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Analytical Quality by Design: Concise Review on Approach to Enhanced Analytical Method Development

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ABSTRACT

In the last few decades, the pharmaceutical industry has been rapidly progressing by focussing on various aspects of formulation and analytical development such as product Quality, Safety, and Efficacy. It is reflected through the increase in number of product development by the increased use of scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). ICH guidelines Q8 to Q11 have specified QbD implementation in API synthetic process and also in formulation as well as analytical development. QbD has earned considerable reputation by formulation developers. It has enhanced the inculcation of scientific outlook and assessment of risks at an early stage. In this review, we have focussed on the implementation AQbD for API synthetic process and analytical methods development. AQbD key tools are identification of ATP (Analytical Target Profile), CQA (Critical Quality Attributes) with risk assessment, and, MODR (method operable design region). AQbD intends to provide product with highest quality through the minimisation of risks and also by providing good input for PAT approach. Thus, AQbD can act as an effective method towards innovative approach of Analytical Method Development along with meeting the necessary desired specifications.

KEYWORDS: *Quality by design, AQbD, Analytical target profile, ATP, risk assessment*

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1. INTRODUCTION

In recent years, the pharmaceutical industry has increased the main focus on product Quality, Safety, and Efficacy. the quality of product has been increased through the implementation of scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). The QbD tools have the ability to minimize the risk by increasing the productivity and quality by varied mechanisms. Also, nowadays QbD approach has been successfully implemented in generic formulation development too. Regulatory authorities increasingly prescribe the implementation of ICH quality guidelines Q8 to Q11. QbD principles which specifically have been applied to the development of analytical methods, and are termed as "Analytical QbD" (AQbD). The results of AQbD could be a well understood, robust method that consistently delivers the intended performance throughout the product lifecycle. Analytical Quality advisedly (AQbD). QbD is a specific approach to development which begins with a set of predefined objectives and focusses on product and process understanding and process control, on the idea of strong knowledge domain along with presence of quality risk management. adore process QbD, the result of AQbD is well understood and suitable intended purpose with robustness throughout the lifecycle. AQbD life comprises of assorted tools such as ATP (Analytical Target Profile), CQA, Risk Assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy and Risk Assessment, AQbD Method Validation, etc

Differences between conventional approach and QbD approach is as shown below in Table-1

Table-1 Differences between conventional approach and QbD approach

QbD	AQbD
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding.
Here, any specifications are based on batch history	Here, any specifications based on product performance requirements.
It includes only data intensive submission which includes disjointed information without "big picture".	It includes Knowledge rich submission which shows product knowledge & process understanding
Here there is "Frozen process," which always discourages any changes further.	Here there is Flexible process within design space which allows continuous improvement during the product life cycle.
It focuses on reproducibility which often avoids or ignores variation.	It focuses on robustness which understands and control variation

2. Scientific QbD Approach for Synthesis and Analysis

The QbD approach for API synthetic process development has been explained by ICHQ11. But here specific discussion is available on AQbD. However, it is highly recommended to implement QbD approach in the process of analytical method development which is termed as AQbD. These two scientific approaches (QbD and AQbD) can be progressed in successive time. The crucial steps in API synthesis and analytical development are performed with implementation of QbD. This simultaneous implementation helps to produce a product with high quality. It may also give better input for process analytical technology (PAT) initiation. The expression of tools in QbD and AQbD is different and specific for synthetic development and analytical development. Both QbD and AQbD tools are presented in Table 2.

Table 2: QbD tools for synthetic development and analytical development.

Synthetic development (QbD)	Analytical development (AQbD)
QTPP identification	ATP (Analytical Target Profile) identification
Define product design space	Method Optimization and development with DOE
CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
Process validation	AQbD Method Validation
Refine product design space	MODR (Method Operable Design Region)
Continuous process monitoring	Continuous Method Monitoring

3. Regulatory Perspective of AQbD

Pharmaceutical quality system (ICH Q10) includes various parameters and attributes related to drug substance and also drug products comprising of instrument operating conditions and their associated methods. Although cGMP regulation is in practice from a long time but many pharmaceutical industries are facing quality control related effects which are associated with the risk management system in analytical methods. Thus, considering the dependency of pharmaceutical development and manufacture on critical robust analytical data, the need as well as time has come for implementation of AQbD in analytical method development, which indicates quality process, product and robustness throughout the product life cycle. FDA has approved a few new drug applications already which are based on analytical QbD and it is referred to the beneficence of QbD in analytical method development process. It focusses the role of analytics in the product development cycle for better understanding of drug-excipient interactions and also for measuring of critical quality attributes (CQA) during experiment, process, control and also continuous process verification for monitoring trends and subsequently maintaining the quality of the product. Although cGMP regulations have been in presence for the last decade, the significant number of QC related warning letters issued by FDA demonstrates that the companies have issues with risk management system in analytical methods in the absence of AQbD. Therefore, Quality Assurance personnel believe that AQbD will provide a better solution to avoid OOT and OOS and reduce the risk in method failures and effects where the risk assessment is described logically and scientifically with risk mitigation planning. The lifecycle concept described in ICH Q8 is able to adapt to analytical procedures on considering an analytical procedure as a process while the output of this process as the reportable results, i.e., the value that will be compared to the acceptance criteria. The aim of applying lifecycle principles to analytical procedures is to practically align an analytical procedure variability along with the requirements of the product to be tested and to improve the reliability of the procedure through understanding and controlling the sources of variability.

