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AN INSIGHT ON QUALITY BY DESIGN IN PHARMA SECTOR

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ABSTRACT

Quality by Design (QbD) is defined by the ICH Q8(R2) guideline as "a systematic approach to development that starts with predefined objectives and emphasizes product and process understanding and Process control, based on sound science and Quality Risk Management." Pharmaceutical QbD is an organized method of development that starts with predetermined goals and places a strong emphasis on understanding and controlling processes and products using good science and quality risk management. Eliminate batch errors, avoid problems with legal compliance, Reliable, agile, and flexible system Increase efficiency in production, reduce costs, project rejections, and waste Establish a foundation of scientific knowledge for every product. Analytical Quality by Design (AQbD) or analytical applications of the QbD principle are also possible. It allows movement within the range of the Method Operable Design (MODR) for analytical procedure. The analytical technique developed using AQbD in the method development process minimizes the amount of Out-of-Trend (OOT) and Out-of-Specification (OOS) discoveries, unlike current methods, because of the method's robustness within the region. The primary obstacle to the adoption of quality by design is a lack of understanding about the pharmaceutical process, despite the fact that QbD is a critical component of the current approach to pharmaceutical quality.

Keywords: Quality by Design, Analytical Quality by Design (AQbD), Out-of-Trend, Out-of-Specification

INTRODUCTION [1-9]

Quality by design (QbD) concept was developed by Dr. Joseph M. Juran. Dr. Juran. He had the opinion that products should be made with quality in mind and that most

quality-related issues and crises stem from poor product design. According to Woodcock, a high-quality drug product is one that is free of contaminants and consistently provides the customer with the therapeutic benefit that is stated on the label. The US Food and Drug Administration (FDA) supports the use of QbD concepts and risk-based techniques in the development, production, and regulation of pharmaceutical products. The pharmaceutical sector is always looking for ways to improve the efficacy, quality, and safety of its products. However, in recent years, the business has faced significant challenges due to medication recalls, manufacturing failure costs, scale-up concerns, and regulatory complexity. In the past, end-product testing was primarily responsible for ensuring the performance and quality of the product, with little knowledge of the process or its crucial factors. Therefore, the implementation of QbD, a science-based strategy that enhances process knowledge by lowering process variance and the enabling process-control measures, is the regulatory bodies' primary priority. In order to maintain the required level of product quality, manufacturing procedures and formulation design and development are included in the QbD approach to pharmaceutical development. Rules and mathematical models are employed to guarantee the creation and application of the knowledge on the subject. Part I of ICH guideline Q8 addresses pharmaceutical development, and Part II is an annex to the guideline that outlines the tenets of quality-by-design. "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," is what the ICH Q8(R2) guideline defines as Quality by Design (QbD).

PHARMACEUTICAL QUALITY BY DESIGN OBJECTIVES [10]

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management. The goals of pharmaceutical QbD may include the following:

1- To attain significant product quality specifications based on clinical performance
2- To expand process potential and minimize product variability and defects by enhancing process design, understanding, and control
3- To improve product development and manufacturing efficiencies

4- To adress root cause analysis and post approval change management

BENEFITS OF QbD [11, 12]

Get rid of batch errors, prevent issues with regulatory compliance, Effective, nimble, adaptable system Boost production effectiveness, cut expenses, project rejections, and waste Create a scientific knowledge foundation for each and every product. Better communicate on scientific matters with industry, include risk assessment, expedite the choice to release, Reduce the number of deviations and expensive inquiries, empowering technical personnel make sure the information is consistent. Cut back on end-product testing

QbD Application [13, 14]

The QbD idea has now spread beyond formulation development to other crucial areas of pharmaceutical development, such as the development of therapeutic substances, analytical methods, stability and dissolution tests, bioequivalence testing, clinical trials, etc.As a result, it is thought to be ubiquitous throughout all of these crucial phases of product development. Benefits from QbD can even be obtained by a formulation scientist after a product is commercially launched and during post-marketing surveillance. Potential applications of QbD approach in diverse stages of product development lifecycle.

Analytical Quality by Design (AQbD)

- The QbD principle can be applied analytically or as Analytical Quality by Design (AQbD). It permits mobility within the Method Operable Design Range (MODR) for the analytical procedure. Due to the resilience of the method within the region, the analytical method developed utilizing Analytical Quality by Design (AQbD) in the method development process minimizes the amount of Out-of-Trend (OOT) and Out-of-Specification (OOS) findings, unlike current methods.
- It simply means that it allows the power to change method parameters within a method's design space, referred to as the Method Operable Design Region (MODR).

