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QUALITY BY DESIGN: THE TOOL FOR REGULATORY COMPLIANCE

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ABSTRACT: QbD decrees the definition of a goal for the method and accentuates thorough evaluation and scouting of alternative methods systematically to obtain ideal method performance. QbD tools like risk assessment and design of the experiment, empowers better quality to be instilled into the analytical method and facilitate prior understanding and identification of variables affecting the method performance. Analytical quality by design (AQbD) permits the analytical method for movement within a method operable design region. Unlike current methods, analytical method development using AQbD approaches diminishes the number of out of trend results and out of specification results due to the robustness of the method. It is a current inclination among pharmaceutical industry to implement AQbD in method development processes as a part of risk management, pharmaceutical development and pharmaceutical quality systems (ICHQ10). It owes to the lack of explanatory reviews. The objective of this review article is to provide a comprehensive understanding of various aspect of QbD.

INTRODUCTION: Quality-by-design (QbD) is a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management methods to gain product and process understanding and eventually process control. The concept of QbD can be extended to analytical methods. QbD mandates the definition of a goal for the method and emphasizes thorough evaluation and inspection of alternative methods in a systematic way to obtain optimal method performance. QbD involves a thorough understanding of the process; a goal and or objective are defined before the actual starting of the process.

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Two key concepts can be introduced that further aid in the implementation and understanding of QbD. The first concept is "design space" [1].

ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and process parameters demonstrated to assure quality" [2]. Understanding the design space for a pharmaceutical process normally involves the identification of critical attributes for the input materials, the process, and the final product [3]. An improved definition of design space has been proposed for analytical methods, wherein the design space includes any combination of the input variables to a method that has been demonstrated to assure the quality of the data produced by the method [4].

Under this definition, changes within the design space of the method are not considered to be a change to the method. Another important QbD concept is "control strategy." The purpose of the control strategy is to assure the final quality of the

product. The control strategy is obtained from the process of understanding gained from forming the design space. Real-time release, risk assessment are other important parameters for the implementation of QbD. International conference on harmonization in its guidelines on pharmaceutical development Q8, quality risk assessment Q9 and pharmaceutical quality system Q10 gives stringent requirements regarding quality of the product. QbD ultimately helps to implement Q8 and Q9. FDA's view of QbD is "QbD is a systematic approach to product and process design and development''. This concept was accepted by the FDA in 2004 and a detailed description was given in 'pharmaceutical cGMPs for the 21st century - a risk-based approach'.

Quality by design (QbD) has become a vital concept for the pharmaceutical industry; it is further 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"(ICH Q9) [5]. The scientific understanding gained during the method development process can be used to develop method control elements and to manage the identified risks.

TABLE 1: DIFFERENCES BETWEEN CURRENT APPROACH AND QbD APPROACH

Current Approach	QbD Approach
Quality is assured by testing and inspection	Quality is built into product & process by design and based on scientific understanding
It includes only data intensive submission which includes disjointed information without "big picture."	It includes knowledge of rich submission which shows product knowledge & process understanding
Specifications are based on batch history	Specifications are based on product performance requirements
It is a "Frozen process," which always discourages changes	It is a flexible process within design space which allows continuous improvement
It focuses on reproducibility which often avoids or ignores variation	It focuses on robustness which understands and control variation

QbD helps in the development of a robust and cost-effective analytical method which is applicable throughout the lifecycle of the product, to facilitate the regulatory flexibility in the analytical method. It means the freedom to change method parameters within a method's design space, referred to as the method operable design region (MODR) [6]. Implementation of AQbD is expected to strengthen the concept of "right analytics at the right time" which plays a significant role in drug product development cycle [7].

Need for Analytical QbD: Though cGMP regulations have been in place in the past one decade or so, the increasing number of quality control related warning letters issued by FDA demonstrates that companies have trouble with a risk management system in analytical methods and related systems. Quality assurance personnel are certain that AQbD will be a better solution to avoid OOT and OOS and to reduce risk in method failure [8]. Analytical method development with of QbD approach is the current area of focus and needs to be executed. The process of developing and validating analytical methods parallel to product QbD benefits the quality of the product furthermore, with a high degree of assurance [8]. ICH Q8 (R2) guidelines do not discuss analytical method development in correlation with design space; however, it is understood that the concept can be executed to analytical design space and continuous improvement in method robustness and understanding. Analytical methods are the indicator of the quality of the process, product, and robustness throughout the life cycle [9].

