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Mini Review

A Mini Overview of Analytical Quality by Design (AQbD)

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ABSTRACT

A methodical, science- and risk-based approach to pharmaceutical development, Quality by Design (QbD) emphasizes incorporating quality into goods rather than depending just on end product testing. Through standards like ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System), regulatory bodies including the US Food and Drug Administration (USFDA) and the International Council for Harmonization (ICH) have actively pushed QbD. The idea of Analytical Quality by Design (AQbD), which attempts to guarantee solid, dependable, and consistent analytical processes, is the result of applying QbD concepts to the creation of analytical methods. An in-depth knowledge of analytical method performance, the Analytical Target Profile (ATP), CQAs, CMPs, and their interactions within a specified Method Operable Design Region (MODR) is the foundation of AQbD. To reduce method variability and guarantee consistent analytical performance throughout the product lifespan, AQbD incorporates risk assessment, design of experiments (DoE), control measures, and lifecycle management. This strategy lowers failure rates, increases regulatory flexibility, strengthens technique robustness, and encourages ongoing monitoring and development. AQbD has many benefits, such as better data quality, cost effectiveness, and stronger regulatory filings, despite obstacles such implementation complexity, a lack of standardized nomenclature, and the requirement for specialist training. All things considered, AQbD is a cutting-edge, data-driven framework that is essential to guaranteeing analytical accuracy and the quality of pharmaceutical products.

INTRODUCTION

QbD is a systemic science and risk-based approach to pharmaceutical and analytical development that focuses on incorporating quality into product rather than depending primarily on end product testing[1]. The notion of QbD is based on having a complete understanding of product attributor, process variables and their interactions in order to assure consistent quality throughout the product lifetime[2]. QbD improves product performance by recognizing and regulating important quality

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attributes, material attributes and process parameters[3].

The adoption of QbD principles has been vigorously promoted by regulatory organizations like the US Food and Drug Administration (USFDA) and the International Council for Harmonization (ICH)[4]. ICH guidelines Q8 (Pharmaceutical development), Q9 (Quality risk management) and

Q10 (Pharmaceutical quality system) provide a thorough description of this concepts[5]. When takes as a whole, these recommendations offer an organized framework for using scientific knowledge quality risk management and continuous improvement across the stages of development and manufacture[6].

Analytical QbD (AQbD) is the result of QbD's recent expansion from formulation and production to analytical technical development within a specified method operable design region (MODR), AQbD guarantee the robustness, dependability and consistency of analytical procedure[7]. QbD's lifetime strategy decreases unpredictability, lowers failure rate, increases regulatory flexibility, and facilitates ongoing monitoring and improvement[8].

ELEMENTS OF AQbD

1. Analytical Target Profile (ATP)

The ICH Q8 R guidelines describe ATP as a method for method development or only as a tool for method development. It outlines the method requirements that must be measured in order to guide the method development process; in other words, it is a mixture of all performance criteria necessary for the suggested analytical application. For every characteristic listed in the control plan, an ATP would be created. The ATP specifies the performance level features such as precision, accuracy, range, sensitivity and the related performance criterion, as well as what the technique must assess (i.e., acceptance criteria). ATP for analytical procedures comprises of :

a) Selection of target analytes (API and impurities)

b) Selection of analytical technique (HPTLC, GC, HPLC, Ion chromatography, chiral HPLC etc.

c) Choice of method requirements.

2. Critical quality attributes (CQA)

CQA is defined by ICH Q8 (8) as a physical, chemical, biological or microbiological property or characteristics that must fall within a suitable range, distribution or limit in order to guarantee the intended product quality. Method parameters and method attributes make up CQA for analytical procedures. CQA can be vary depending on the analytical method used.

a. CQA for HPLC (UV or RID) include mobile phase buffers, mobile phase pH, diluent, column selection, organic modifier and elution technique.

b. The GC methods CQA includes the oven temperature and its program, injection temperature, gas flow rate, sample diluent and concentration.

c. TLC plate, mobile phase, injection volume and concentration, plate development time, color development reagent and detection techniques comprise CQA for HPTLC[9].

