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RESEARCH ARTICLE

Analytical Quality by Design in Pharmaceutical Method Validation

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Abstract: Analytical Quality by Design is an application derived from the principles of Quality by Design, it is mainly applicable for developing the analytical method for the pharmaceutical formulation. The method can be developed by without wasting time and solvents and saving time, by the application theoretical and practical experience and the serious of steps shall be followed such as, Analytical Target Profile (ATP), Critical Quality Attributes (CQA), Risk Assessment, Method Optimization and Development with DoE, Method Operable Design Region (MODR), Control Strategy and Risk Assessment, AQbD Method Validation and Continuous Monitoring of Method for fixing the drug or formulation to be analysed, which method is going to applicable for analysing formulation, risk associated with the method, fixing the range for the method, control the risk associated with the method, validation of method and monitoring the method respectively. If any risk found, the process will starts again to develop the reproducible method, hence it is a cyclic process. It is a systemic process for developing analytical method. Hence, it a valuable tool in the development of pharmaceutical analytical method.

Keywords: Method development; Validation; Quality by design; Risk assessment; Analytical Target Profile.

1. Introduction

Many pharmaceutical company has fix the goal to develop the quality, safety and efficient product to satisfy the consumer and maintain their reputation by using the valuable tool called Quality by Design (QbD) and Process Analytical Technology (PAT). By applying the QbD approach, the productivity is inversely to the risk arise during the development of the product. Nowadays the application of QbD has successfully introduced in the development of the new drug formulation. USFDA has fix a guideline for QbD for intermediate and extended drug release drug product. ICH also include the QbD approach in the guideline from Q8 to Q11 (4 guideline).[1] Analytical Quality by Design (AQbD). According to ICH, QbD can be explained 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."

As an outcome of QbD, AQbD is an approach of science and risk based paradigm for analytical method development, striving to attain the predefined objectives for enhanced method performance, robustness, ruggedness, and flexibility for continual improvement. Nevertheless, there is hardly sufficient experience or sizable exposure available among the analytical researchers today on envisioning and implementing AQbD approach in developing apt analytical methods.[2] For the analytical method development through AQbD approach the following tools were applied systematically for the robustness throughout the lifecycle. They are:

- Analytical Target Profile (ATP)
- Critical Quality Attributes (CQA)
- Risk Assessment
- Method Optimization and Development with DoE
- Method Operable Design Region (MODR)

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- Control Strategy and Risk Assessment
- AQbD Method Validation
- Continuous Monitoring of Method.

ICH Q11 guideline has defined the API development of synthetic process by QbD but there is no discussion about AQbD methods of development. The ICH guideline put forward to apply the QbD approach (QbD & AQbD) in the analytical method development called as the AQbD. These two scientific approaches can be achieved at the same time. While implementing both the strategy, one can yield the better quality of product. It may rise to give better initiation for Process Analytical technology (PAT). The difference between the two scientific approaches given in Table 1 [3]

Table 1 Difference between QbD and AQbD

STEPS	QbD	AQbD
I	Define QTTP	Define ATP
II	CQA	CQA
III	Assessment of risk	Assessment of risk
IV	Space for design	MODR
V	Control Strategy	Control Strategy
VI	Management of Life Cycle	Management of Life Cycle

There was a vast differences between the analytical method development through traditional method and scientific approach. Traditional method of development doesn't explain about the statistical calculation and the risk assessments while the scientific method proceed with ATP, CQA, DoE and validation of AQbD method and Continuous Monitoring of Method

2. Analytical Target Profile (ATP)

ATP is the process of selection of method requirements that is what we are going to analyse it (assay, impurities), selection of analytical technique and their specification. Initially risk assessment should be studied for expectation of method requirement and analytical attributes. Generally ATP follows the following procedure as follows [4,5]

- Selection of Target analyte.
- Selection of Technique
- Selection of Method requirements

2.1. Selection of Target analyte

The consideration of impurities in the active pharmaceutical ingredient (API) synthetic route is addressed in the ICH Q3 guideline and other regulatory guidance. The impurities can be categorized as follows:

2.1.1. Starting materials

These are the initial reagents or raw materials used in the synthetic process.

2.1.2. Intermediates

These are the products formed during the intermediate stages of the synthesis before the final API is obtained.

2.1.3. Reagents, catalysts, and solvents

These are the substances added at various stages of the synthesis to facilitate the reactions or purification steps.

2.1.4. Degradation products

These are impurities formed by the decomposition or degradation of the API or intermediates, either during the synthetic process or upon storage.

2.1.5. Side products

These are byproducts or impurities formed as a result of side reactions occurring during the synthetic process.

2.1.6. Carryover impurities

These are impurities that may remain in the final API due to incomplete purification or separation steps.

2.2. Selection of Technique

The analytical technique selection is not only rely on the nature of the analyte and its specific principles but also on the test of analyte item and the need of the test. The following are examples of analytical test items and techniques:

- Identification by IR: FT-IR spectrophotometer.
- Impurity profile (Chromophore): HPLC with UV detector.
- Impurity profile (non-Chromophore): HPLC with RID/ELSD and so forth.
- Assay by HPLC (Chromophore): HPLC with UV detector.
- Assay by HPLC (non-Chromophore): HPLC with RID/ELSD and so forth.

