chromatographic techniques like.[11]

- HPLC (For stability studies, method development, and determination of impurities.
- A hyphenated technique like LC-MS.
- Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis.
- Karl Fischer titration for determination of moisture content.
- Vibrational spectroscopy for identification and quantification of compounds e.g. UV.
- Analysis of genotoxic impurity.
- Dissolution studies.
- To biopharmaceutical processes.

Application QbD or elements of QbD to analytical method

In determination of impurity

Gavin gives a quality by design approach to impurity method development for atomoxetine hydrochloride. An ion-pairing HPLC method was developed and associated system suitability parameters for the analysis of atomoxetine hydrochloride are studied. Statistically designed experiments were used to optimize conditions and demonstrate life cycle robustness for the separation of atomoxetine and impurities. Weiyong Li describes a three-step method development/optimization strategy for HPLC assay/impurity methods for pharmaceuticals i.e. multiple-column/mobile phase screening, further optimization of separation by using multiple organic modifiers in the mobile phase, and multiple-factor method optimization using Plackett–Burman experimental designs. Commercially available chromatography optimization software, Dry Lab was used to perform computer simulations.

In screening of column used for chromatography

The particulars of the experimental design, evaluation criteria used and some of the most commonly used analytical columns from reputed column manufacturers. A systematic approach is used to evaluate seven RP-HPLC columns against predefined performance criteria. This approach is a fundamental part of a QbD method development.

In development of HPLC method for drug products/substances

A novel approach to applying quality by design (QbD) principles to the development of high pressure reversed phase liquid chromatography (HPLC) methods. Four common critical parameters in HPLC – gradient time, temperature, pH of the aqueous eluent, and stationary phase are evaluated within the quality by design framework by the means of computer modeling software and a column database.[12]

Instability studies

An application of quality by design (QbD) concepts to the development of a stability indicating HPLC method for a complex pain management drug product containing drug substance, two preservatives, and their degradants are described. The initial method lacked any resolution in drug degradant and preservative oxidative degradant peaks, and peaks for preservative and another drug degradant. The method optimization was done using Fusion AE™ software that follows a DOE approach. The QbD based method development enabled in developing a design space and operating space with particulars of all method performance characteristics and limitations and method robustness within the operating space.

In UHPLC

Rapid high-performance liquid chromatography with high prediction accuracy, with design space computer modeling, which demonstrates the accuracy of retention time prediction at high pressure (enhanced flow-rate) and shows that the computer-assisted simulation can be used with enough precision for UHPLC applications.

The validation and verification experiments demonstrate that the method is robust across the parameter ranges provided in Table 2. However, in this particular method example, a method control strategy was enacted that constrained the organic modifier to 63% (rather than the verification level of 62%) and fixed the flow rate to 1.00 mL/min to ensure acceptable retention of degradation products. [13]

Opportunities of and barriers against a QbD approach to analytical methods [14]

There are several opportunities of this QbD approach to analytical methods, including:

- Methods will be more robust and rugged, resulting in fewer resources spent investigating out-of-specification results and greater confidence in analysis testing cycle times.

- Resources currently invested in performing traditional technology transfer and method validation activities will be redirected to ensuring methods are truly robust and rugged.

- The introduction of new analytical methods—from research and development to quality control laboratories—using a QbD approach will lead to a higher transfer success rate than with traditional technology-transfer approaches.

- A specified process will help the systematic and successful implementation of the QbD methodology and fosters a team approach.

- A true continuous learning process is established through the use of a central corporate knowledge repository that can be applied to all methods.

- By registering only a commitment to ensure method changes meet the registered method performance criteria, flexibility to continuously improve methods can be achieved.

- The QbD approach to analytical methods also faces several barriers, including the following:

- Current expectations of analytical technology transfer and method validation must change because current validation guidance does not lead to methods that can always be reliably operated.

- Acceptance must be gained for registration of the method performance criteria rather than the method conditions.

- External guidance must be developed in this area; ICH guideline Q2(R1) requires revision (or removal) and Center for Drug Evaluation and Research guidance must be created for analytical methods.

- A common language for some of the new terms is required, including analytical method design space, analytical method control strategy, and method performance criteria.

- Analysts must learn new tools and skills.

- A consistent worldwide approach is required for this initiative to be effective.

Risk and Benefits:

Benefits of AQbD

1. Development of a robust method.

2. Sources of variability can be better controlled.

3. Better Regulatory flexibility - Movements within "Analytical Design Space" are not considered a change in method. This high cost is avoided by the firm.

4. Method Transfer success is greater when a method is transferred from research level to quality control department.

5. It provides a space for the invention of new techniques by continuous improvement throughout the lifecycle.

6. Enhanced understanding of the knowledge space.

7. Fewer OOS, OOT, OOC results.

Factors impeding implementation on AQbD

1. Complete understanding of AQbD is still lacking in the pharmaceutical industry.

2. Proper definitions of the MODR, ATP, analytical method control strategy, and method performance criteria and other elements of AQbD must be given. Global harmonization of these terminologies is a must.

3. Revision of ICH guideline Q2 (R1) requires revision to include AQbD elements. Additional guidelines need to be developed for implementation of AQbD.

4. Analysts must learn new tools and skills.

5. A consistent worldwide approach is required for this initiative to be effective.

QbD can be applied for various analytical methods which include

1. Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).

2. A hyphenated technique like LC-MS.

3. Advanced techniques like mass spectroscopy, UHPLC, and capillary electrophoresis.

4. Karl Fischer titration for determination of moisture content.

5. Vibrational spectroscopy for identification and quantification of compounds e.g. UV method.

6. Analysis of genotoxic impurity.

7. Dissolution studies.

CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. The process detailed in this article illustrates how QbD can be applied to the development and evaluation of analytical methods. Analytical methods play an essential role under QbD.

- Support product and process development.
- Enable advanced strategies like PAT.

Regulatory flexibility is achievable by applying QbD approach to the design of analytical methods but requires a very high degree of understanding and robust quality systems Rather than continuing to perform analytical technology transfer exercises and ICH validation, a QbD approach based on a risk-assessed change control procedure should be adopted. Each time a method is changed, a risk assessment should be performed. Where the change is identified as having a potential to take the method outside its known design space, a method evaluation and, if appropriate, an equivalency exercise should be performed to ensure method performance criteria are still met.

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