A. Multivariate optimization for simultaneous determination of aspirin and simvastatin by reverse phase liquid chromatography method using AQbD approach **[15]**

B. Development and Validation of Stability-Indicating Liquid Chromatographic Method for Estimating Olmesartan Medoxomil using Quality by Design **[16]**

C. Using an innovative Quality-by-Design approach for development of a stability indicating UHPLC mehod

for ebastine in the API and pharmaceutical formulations **[17]**

D. Application of quality by design elements for the development and optimization of an analytical method for protamine sulfate **[18]**

E. Chaotropic salts in liquid chromatographic method development for the determination of pramipexole and its impurities following quality-by-design principles **[19]**

Regulatory aspects of Quality by Design (QbD) [20-23]

1- FDA Perspective - In 2005 USFDA asked participating firm to submit chemistry manufacturing control (CMC) information demonstrating application of QbD as a part of New Drug Application (NDA). QbD involves thorough understanding of process; a goal is defined before actual start of process. This Quality by Design (QbD) concept was accepted by FDA

2- ICH guideline and QbD

The underlying principles of Quality by Design (QbD) like science and risk-based product development, risk assessment, lifecycle approach and method design are explained in the quality guidelines of International Conference on Harmonization (ICH); ICH Q8(Pharmaceutical Development), ICH Q9(Quality Risk Management), ICH Q10(Pharmaceutical Quality System).

Regulatory Perspective of AQbD - Implementation of Analytical Quality by Design (AQbD) is expected to strengthen the concept of "right analytics at right time" which plays significant role in drug product development cycle. Few months ago, FDA has approved a few new drug applications based on AQbD and referred the importance and benefits of QbD in analytical method development

ELEMENTS OF QbD [24]

The elements of QbD include:

1- Quality Target Product Profile (QTPP) – it identifies the CQAs of drug product.

2- Product design and identifying Critical Material Attributes (CMAs).

3- Process design and identifying Critical Process Parameters (CPPs). This includes linking the CMAs and CPPs with CQAs.

4- Controls strategy: developing specifications for active pharmaceutical ingredients (APIs), excipients and final drug product;

also controls for every step of the production process

Quality Target Product Profile-

With safety and efficacy of the medicinal product taken into consideration, QTPP is a prospective summary of the quality attributes of a drug product that will ideally be reached to assure the required quality. It includes the following:

- Intended use in a clinical setting, route of administration, dosage form, and delivery system(s)
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics appropriate to the drug product dosage form being developed
- Drug product quality criteria appropriate for the intended marketed product

Product design and identifying Critical Material Attributes (CMAs).

The ICH Q8 (R2) advice discusses process design, knowledge, and control, which has been the focus of QbD over the years. It is imperative to underscore the equal significance of product design, comprehension, and control. Clinical investigations verify if a product can meet patients' demands; this is determined by its design. Stability tests verify if a product can sustain its performance over its shelf life, a factor that is also determined by its design. Product design is flexible and can take many different forms. This include the following:

- Physical, chemical, and biological characterization of the drug substance(s)
- Identification and selection of excipient type and grade, and knowledge of intrinsic excipient variability
- Interactions of drug and excipients

Process design and identifying Critical Process Parameters (CPPs).

To create the required quality output, a pharmaceutical manufacturing process typically comprises of a number of unit operations. The input operating parameters or process state variables of a process step or unit operation are referred to as process parameters. When a process parameter's unpredictability affects a crucial quality attribute, it's considered critical and needs to be watched over or managed to guarantee the process yields the required level of quality. Steps of process are described below:

- Identify all possible known process parameters that could impact the performance of the process
- Use risk assessment and scientific knowledge to identify potentially high-risk parameters

- Establish levels or ranges of these potentially high-risk parameters
- Design and conduct experiments, using DoE when appropriate
- Analyse the experimental data and, when possible, determine scalability and apply first principal models to determine if a process parameter is critical.

Control Strategy [16]

The knowledge gained through appropriately designed development studies culminates in the establishment of a control strategy. It can include Control of input material attributes (*e.g.*, drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality, Product specification(s), Controls for unit operations that have an impact on downstream processing or product quality, In-process or real-time release testing in lieu of end-product testing (*e.g.*, measurement and control of CQAs during processing), A monitoring program (*e.g.*, full product testing at regular intervals) for verifying multivariate prediction model

Process Capability and Continual Improvement

In respect to the specified acceptance criteria, process capability quantifies the intrinsic variability of a stable process in a statistically controlled state. Its capacity to meet needs is improved by ongoing improvement. It has five phases as follows **[25]**

- Define the problem and the project goals, specifically
- Measure key aspects of the current process and collect relevant data
- Analyse the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect if any.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

PHARMACEUTICAL QUALITY BY DESIGN TOOLS [26-31]

Prior Knowledge-The word "prior knowledge" has been used often in workshops, seminars, and presentations even though it is not officially defined. Applicants sometimes try to substitute previous knowledge for relevant scientific investigations or scientific arguments in

regulatory filings, arguing that this is a "legitimate" basis.

Risk Assessment- "The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk," according to ICH Q9 quality risk management. The degree of effort, formality, and documentation of the quality risk management process should be proportional with the amount of risk. The assessment of the risk to quality should be founded on scientific knowledge and eventually lead to the protection of the patient. The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development. ICH Q9 provides a no exhaustive list of common risk assessment tools are Basic Risk Management Facilitation Method, Failure Mode Effect 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). Some of the well-recognised risk assessment tools in Analytical Quality by Design (AQbD) are Failure Mode Effect Analysis (FMEA), Ishikawa cause and effect analysis or Fishbone diagram.

