QBD Based Analytical Method Development and Validation of Test Method as Per ICH Q2 (R1): A Review

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Abstract: Analytical Quality by Design, or AQbD, is the term used to describe the concept of QbD to the development of analytical methods. Analytical quality by design (AQbD) is a practise used informally in the pharmaceutical industry as a component of risk management, pharmaceutical development, and pharmaceutical quality system. Regulatory bodies receive more assurance from QbD-based product development. The analytical techniques that are used to analyse pharmaceutical products are equally vital, and any problems with the analytical technique's design might put patients at risk for poor quality care. Despite the fact that there isn't a specific regulatory agency directive on analytical quality by design (AQbD), a lot of work has been done recently in this area. The use of AQbD in method development helps to ensure the method's resilience. Regulation-related suggestions for pharmaceutical development have been released by the International Conference for Harmonisation (ICH). The main tenets of Analytical Quality by Design (AQbD) are discussed in detail in this article, including the Quality Target Method Profile (QTMP), Critical Method Parameters (CMP), Design of Experiments (DoE), and Method Sensitivity and Control Strategies.

Keywords: Quality by Design, Analytical Quality by Design, Method Development, Method Validation, ICH

1. 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.” The fundamental principle of "Total Quality Management" is that quality must be included into the design process and cannot be assessed in a finished product. Understanding data from pharmaceutical development studies and production gives the scientific framework needed to achieve this objective of reforming high-quality product. [1-3]

1.1 Pharmaceutical Quality by Design Objectives

One of the main goals of QbD is to ensure the quality of products, for which the characteristics of the products and the processes are essential for expressing desires; they must be the outcome of a mix of historical data and unique estimation during development.

1.1.1 Advantages of QbD: [4-5]

- In case of variations in conditions, the developed method will be extra robust which gives higher level of confidence.
- It helps to escalate understanding of the method.
- This approach proposed superior transfer achievement when method is transferred from research level to quality control department.
- Design space concepts avoid post-approval amendments that could force any enterprise to pay a high price for any of the firm.
- It provides a space an area for invention of latest techniques by continuous improvement during life cycle.

1.1.2 QbD activities within FDA:

The application of QbD is guided by the following steps:[6]

Based on the submission of the product and comprehension of the method, the FDA's "Office of New Drug Quality Assessment (ONDQA)" recognised a new risk-based "pharmaceutical quality assessment system (PQAS)".

Figure No. 1.1 FDA-View-On-Quality-by-Design-in-pharmaceuticals

Pharmaceutical development is said to be completely dependent on analytical sciences. Product development and analytical methods work hand in hand throughout the whole life cycle of any pharmaceutical product. Due to the high level of variability involved at each stage of method development, the traditional technique to developing analytical methods is highly time-consuming.[7] The methodical QbD-based methodology has been gradually ingrained into the mindset of analytical scientists in order to remove the hitches experienced during method development. As a result, efforts have been made to apply the QbD approach to the development of analytical methods, attempting to comprehend the predefined objectives to control the critical method variables (CMVs) that affect the critical method attributes (CMAs) in order to achieve improved method performance, high robustness, ruggedness, and flexibility for ongoing improvement. [8-9]

1.2 Analytical Quality by Design (AQBD)

Analytical Quality by Design (AQbD), a systematic approach to method design, starts with the identification of the separation objectives and target method profile.[10] The primary fields of attention in AQbD are the comprehension of method parameters and controls, based on reliable science and high-quality risk management. Along with other elements like process parameters, material attributes, equipment operating conditions, in-process controls, and finished product specifications, AQbD is a crucial component of the product development control strategy. Although regulatory bodies do not outline a specific AQbD process, a parallel strategy can be developed based on product QbD, for example. Critical quality attributes (CQA) can be considered to be tailing factor, the resolution between adjacent peaks, plate count, etc. in the Quality Target Product Profile (QTTP) and Quality Target Method Profile (QTMP), respectively. Method operable design range (MODR) is another name for design space. [11-12]

1.2.1 QbD Principles for Analytical Method Development:

The QbD and PAT could succeed in tandem with the analytical approach to ensure a high-quality product. It should be placed on the regulatory requirements for AQbD that describe the method development in

accordance with DoE and provide information on the necessary quality systems as well as risk management.

