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ANALYTICAL QUALITY BY DESIGN ASSISTED METHOD DEVELOPMENT: A REVIEW

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ABSTRACT

Analytical techniques must be created for different phases of the P'ceutical product life cycle. If these processes are not effectively organized using scientific knowledge and process understanding, they can lead to an expensive and time-intensive procedure. The pharmaceutical industry is actively exploring novel policies or elements that can be incorporated into or substituted for existing components in their quality and risk management systems. The concept of Quality by Design was initially outlined by the renowned quality expert Joseph M. Juran. This concept can also be extended to analytical method development, referred to as Analytical Quality by Design. Quality by Design is a systematic approach to development that begins with predefined objects and emphasises product and process understanding and process control. AQbD is essential in modern method development, contributing to a systematic approach to drug development. This review article's main objective is to delineate the steps in method development with Analytical quality by design, addressing implementation concerns. The analytical method development process includes Critical Performance Attributes (CPAs), MODR, Analytical Method Validation, Control Strategy, and Continuous Method Improvement.

Keywords: Analytical Quality by Design, Analytical Target Profile, Critical Performance Attributes, MODR

INTRODUCTION

The US Food and Drug Administration's Quality by Design (QbD) the lead established it an essential standard for the pharmaceutical industry. Quality is a fundamental prerequisite for the approval and adoption of any pharmaceutical product, in addition to safety and efficacy. It concerns the suitability of a drugs substance or products for the intended purpose **[1]**.

Due to these techniques are essential to the development of new products, analytical methods are critical to the manufacturing of pharmaceuticals. In besides ensuring that the treatment satisfy quality requirements for its intended use, an effective, accurate, and precise analytical method provides a purity check all throughout the entire development process. Neglecting this can lead to costly and time-consuming issues. During method development, it's important to establish ruggedness and robustness early on to ensure consistent performance over time. In today's context, analytical method failures, especially during method transfer, are becoming more common. Using the Quality by Design (QbD) approach to create a design space helps establish effective method control, preventing batch failures, increasing efficiency, and reducing costs **[2]**.

A "Methodical development approach that commences with predefined goals, focusing on an extensive knowledge of both the product and the process, grounded in solid scientific principles and quality risk management" is how the ICH Q8 guidelines define Quality by Design (QBD)" **[3]**.

Table 1: Historical background of quality by design [4-6]

YEAR	ACTIVITIES
1950	Windows of operation
1970	Established by Joseph M. Juran, QBD
Sept 2002	USFDA involves QBD concept into cGMP
Sept 2004	USFDA releases its final "Pharmaceutical cGMP" report.
Sept 2004	USFDA Industry Guidance: PAT - A The framework for Creative Drug Development, Manufacturing, and Quality Control
Nov 2005	Quality Risk Management (ICH: Q9)
June 2008	Pharmaceutical Quality System (ICH: Q10)
Nov 2009	Pharmaceutical Development (ICH: Q8(R2))

QUALITY BY DESIGN (QBD) APPLICATIONS [7]

Analytical Research Development

Understanding each critical factor within the MODR at an advanced level will make it easier to transfer the method from Research and Development to Quality Control. This,

in turn, will reduce variability in analytical attributes and enhance the robustness of the method.

Quality Control & Manufacturing Facility

Together with other Quality by Design (QbD) tools, a detailed model predictions how the product will react to modifications in each Critical Material Attribute (CMA) and Critical Process Parameter (CPP) throughout a design space.

Quality Assurance

Quality Risk Management during development makes it easier, more efficient, and faster to investigate variability or batch failures, leading to the elimination of batch failures, reduced deviations, and cost savings in investigations.

Regulatory Affairs

The process of review and approval will be expedited and simplified. Furthermore, having a well-established and validated design space will provide regulatory adaptability in handling changes post-approval.

Analytical quality by design: What is it? [8-9]

To ensure product quality and performance, the industry has grown beyond based only on Quality by Testing (QbT) as a result of the use of Analytical Quality by Design Establishing a design space and determining suitable process controls are facilitated easier by information that is gathered during development. Similar to process QbD, Analytical quality by design leads to a well-understood, intentional, and reliable method that consistently meets performance objectives throughout its lifecycle. Analytical quality by design enhances our scientific comprehension of pharmaceutical processes and techniques, helping to determine important quality attributes and evaluate how they affect the quality of the finished product. Not only does Analytical quality by design provide the necessary design space for development, but it also allows for Continuous growth throughout the final stages of the method. This approach helps mitigate regulatory compliance issues by minimizing deviations and scientific variations, ultimately enhancing robustness. Well-known Due to their flexibility, durability, and diminished sample requirements, chromatographic analytical techniques including Supercritical Fluid Chromatography (SFC), Gas Chromatography (GC), High-Performance Thin-Layer Chromatography (HPTLC), and High-Performance Liquid Chromatography (HPLC) are preferred. When automated,

these techniques also reduce the likelihood of human errors.