Design of Experiment (DOE) [32-40]

According to requirement of ICH Q8 guideline, regarding ‘design space’ in product development, Method Operable Design Region (MODR) can be established in method development phase, which facilitates a source for robust and cost-effective method.

- MODR is the operational range for the critical method input variable which produces results that consistently meets the goals set out in the Analytical Target Profile (ATP).
- MODR allows the flexibility in various input method parameters It is based on science, risk-based approach and multivariate approach to determine influence of various factors on factor performance.
- It is recommended by Food and Drug Administration (FDA) to conduct MODR together with method validation. Once it defined, proper method control can be put in place and method validation can be performed.

Screening- In screening, qualitative input variables can be eliminated. It addresses determining the different Critical Method Parameters (CMP) that optimization studies must take into account. The screening tests ought to provide insight into the set of CMP

in the MODR that must be either regulated or exposed to DOE procedures.

Optimization

Quantitative metrics for the CMP can be included in the optimization stage from risk assessment or screening. It provides a foundation for the scientific understanding of the relationship between input variable quantities and output response, which will have a significant impact on the ATP and method performance.

Method Operable Design Region (MODR) and Surface Plots

The MODR concept uses a contour plot of the model. The contour plot is a two-dimensional response plot that illustrates how pH and aqueous phase percentage affect analyte retention time while controlling other variables such as flow rate and instrument design.

Selection of DOE Tools

There are numerous methods for deriving mathematical relationships throughout the optimization process. The number of input variables, familiarity with regulated parameters, and scientific comprehension of the relationship between variable and result are crucial factors to take into account while choosing a DOE tool. To interpret the interplay and contribution of factors in method answers, statistical knowledge is required.

Product and process understanding is a key element of QbD.

Pharmaceutical scientists can systematically modify elements in accordance with a predetermined plan by using the superb instrument known as DoE. Relationships between input components and output reactions are also disclosed by the DoE. The capacity to accurately identify how factors jointly affect the output responses is the strength of DoE over the conventional univariate approach to development research.

Process Analytical Technology

The control strategy may include the use of PAT. The use of PAT to make sure the process stays inside a predetermined design space is identified by ICH Q8 (R2). To make decisions about whether to proceed and to show that the process is being maintained in the design space, PAT can offer continuous monitoring of CPPs, CMAs, or CQAs. Measurements of CMAs, CQAs, and in-process testing can also be made online or in accordance with PAT. If a variation in the environment or input materials is found that could negatively affect the quality of the medicinal product, PAT can enable active control of CMAs and/or CPPs in a more robust process. It can also enable quick adjustments to the operating parameters.

Application of PAT involves four key components as follows:

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management

CHALLENGS [41-44]

Although the modern approach to pharmaceutical quality includes quality by design (QbD) as a crucial component, the root reason and main barrier to QbD adoption is a lack of knowledge about the pharmaceutical process. Pharmaceutical businesses have historically placed more of a focus on the final product and less on the scientific understanding of the underlying process. Businesses requested clarification from the FDA regarding QbD nomenclature, permissible procedures, standards for evaluating the sufficiency of controls, criteria for selecting and deselecting essential quality attributes, and requirements for substituting analytical methods. Like Internal misalignment, Lack of belief in business case i.e. there is a lot of uncertainty over timing of and investment requirements for QbD implementation, Alignment with third parties, The next six challenges are directly related to the regulatory authority, Regulators not prepared to handle QbD applications, Misalignment of international regulatory bodies Current interaction with companies is not conducive to QbD

How to implement AQbD approach in the current practice

In the future, the method development process will need to incorporate Analytical Quality by Design (AQbD) and validate the method performance together with the validation protocol. To use AQbD for a particular drug product, the following factors might be taken into account:

Step-1 Construct a Quality Target Product Profile (QTPP) based on the product specifications as outlined in FDA approval

Step- 2 Analyse each product specification as per criticality

Step 3 Assess and justify the analytical method development and its suitability to support the criticality

Step- 4 Select the suitable analytical method like HPLC, UV and IR to meet Analytical Target Profile (ATP) and QTPP

Step- 5 Perform risk assessment for selected method

Step- 6 Identify the quantitative and qualitative variable that affects the method performance and the method responses to be measured

Step- 7 Use suitable Design of Experiment (DOE) to optimize variable and establish scientific understanding

Step- 8 Find the region, models to assess the robust, and economic operation for the method variable

Step- 9 Validate the models and Method Operable Design Region (MODR) using experimental verification at different points to prove robustness

Step- 10 Then validate the method in the operable region for the method performance and subject to control strategy and improvement.

Benefits of Application of Quality by Design

In development of robust method, Understand, minimize and control sources of variability, It is applicable throughout the lifecycle of the method, It provides regulatory flexibility (movement within "Analytical design space" is not considered as a change in method)

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