1.2.2 Elements of AQbD[13-17]

Critical Quality Attributes (CQA)

CQAs are the variables that affect the way a technique performs and can have an effect on its results. The methods employed (such as High-performance liquid chromatography and Gas chromatography) and the method goal (such as assay, impurity estimation, and drug release determination) are taken into consideration when choosing CQAs. The CQAs for the assay determination technique are the tailing factor, plate counts, percentage relative standard deviation of duplicate injections of the reference standard, and extraction effectiveness (% recovery). The resolution between adjacent peaks could be used as an extra CQA for the impurity estimate approach in addition to these CQAs.

Quality target method profile (QTMP)

The quality target method profile, which is determined based on the method's intended purpose and regulatory criteria, is the target profile of CQAs. Pharmaceutical items are scrutinised to make sure they operate as intended. Drug efficacy and safety are components of product performance. Pharmaceutical items are often examined for assay and drug release to determine the effectiveness of the medicine. Impurities in pharmaceutical items are calculated similarly to how safety is determined. Therefore, the most common objectives when creating an analytical method are assay estimation, drug release determination, and quantification of impurities in pharmaceutical products.

Method development:

The method-development step is essential for the design selection process. Understanding both the desired operational goal of the ultimate end user and the method performance criteria is necessary for developing a QbD method.

1.2.3 Application of QbD in analytical methods of measurement: [18-19]

QbD can be applied for various analytical methods:

- HPLC (For stability studies, method development, and determination of impurities)
- Advanced techniques like mass spectroscopy,
- Karl Fischer titration for determination of moisture
- Hyphenated technique like LC–MS
- Capillary Electrophoresis

1.3 Analytical Method Validation [20-22]

Method validation guarantees that the analytical methodology used for a particular test is suitable for its intended use. The findings of method validation may be used to evaluate the quality, consistency, and reliability of analytical results; it is an important part of any good analytical practice.[20]

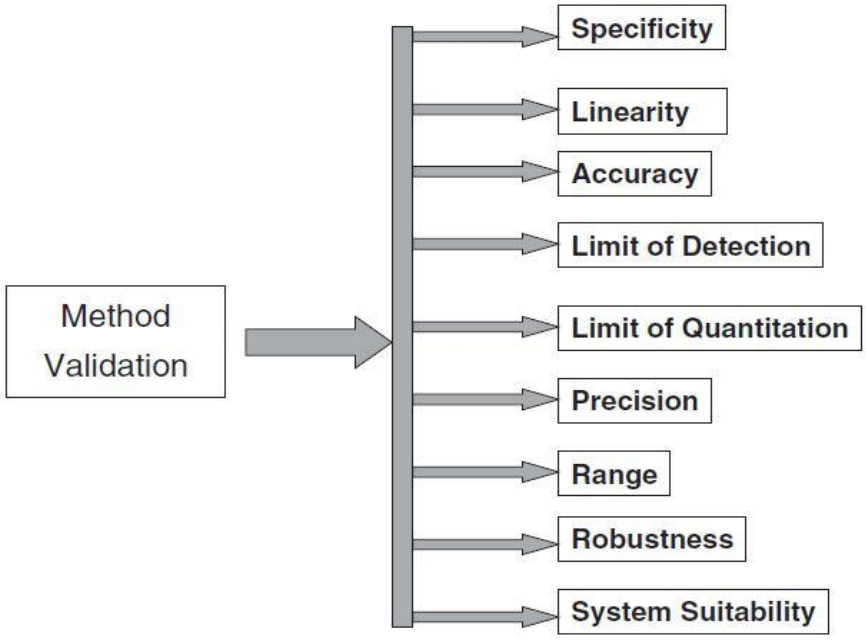

Figure No. 1.2 Analytical Method Validation

1.3.1 Accuracy

The exactness of an analytical procedure is defined as the degree of conformity between the value accepted as a conventional real value or an accepted set point and the value discovered.