Benefits of Analytical QbD: [10]

1) liability in API analysis, metabolites in biological samples, impurities in dosage forms, and stability samples
2) To keep the values of analytical attributes within the pharmacopoeia monographs, and away from Out of Specification (OOS) limits
3) Decrease in the range of analytical characteristics to increase the robustness of the method
4) Smooth process of method transfer to the production level
5) Enhanced understanding and control
6) Beyond the conventional ICH method validation procedure Revalidation is not required within MODR.

QbD Standards for Developing Analytical Methods:

The analytical technique shall be in compliance with QbD and PAT techniques principles for ensuring product quality. It's important to emphasize adherence to regulatory guidelines for Analytical quality by design, which outline method development using DoE, including risk management and the necessary quality system details.

Elements of AQbD [11]

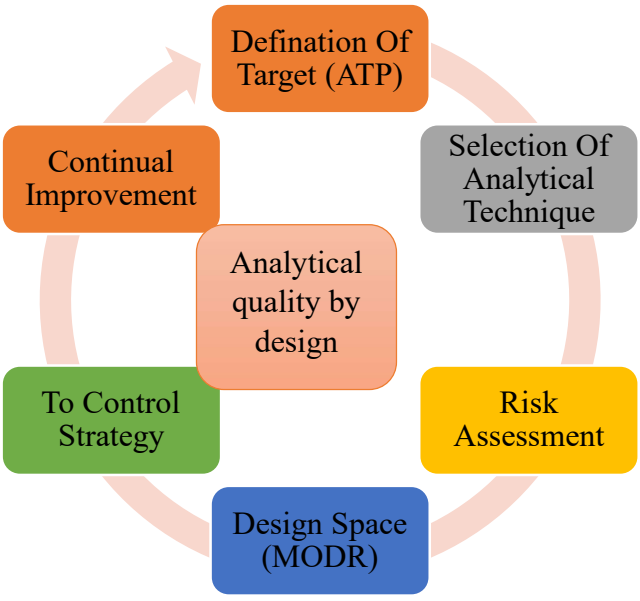

Figure 1: Elements of AQbD

Analytical target profile (ATP) [12-13]

When establishing a method, ATP is a beneficial instrument to help determine which requirements will be measured. It provides an idea about the acceptance criteria that this technique will measure and the limit that indicates the measurement is required. (I.e. Accuracy, range, precision, sensitivity). For the method development, identifying the characteristics of the method that can be used as performance indicators for its intended use is essential. ATPs are selected based on the validation parameter that are describe in the ICH Q2 (R1) guideline.

CPA (Critical Performance Attributes)

According to ICH Q8, a Critical Quality Attribute (CQA) or Critical Process Parameter (CPP) is described as a property or characteristic linked to the physical, chemical, biological, or microbiological aspects of a product. It must adhere to defined limits, a described range, or a particular distribution to enhance the intended the product's quality **[14]**.

During this phase, the analyst must identify the crucial factors that directly influence the effectiveness of the method. These significant factors may vary from one endeavour to another. Critical Method Parameters (CMPs) are divided into three categories: those associated with the substance under analysis, those connected to the instrument, and those related to the operating conditions. Common Critical Parameters (CPAs) in chromatographic experiments encompass elements such as sampling, sample preparation, standards, reagents, column chemistry, mobile phase composition, pH, mobile phase flow rate, column temperature, and detector selection. Aligned with these parameters, the Critical Quality Attributes (CQAs) or key responses monitor include Resolution, retention time, tailing factor, detection limit, and robustness are all significant responses to keep an eye on. The chemical and physical characteristics of the drug substance and it's contaminants, which includes their solubility, pH value, boiling point, polarity, charged functional groups, and stability in solution, serve as defining factors for Critical Quality Attributes (CQAs) in the procedure of developing an analytical method **[15]**.