In current practices, chromatographic methods are more commonly employed as right analytics at all the stages during the product life cycle. Common analytical methods for content uniformity, assay, impurity profile, and stability indicating assay are based on High-Performance Liquid Chromatographic (HPLC) or Ultra-Performance Liquid Chromatographic (UPLC) or Rapid Resolution Liquid Chromatographic methods (RRLC). In connection with chromatography, due to complex parameters involved in the method development phase, low sensitivity, selectivity, and inadequate understanding between method performance and method parameters, revalidation protocol has been

recommended in most of the procedures. On the other hand, in current practice, the implemented analytical methods were based on one factor at a time (OFAT), in which one parameter alone is optimized for the expected response while others remained constant [10]. This practice has always presented a narrow robust behavior of the method for instrumental variables used in the method development phase. Hence, the present strategy of the analytical method (*i.e.*, OFAT) development has high risk in method failure and always requires revalidation protocol after method development.

Statistical Tools for Support of Analytical QbD: In addition to the well-established statistical analysis tools used during method development, such as Design of Experiment and Measurement Systems Analysis, other statistical approaches have been implemented to assist in the development of QbD analytical methods. For example, it has been proposed that changes with the potential to take a method outside of its known design space could be evaluated and subjected to a validation exercise to ensure method performance criteria are still acceptable. To assist with such changes, a more advanced statistical approach based on two one-sided tests (TOST) was found to have advantages over intermediate precision studies for the demonstration of method equivalence, and for reliable inter-method comparisons to established specifications [11]. Also, the setting of acceptance criteria, which represent an acceptable bias between the original and changed method, was linked with both the design and sample size of an equivalency study [12].

Elements of Analytical QbD:

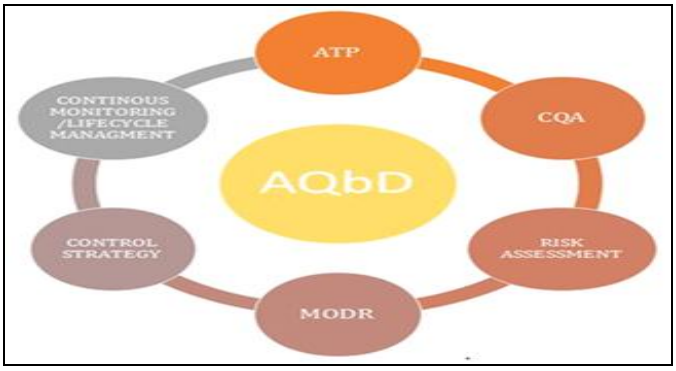

FIG. 1: ELEMENTS OF QbD

Analytical Target Profile (ATP): ATP is way/tool for method development has been mentioned in the ICH Q8 R (2) guidelines. It defines the method requirements which are expected to be measured that direct the method development process *i.e*. it is the combination of all performance criteria required for the proposed analytical application. An ATP would be developed for each of the traits defined in the control strategy. The ATP defines what the method must measure (*i.e*., acceptance criteria) and to what level the measurement is required (*i.e*., performance level characteristics, such as precision, accuracy, range, sensitivity, and the associated performance criterion). The ATP is defined with the help of knowledge and scientific understanding of the analytical process. Preliminary risk assessment should be carried out for the expectation of the method requirements and analytical criticalities.

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.

Accuracy and precision are the most important among the performance characteristics that provide the critical information needed to quantify an unknown amount of the substance using the proposed method. A method cannot be accurate and precise without acceptable specificity, linearity over a stated range, sufficient peak resolution for accurate integration, repeatability of injections, etc. To achieve an accurate and precise method, the above important characteristics must be evaluated during method development as they provide an extensive data set for setting method controls.

Critical Quality Attributes (CQA): ICH Q8 (8) defines CQA as physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQA for analytical methods comprises of method attributes and method parameters. CQA can differ from one analytical technique to another.

a) CQA for HPLC (UV or RID) is buffers used in the mobile phase, pH of the mobile phase,

diluent, column selection, organic modifier, and elution method.

b) CQA for GC method is oven temperature and its program, injection temperature, the flow rate of gas, sample diluent and concentration.

c) CQA for HPTLC is TLC plate, mobile phase, injection concentration and volume, the time taken for plate development, a reagent for color development, and detection methods.