2.3. Selection of method requirements

Method requirements shall varies from one method to another method [6,7]. Some common ATPs for impurity profile by HPLC method are listed in Table 2.

Table 2. Common ATPs for impurity profile by HPLC method

S.No.	Method requirements for impurity profile	S.No.	Method requirements for impurity profile
1	Number of analytes (API and impurities)	11	Column type (stationary phase and dimensions)
2	Separation of all analytes	12	Detection (UV/RID/ELSD)
3	Mobile Phase (buffer and organic modifier)	13	RRT, RRF establishment
4	Elution method (gradient or isocratic)	14	Flow rate
5	Sample concentration	15	Injection volume
6	Sample diluent	16	Column oven temperature
7	Sample solution stability	17	Runtime
8	Sample preparation process (dilution process and sonication time, etc.)	18	System suitability parameters selection with limits
9	Filter or centrifuge	19	LOD and LOQ concentrations establishment
10	Impurity specification limits	20	Impurities calculation method.

3. Quality attributes (CQA) and Initial Risk assessment

3.1. Critical Quality Attributes

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

3.2. Risk Assessment

Risk Assessment is a process that uses science to identify material attributes and method parameters (ATP). It can be used from initial stages of method development to continuous method monitoring. The AQB D approach involves identifying risks at early stages of development and then developing mitigation plans with control strategies. [8]

3.3. Design of Experiments (DoE)

Once the Critical Quality Attributes are evaluated with initial risk assessment, then DoE can be performed to finalise and extract critical method variable based on statistical significance. It can be determined per unit operation or combination of selected multiple method variables and their interactions and responses (critical method attributes). This approach yield a good opportunity to screen the numerous condition generated from the limited number of experiments. Then, datum were evaluated by statistical tools are important to determine critical method variables and the appropriate optimal ranges for method variables where a robust region for the critical method attributes could be obtained [9,10].
According to ICH Q8 guidance, "Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality." Initial materials properties will affect the drug substance synthetic process robustness, impurity profile, physicochemical properties, process capability, and stability. Understanding the process will provide the maximum knowledge about the robustness establishment process by evaluating Starting materials properties will affect the drug substance synthetic process robustness, impurity profile, physicochemical properties, process capability, and stability.

3.4. Method Operable Design Region (MODR)

MODR of analysis also termed as proven acceptable range (PAR) is the multidimensional integration and interaction of input variables (i.e., CMPs during analysis) demonstrated to provide assurance of quality. It is based on the ICH Q14 guideline. MODR can be established in the method development phase, MODR permits the flexibility in various input method and expected method criteria and method response without resubmission to FDA. [11, 12]

4. Control strategy and final risk assessment

4.1. Control strategy

It is a set of control plan derived from analyte nature, they are based on the complete statistical data collecting during the DoE stages, it ensures the method performance and product quality [13,14]. The control strategy can be in the form of system suitability. The concept of control strategy "Emerged in ICH Q8 and it is further developed in ICH Q10 and Q11 and expanded as ICH Q14". Analytical procedure development the traditional approach of developing analytical procedure and control strategies set points and operating ranges are after strictly set based on observed data

4.2. Final risk assessment

As per ICH Q9 guideline, "It is the systemic process for the assessment, control, communicate and review of this to the quality across the method development". It is like analysing the whole process, monitoring each steps and finding out the problem and solve it. It is based on the prior knowledge and scientific process[15], it is the key step to the success of AQbD, it shows the procedure development efforts and their effectiveness. The various step carried out in the risk assessment are; Risk identification[24], Risk analysis and Risk evaluation

4.3. AQbD method validation

AQbD approach is used to develop an analytical method over a range of different API batches. It applies the knowledge of both DoE and MODR for designing the method validation for manufacturing all kinds of API [16] without entering into the process of revalidation [17,18]. It provides ICH validation elements and information on interaction, measurement, uncertainty, control strategy and continuous improvement [19,20]. This method development needs lesser resources than the conventional validation approach without incriminating the quality.

4.4. Continuous monitoring of method (CMM) and continual improvement

A control strategy for implementing design space at the commercial stage is life cycle management. The last step in the AQbD life cycle is CMM, which is a continuous process [21] of sharing got fully throughout the development and implementation of design space [22]. This contains the outcomes of risk analyses, presumptions made in consideration of proven information, statistical design considerations, and a connection between the design space [22], MODR, control strategy, CQA, and ATP. After a method validation is finished, it can be utilised regularly and its performance can be tracked continuously. Control charts, tracking system appropriateness data, method-related research, and other tools can be used to accomplish this [23]. With the aid of CMM, an analyst is able to promptly recognise and handle any out-of-trend performance. Following are the advantages of CMM: [24]

- Saves time and economy.
- Reduces the failure rate[25].
- Risk can be analysed before the development of method.
- Reproducible results can be obtained [26].
- The success rate is more than the conventional method development [27,28].
- Better understanding on the design space and control strategy

5. Conclusion

AQbD is an important tool in the pharmaceutical industry for assuring the quality of the product. The result of AQbD is the understanding from product development to commercial production. The quality of the product can be elevated by analysing the risk by initial risk assessment and with the aid of scientific knowledge. The main tools used in AQbD approach are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation and Continuous Method Monitoring (CMM), and continuous improvement. Thus, AQbD approach, yields appropriate analytical method within the minimum period of time.

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