Risk Assessment

As per the ICHQ9 guideline, it's a structured process to evaluate, manage, communicate, and review quality-related risks during method development. This step is crucial for ensuring the method's reliability. After identifying the Analytical Target Profile

(ATP) and Critical Process Parameters (CPA), Analytical quality by design focuses on thoroughly assessing the factors that could introduce variability into the method. These elements encompass the analyst's Procedure, Conditions of the environment, sample preparation, sample characteristics, measurement and method parameters, and instrument configuration. As per ICH Q9, the process of risk assessment involves three stages: Risk assessment, analysis, and identification. The evaluation of risks can be conducted throughout the entire method development process, from the initial stages to continuous method monitoring **[16]**.

Figure 2: Various risk assessment steps

Risk identification

Ishikawa Fishbone Diagram

Identify risks using the Ishikawa Fishbone diagram by categorizing factors based on their source and uncovering the causes and effects of these factors on method performance. Another way to identify risks is by using SIPOC, which helps pinpoint potential gaps in the process (S stands for supplier; I for input; P for high-level process; O for output; and C for customer) **[17]**.

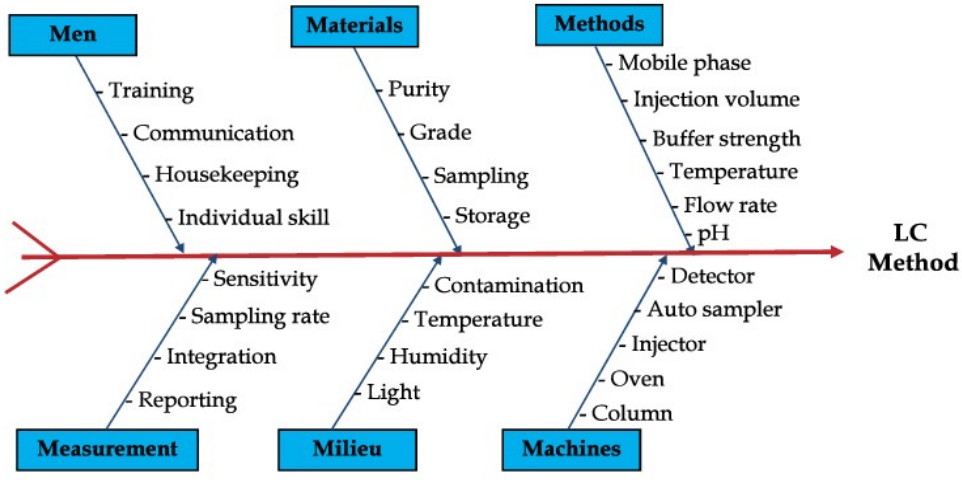

Figure 3: Ishikawa Fishbone Diagram

Risk Analysis

Certain techniques, like Analysis of failure modes and effects and Analysis for Relative Risk Matrix, can be used to carry out risk analysis. In the initial phase of relative risk matrix analysis, the Analytical Test Parameters (ATPs) are categorized and ranked as low, medium, or high risks based on their impact on the Critical Process Attribute (CPA). These risks encompass aspects such as the instrument's operating method, characteristics of reagents, cycle time, and so forth. Factors deemed low risk can be accepted without further investigation, while High- and medium-risk factors are not acceptable and necessitate additional examination to mitigate the risk. This is where Failure Mode Effect Analysis becomes relevant. An alternative method for risk analysis involves assigning a numerical value from 1 to 5 to risks according to their intensity, incidence, and identification. The multiplication of these values yields a Risk Priority Number (RPN). Subsequently, a bar graph is constructed, with method attributes or factors on the x-axis and on the y-axis Risk Priority Number .Following the Risk Priority Number, all elements are grouped in descending order using a Pareto Graphic. Factors with higher possibility scores are classified as "Critical". Among all the risks, method attributes with Risk Priority Number exceeding 25 are given the highest priority. These attributes are considered the most critical material attributes of the API and necessitate optimization and control.

Risk evaluation

The identified risk and the risk investigation are contrasted according to the established risk measures. It consists of the three basic questions' appropriate potential of evidence. In order to perform an effective risk evaluation, the robustness of the data set must be considered just as important as determining the quality of the outcome. A risk assessment's output may consist of either a qualitative or quantitative range of risk. When risk is expressed quantitatively it is done in the form of numerical probability. Sometime 'risk score is used to further define the description for risk ranking.