Physical and chemical properties of the drug substance and impurities can also describe CQA for analytical method development such as polarity, charged functional groups, solubility, pH value, boiling point, and solution stability.

Risk Assessment: Risk assessment strategy is a systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle" (ICH Q9). This step is vital to reach a confidence level that the method is reliable. Once the technique is identified, AQbD emphases on detailed risk assessment of the factors that may lead to possible variability in the method, like analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. Traditional method development relied on testing the method after transfer, whereas analytical QbD demands the risk assessment step before method transfer and throughout the product life cycle. According to ICH Q9, risk assessment can be carried out in three steps *viz.*, risk identification, risk analysis, and risk evaluation. One of the common ways to perform risk assessment is to use a Fishbone Diagram, also known as Ishikawa. The risk factors are classified into the following categories:

a) High-Risk Factors: *e.g.,* Sample preparation methodology. These are to be fixed during the method development process.

b) Noise Factors: These are subjected to an MSA study. It can be done through staggered cross-nested study design and variability plots, ANOVA *etc.* These factors are subjected to robustness testing.

c) Experimental Factors: *e.g.,* Instrumentation and operation methods. Subjected to rugged-ness testing and the acceptable range is identified. The third step is risk evaluation which is done through failure mode and effects analysis (FMEA) and the matrix designs.

Methods of Risk Assessment (ICH Q9): Some methods of risk assessment are mentioned in ICH guideline Q9 as follows:

- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA); Risk ranking and filtering;

Method Operational Design Region (MODR): MODR is used to develop operational region for routine operation (*e.g.*, analysis time, procedure and limits) by the requirement of ICH Q8 guidelines, MODR can also be established in the method development phase, which could serve as a source for the robust and cost-effective method. Understanding of method performance regions helps to establish the desired operational conditions. Critical method parameters and analytes sensitivities should be evaluated. MODR is the operating range for the critical method input variable (similar to CQAs) that produces results which consistently meet the goals set out in the ATP. MODR permits the flexibility in various input method parameters to provide the expected method performance criteria and method response without resubmission to the FDA. It is based on a science, risk-based and multivariate approach to evaluate the effects of various factors on method performance.

Method Control Strategy: Establishing a control strategy is of utmost importance while ensuring that the method is performing as intended on a routine basis as goals described in ATP. It's a planned set of controls aimed at minimizing the variability in the process. The strategy is data dependent.

Data generated during method development and method verification forms the basis of the control strategy. A factor identified to have risk has to be controlled. More attention is given to high-risk

factors. If the risk is low and manageable, then the method control strategy can be defined, which generally consists of appropriate system suitability check and verified time to time by having control over it so that method delivers the desirable method attributes. Interestingly, the control strategy of AQbD is not different from the traditional control strategy.

Lifecycle Management: Going through all the elements of AQbD for a specific analytical method the key steps that ensure the fitness of the method for its intended use includes the method validation, verification, and transfer. Combining all is termed as 'lifecycle management of analytical procedure,' which commence with the establishment of ATP and continues till the methods are in use. The resultant confirmation concerning ATP is the primary focus of performance qualification, *e.g*., precision study at the site of routine use. Continual verification involves activities, which assure that the method is under control throughout its lifecycle [13].

Applications of AQbD:

- ✓ Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
- ✓ 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 method.
- ✓ Analysis of genotoxic impurity.
- ✓ Dissolution studies.
- ✓ Biopharmaceutical processes.

Outcomes of Analytical QbD:

- Although the field is in its infancy, the outcome of science- and risk-based approaches will ensure optimal performance and reliability of methods and the data generated.
- The most important outcome of a successful AQbD is a robust, rugged method that will likely be useful for many years with few problems.
- The incorporation of the analytical target profile (ATP) in the development cycle is viewed as having the potential to reduce the burdens of post-approval variations.
- Method transfer in QbD is feasible for analytical methods and will enable better, more efficient and continuous improvements for future methods.
- Applicable throughout the life cycle of the product.
- Movements within "Design Space" are not considered a change in method.

CONCLUSION: It was found that employing AQbD in pharmaceutical industries has started to show a remarkable decrease in warning letters and explanatory reviews. The compliance towards the regulatory needs are being fulfilled .it has ensured safe efficacious and cost-effective drugs for the health care industries with a very less number of OOS and OOT.

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