4. Comparison of Traditional approach and AQbD

Traditional approach	AQbD
Start with hit and trial approach to meet method intent	Start with pre-defined objectives (ATP)
Limited understanding of analytical variables	Systematic evaluation of individual variables and interaction effects(s)
Method performance evaluated during validation	Focus on performance through establishment of ATP
Method quality based on method validation	Performance qualification is the assurance of method quality
Method verification and transfer are separate exercises	Performance qualification and verification are continuous exercises throughout the life cycle
No regulatory flexibility with respect to changes	Working with the MODR would not be considered as change there by reducing post-approval changes

5. Elements of AQbD

A. ATP (Analytical Target Profile)

ATP identification comprises of the selection of method requirements like target analytes (product and impurities), analytical technique category, and finally the product specifications. Initial risk assessment can be performed for determination of the method requirements and analytical critical matters. It is an effective way for method development and it has been mentioned in the ICH Q8 R (2) guidelines. It defines the method requirements which are expected to be measure the direct method development process which is a combination of all performance criterion crucial for the proposed analytical application. General ATP for analytical procedures is as follows: (a) selection of target analytes (API and impurities), b) technique selection (HPLC, GC, Ion Chromatography, etc.), (c) selection of method requirements (assay, impurity profile or residual solvents). Accuracy and precision are the most important criteria among the performance characteristics which provides the key information essential to quantify an unknown amount of the substance using the proposed method. A method cannot be termed as accurate and precise without the presence of acceptable specificity, linearity over a stated range, sufficient peak resolution for accurate integration, repeatability of injections, etc. In order to achieve an accurate and precise method the above-mentioned key characteristics should be evaluated during method development as they can provide rigorous and extensive data for setting method controls.

B. CQA (Critical Quality Attributes)

CQA is can be defined as a physical, chemical, biological, or microbiological property or characteristic which should be

within an appropriate limit, range, or distribution in order to ensure the desired product quality. CQA for analytical methods includes method parameters and attributes. CQA also can differ from one analytical technique to another. The key CQA attributes for various techniques are:

1. CQA for HPLC (UV or RID) are buffers used in mobile phase, diluent, organic modifier, column selection, pH of mobile phase, and elution method.
2. CQA specifications for GC method are oven temperature along and its program, injection temperature, gas flow rate, sample diluent and also concentration.
3. CQA for HPTLC is TLC plate, mobile phase, injection concentration and volume, time taken for plate development, reagent for colour development, and detection methods.

   Physical and chemical properties of the drug substance along with the impurities can also describe CQA for analytical method development.

C. MODR (Method Operational Design Region)

MODR is a method which is beneficial to develop operational region for routine operation (e.g., analysis time, procedure etc.). According with the requirements of ICH Q8 guidelines, including "design space" in product development, method operable design region (MODR) can also be developed and established in method development phase, which could act as a source for a useful, robust and cost-effective method. Understanding of method performance regions helps to identify and establish the desired operational conditions. Critical method parameters and analytes sensitivity should be assessed. MODR acts as an operating range for the critical method input variable which produces results which consistently meet the goals which are subscribed in the ATP. MODR allows flexibility in various input method parameters so as to provide the expected method performance criteria and also the method response without any kind of resubmission to FDA. Its basis lies on a science, risk based and multivariate approach for assessing the effects of various factors on method performance,

D. Risk Assessment

Risk assessment strategy according to ICHQ9 guideline is defined as: "a systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle". This step is crucial in to reach a confidence level that the method which is utilized is found to be reliable. Once the technique is identified, AQbD focusses on detailed risk assessment of the factors which may lead to possible variation in the method, like analyst methods, instrument configuration, measurement and method parameters, sample preparation and its characteristics along with environmental factors. Risk factors are classified as follows:

1. High risk factors: These factors are to be assessed during the Method Development process.
2. Noise Factors: It can be done through staggered cross nested study design ANOVA etc. These factors are subjected to testing by robustness.
3. Experimental Factors: e.g. Instrumentation and operation methods. Subjected to ruggedness testing and acceptable range is identified. Risk Evaluation is done through Failure Mode and Effect Analysis (FEMA) and matrix design.

E. Method Control Strategy

It is basically a planned set of controls focussed at minimizing the level pf variability in the process. The strategy is independent of information. Data generated during method development and method identification and verification forms the crux of the control strategy. a factor identified to have risk needs to be controlled. More attention is dedicated to high-risk factors. If the risk is low and manageable then the method control strategy can be defined, which usually comprises of appropriate system suitability check and needs to be verified from time to time by having control over it so that the concerned method delivers the desirable method attributes. The control strategy is not quite different from traditional approach.

6. Implementation of AQbD in current regulatory scenario

In future, analytical QbD needs to be introduced in the method development phase and at the same time it has to be validated further for the method performance along with the validation protocol which is essential.

7. Applications

In modern day drug formulation and analytical development, the AQbD technology can be successfully utilized to reduce method variability, to develop multivariate analytical understanding, to reduce stability failures etc.

8. Conclusion

Analytical QbD serves as a unique methodology for the emancipation of the process and protocol for Analytical Method Development. Thus, ultimately it helps to develop a better, superior and reliable method which provides a great level of quality assurance which in the end meets the pre-defined specifications. It is probably notable that as this topic gains momentum, it is to be noted that software developers will have an increasing demand upon them to assist the industry to be able to describe MODR's for the ATP. Scientists can easily identify the risk firstly so that quality can be enhanced. AQbD tools are ATP, CQA, Method Optimization, MODR, and Control Strategy with Risk Assessment, Method validation and Continuous Method Monitoring (CMM), and continuous improvement. AQbD requires the right ATP and Risk Assessment and wise use of right tools and performing the appropriate and sufficient quantity of work within proper timelines.

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