Experimental design

Experimental design is a statistical method for organizing experiments to gather necessary information accurately and efficiently. Before choosing the right design, it's important to define the specific area of interest within the range of factors you're exploring **[21]**.

Design of experiments:

Optimization to identifying the ideal composition and operational parameters to

enhance something to its highest level of perfection. In pharmaceutical design and development, multiple variables are at play. Independent variables, also known as factors, are those which impact the analytical approach's component elements and their results while remaining under the manufacturer's control. The values associated with these factors are represented by levels. The characteristics the fact that the end products demonstrate are referred to as depending or response variables. Adjustments in the independent variables lead to corresponding changes in the dependent variables **[20]**.

Figure 4 shows various Design of Experiments (DoE) optimization methods. DoE has developed into an effective tool that efficiently yields a plethora of data with few experiments.

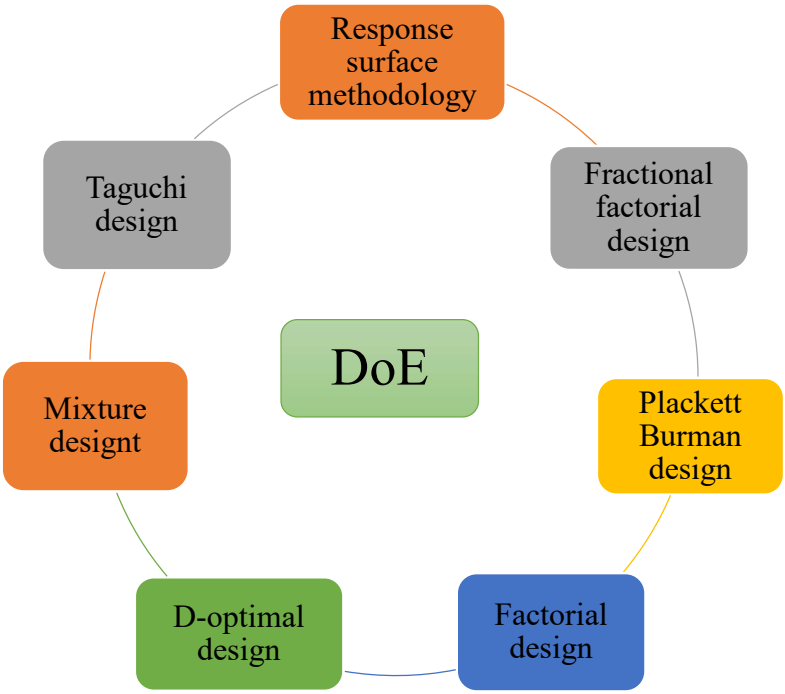

Figure 4: Design of experiments optimization methodologies

Selection of Designs:

a) Screening

During the screening phase, we can exclude qualitative input variables and identify the crucial method parameters (CMP) that require attention in subsequent optimization experiments.

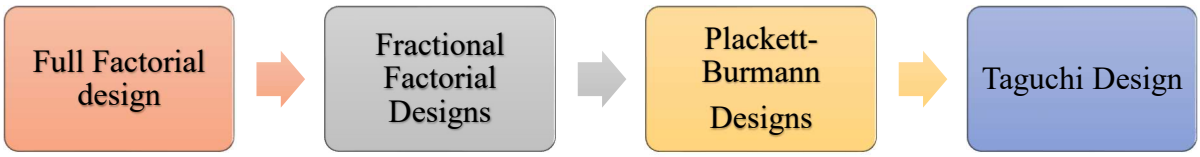

Figure 5: Experimental design for screening

When faced with numerous factors to screen, fractional factorial designs or Plackett-Burman designs can be employed. Opting for fractional factorial design is suitable when the factors range from more than four but fewer than six, whereas the Plackett-Burman design is preferred when dealing with more than six factors.

b) Optimization

To enhance optimization, one can opt for response surface designs, factorial designs, or mixed designs. When the objective is to assess the key impacts along with interactions among factors, especially when there are over two but fewer than five factors, selecting full factorial designs is appropriate. If the aim is to optimize identified critical factor selecting mixture designs is recommended in situations where the goal is to optimize the portion of critical components in a mixture and the factors involve mixture components, ranging from between two and four in number, Designs for response surfaces are the most effective option. In scenarios where the goal is to optimize the proportion of essential elements in a mixture, and the elements involve components of that the mixture, selecting combinations of designs is advisable. Simple Lattice and Restricted Mixture are two possibilities for mixture designs; Box-Behnken and Central Composite are options for response surface designs. Determine the dependent responses (CPAs) for each experimental run involving various combinations of each factor being examined after determining on the experimental design. Following the model evaluation, specify both numerical and graphical optimization for all factors based on the responses