3. Critical Method Parameters (CMP)

The sensitivities of the analytical method are crucial technique parameters. CMP has an impact on the designated CQAs and CMP. Among the various forms of CMP are material properties, instrument-related CMP, instrument operational parameters and other technique parameters. The methodology (HPLC, TLC, GC etc.) is also used to categorize critical technique parameters. While the Ph of the mobile phase, the organic modifier in the mobile phase and the temperature of the column oven are the key method parameters for an HPLC techniques, critical method parameters for GC method could include the injector temperature, detector temperature, type of carrier gas and split ratio.

4. Risk Assessment

The ICHQ9 guideline defines risk assessment strategy as "a systematic process for the assessment, control, communication, and review of risks to the quality across the product lifecycle." To achieve a degree of confidence in the method's dependability, this phase is essential. After the technique has been identified, AQbD places a strong emphasis on a thorough risk assessment of the variables that could cause method variability, such as analyst techniques, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. Analytical QbD requires the risk assessment stage before method transfer and throughout the product life cycle, whereas traditional method development depended on testing the technique after transfer. As a result, the risk factors are divided into the following groups:

a) High-risk elements, such as sample preparation techniques. During the Method Development phase, these will be corrected.

b) Noise Factors: An MSA research is conducted on them. Staggered cross-nested study designs, variability plots, ANOVA, and other methods can be used to accomplish this. Robustness testing is used to these factors.

c) Experimental factors, such as equipment and operating procedures. Ruggedness testing is conducted, and an acceptable range is determined. The third stage is risk evaluation, which is carried out using matrix designs and failure mode and effects analysis (FMEA)[10].

5. Design of experiment

Doe; DoE may be used to validate and enhance significant technique variables based on their statistical significance once the first risk assessment has identified potential and crucial analytical method variables. It can be computed separately or in conjunction with a variety of other method components, their correlations, and their outcomes for each unit operation. This method provides an excellent opportunity to assess a variety of conditions produced by a limited number of trials Data studies using statistical methods are therefore necessary to identify the relevant method variables and the appropriate optimal ranges for those variables, where a stable area for the core method characteristics may be constructed. The robustness, impurity profiling, physico-chemical features, process capability, and stability of the pharmaceutical drug substance manufacturing process are all impacted by the properties of the starting materials. By examining different operating scenarios, sizes, and pieces of equipment, process understanding will provide the knowledge needed to create robustness parameters.

6. Method operable research region

Method Operational Design Region, or MODR (e.g., duration of analysis, process and its restrictions) is used to define operating zones for routine procedures. As a source for reliable and reasonably priced methods, the MODR may be created throughout the method development phase in compliance with the ICH Q8 criteria, respecting "design space" in product development. Understanding method performance regions makes it easy to set up the necessary operational conditions. It is important to evaluate the sensitivity of analytes to analysis and important method parameters. Whether the results are in line with the stated goals of the ATP depends on the operating range (OR) of a critical method input variable, like a CQA (ICH, 2005)[11]. Without having to resubmit it to the FDA, MODR provides the flexibility of various input process parameters to generate the expected method performance standards and method response. It is predicated on a method that takes risk, science, and multivariate research into account to assess how different characteristics affect the treatment's effectiveness.

7. Control strategy

Developing a control strategy is essential to guaranteeing that the approach continuously meets the goals specified in ATP. It is essentially a carefully thought-out set of controls intended to lower process variability. The data determines the methodology. Data generated during method development and verification serves as the foundation for the control approach. An element that has been identified as hazardous must be contained. High-risk factors are given more weight. If the risk is low and controllable, an established method control plan can be created. In order to ensure that the method offers the required method attributes, this approach often entails an adequate system suitability check, which is frequently checked by exercising control over it.