The precision of an analytical procedure should be determined over its entire range. When determining the accuracy of a drug in a formulated product, the analytical method can be applied to synthetic mixtures of the drug product components to which a known amount of analyte has been introduced within the method's range. For establishing accuracy in drug substance assay, test doses ranging from 50 % to 120 % are commonly used (or a finished product). At each location, the average drug recovery should be 98 to 102 percent.

1.3.2 Precision

The degree of scatter between a set of measurements obtained from serial sampling of the same homogeneous sample under the stipulated conditions is expressed by the precision of an analytical method. There are three levels of accuracy: repeatability, intermediate precision, and reproducibility. The variance, standard deviation, or coefficient of variation of a sequence of data is commonly used to express the precision of an analytical technique. The RSD of all samples in the precision results should not exceed 2%.

1.3.3 Reproducibility

The precision between laboratories is expressed by reproducibility (collaborative studies, usually applied to standardization of methodology). An inter-laboratory trial can be used to determine reproducibility. When standardizing an analytical process, for example, for inclusion in pharmacopoeias, reproducibility should be taken into account.

1.3.4 Specificity

The ability to assess the analyte definitively in the presence of components that may be present is known as specificity. Impurities, degradants, matrix, and other substances are common examples.

1.3.5 Linearity and Range

Linearity and Range Determination:

A minimum of 5 concentrations is suggested for determining linearity. A set of samples with concentrations spanning 80-120 percent of the expected concentration range can be used to determine linearity. Graphically, linearity is assessed.

1.3.6 Ruggedness

Ruggedness is determined by:

By analysing aliquots from homogeneous lots in multiple laboratories, using different instruments, and

under different operational and environmental conditions, all while adhering to the assays defined criteria. The degree of test result repeatability is then assessed as a function of the assay variables.

- Different operator in same laboratory, Different equipment in same laboratory.
- Different source of segment and solution, Different source of column.[21]

1.3.7 Applications and Advantages:

i. An appropriate method for separating diverse components in plant extracts that are structurally similar and so require a precise and sensitive procedure.

ii. A multi-component separation technique capable of analysing real-life samples and complex mixtures.

iii. This approach is used to determine the composition of various medications. The examination of diverse degradation products is possible, reflecting the development of HPLC systems and methods.[22]

1.4 Opportunities of and barriers against a QbD approach to analytical methods

A QbD methodology will result in a higher rate of success for transferring new analytical methods from research and development to quality control laboratories than conventional technology-transfer methods. A defined procedure encourages a team approach and will aid in the systematic and effective use of the QbD methodology. Because current validation guidance does not result in methods that can always be operated reliably, current expectations of analytical technology transfer and method validation must change. Analysts must pick up new techniques and abilities. This needs the creation of external guidance, the revision (or elimination) of ICH guideline Q2 (R1), and the development of analytical technique guidance by the Centre for Drug Evaluation and Research. This endeavour needs a global strategy that is consistent for it is to be successful.

1.4 CONCLUSION

A scientific method, QbD is widely utilised in the pharmaceutical sector for developing new products since it lowers risk and product variability. A lot more analytical procedures are currently being developed based on the QbD concept, and AQbD is also increasingly emerging in this context. The AQbD entails identifying the important quality characteristics and target method profile as well as doing risk analysis and utilising DoE to optimise the key method parameters. Based on the results of the DoE, the MODR and control plan are determined. Additionally, it aids in increasing regulatory flexibility. The most prevalent advantage is that procedures are more durable and tough, and can withstand the difficulties of long-term use throughout the product life cycle.

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