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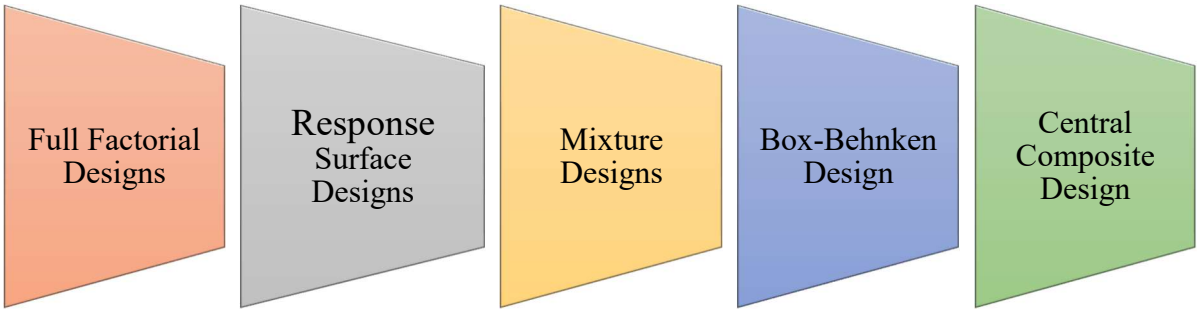

Figure 6: experimental design for optimization

Table 2: Experimental designs with number of variable

Design	Number of variable
Full factorial design	Optimization of 2-5 variables
Taguchi design or fractional factorial design	Optimization and screening of more than 5 variables
Placket-Burman Design	Screening and identifying vital factors from large number of variables

MODR

The MODR (MODR) involves conducting multiple types of experiments during which input factors are intentionally influenced. This process helps to identify the reasons behind significant changes in output responses, facilitating the assessment of the relationship between factors and responses, all conducted concurrently, methodically, and efficiently. During the method development stage, one can establish a MODR to formulate a resilient and cost-effective method. The MODR represents the range of critical input variables that consistently achieve the desired results outlined in the ATP (Analytical Target Profile). Without with to submit once again to the FDA, MODR permits flexibility in enhancing various input method parameters to meet the anticipated procedure performance requirements and responses. Once defined, can implement suitable method controls and proceed with verification and method validation. If there are more than four factors, start by identifying the critical factors using screening designs and then fine-tune them with optimization designs. If there are fewer than four factors, you can directly optimize them using optimization designs **[18-19]**.

Control strategy:

The control strategy is a set of standards that can be affected by the analyst's understanding and expertise about the MODR. The creation of the method control strategy involves utilizing the statistical data

gathered during the MODR process. This control approach is not a one-off procedure limited to the stage of method development; rather, it can adapt and evolve over the entire lifecycle of the method. It's noteworthy to highlight that the method control strategy in QbD approaches does not fundamentally differ from conventional approaches **[20]**.

Lifecycle management:

This represents the concluding phase of Quality by Design (QbD), constituting an ongoing procedure of disseminating knowledge gained during the method development stage. This knowledge encompasses outcomes of risk assessments, initial assumptions, MODR, control strategy, CQA, and the Analytical Target Profile. It is crucial to emphasize that lifecycle management in QbD approaches exhibits distinctions from conventional methods **[21]**.

CONCLUSION

QbD plays crucial Role in P'ceutical processes such as drug development, formulations, analytical methods, and biopharmaceuticals. The primary motivation for embracing QbD is compliance with regulatory requirements. Analytical Quality by Design is particularly significant in the P'ceutical industry to guarantee product quality. Analytical quality by design yields a thorough understanding from commercial production to product development. This review article help researcher to find the approach of QbD on the analytical method development. These parameters of Method Development include analytical target profile, Critical Performance Attributes, risk assessment, risk identification, and risk analysis. It also emphasizes the significance of applying the QbD approach to achieve a more accurate method. Successfully implementing a QbD approach necessitates the identification of appropriate Analytical Test Parameters (ATP) and conducting thorough risk assessments. It also requires the use of suitable tools and executing the necessary amount of work within specified timelines. The P'ceutical Companies needs to demonstrate the commitment for this approach to be successful.

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