8. Lifecycle management

Monitoring its performance over time to make sure it satisfies predetermined criteria is part of establishing an analytical approach for quality control. The pharmaceutical business uses control charts and other tools to monitor system appropriateness data. From raw material testing to stability testing, this continuous monitoring makes it possible to identify and fix the method's anomalous or OOT performance[12]. The validation of the method, verification, and transfer are the critical stages that ensure the method is suitable for its intended use when going through each of the AQbD components for a particular analytical method produced. The term "lifecycle management of analytical method" refers to the complete process, which starts with ATP creation and continues until the procedures are put to use. Similar to precision testing at the regular use location, performance qualification is based on the subsequent ATP validation. The ongoing verification efforts guarantee that the technique is under control for the duration of its existence.

ADVANTAGES

- It provides a higher level of quality assurance for pharmaceutical products.
- It offers cost savings and efficiency to the pharmaceutical industry.
- It makes the process of scaling up, validating and commercializing clear, rational of predictable.
- It increases the sponsor's transparency and helps them understand the control strategy required for the drug product to be approved and finally put on scale.

- In order to meet unmet medical requirements, it promotes innovation. It increases the efficiency of pharmaceutical manufacturing operations while lowering production costs and product rejects.
- It lessens or eliminates costly fines, potential compliance actions and drug recalls.
- There is potential for continued improvement in this.
- It makes regulatory oversight more effective
- After clearance, it streamlines manufacturing changes

Challenges or limitations in implementation of AQbD

- Since AQbD is relatively new to the analytical sciences, there are several obstacles to its implementation, particularly since it is not yet a regulatory requirement but will soon become one.
- To start, there may need to be a paradigm change from submitting typical information rich documents to scientifically sound, knowledge-rich documents where there are no regulatory requirements for technology transfer and technique revalidation.
- Since many terms are used worldwide in relation to AQbD, very precise & succinct definitions of MODR, control strategy, CMA, and method performance criteria must be defined. Another obstacle to the successful domain is the training and education of resources in the industry and regulatory authorities.
- In order for knowledge created during method development to be used for regulatory submissions, there is also an urgent need for well-defined criteria surrounding its documentation[14].

APPLICATION OF AQbD

- Improved scientific basis for evaluation.
- Facilities improved cooperation between inspection, compliance and review.
- Enhances data in submissions to regulations.
- Enables greater uniformity in analytical approaches.
- Enhances review quality (creating a QMS or CMC).
- Make decision-making more flexible.
- Guarantees that choices are based on rather than empirical data.
- Makes decisions using a variety of discipline.
- Makes use of resources to deal with greater hazards[15].

FUTURE PERSPECTIVES

Creating a robust, high-quality process that consistently produces the desired results is the aim of AQbD. The creation of MODR, the design space for the analytical process, is supported by the data gathered during risk assessment, method development, optimization, and validation[16]. AQbD has been used to establish a number of analytical techniques for medicinal plants, including mass spectrometry analysis, capillary electrophoresis analysis, supercritical fluid chromatography analysis, gas chromatography analysis, and more. Numerous investigations have reported using AQbD to develop an HPLC

analysis. The general tactics to build an optimal method of analysis for one or many APIs were effectively reported in earlier research works[17].

CONCLUSION

Analytical QbD is crucial to the pharmaceutical sector since it ensures the method's dependability and the final product's quality. The outcomes of AQbD include comprehending technique development and implementing the method in large-scale commercial production. The ATP, CQA, MODR, and Control Strategy with Risk Assessment, Method Validation, and Continuous Improvement are the AQbD tools. During method development, the inputs—which represent potential influences—and the outputs—which represent critical analytical answers—are examined to determine the connections. During process development, significant analytical factors are found using a technique similar to that described in ICH Q8 and Q9. In order to increase product quality, the AQbD strategy actively participates in identifying potential risks and then strives to reduce those risks.

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