An Overview of Analytical Quality by Design

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Abstract: By combining systematic risk assessment with in-depth method knowledge, Analytical Quality by Design (AQbD) creates an organized, scientific foundation for creating dependable and robust analytical techniques. This strategy, which emphasizes method control, A consistency, and lifecycle management, is in line with ICH Q8–Q10. Important components including the Analytical Target Profile (ATP), Critical Quality Attributes (CQAs), Critical Analytical Attributes (CAAs), and Critical Method Variables (CMVs) are well specified within the AQbD architecture. The Method Operable Design Region (MODR) is created utilizing risk-driven assessments in conjunction with Design of Experiments (DoE) techniques, such as factorial, Plackett–Burman, and Box–Behnken designs, to produce reliable and repeatable method performance. A well-established control strategy, combined with provisions for continual improvement, further strengthens method reliability and regulatory flexibility. By integrating statistical evaluation with scientific understanding, AQbD promotes proactive quality assurance and ensures that analytical methods remain consistent and compliant throughout the product lifecycle.

Key words: Analytical Quality by Design, Analytical Target Profile, Critical Quality Attributes

I. INTRODUCTION

A methodical approach to pharmaceutical development, Quality by Design (QbD) starts with well-defined goals and concentrates on developing a comprehensive understanding of the product and its production process. To guarantee efficient process control, it is based on solid scientific concepts and organized quality risk management. QbD has been used extensively in the creation of generic medications in recent years. The USFDA has released particular QbD recommendations for both immediate-release and modified-release dose forms to encourage its implementation[1].

ICH recommendations QbD ideas are well defined in Q8(R1): pharmaceutical development, Q9: quality risk management, and Q10: pharmaceutical quality system. A few conferences in late 2013 and early 2014 insisted on using the present QbD paradigm to develop analytical techniques. According to certain experts, there are chances to adapt QbD to analytical methodologies, just like with industrial processes. In addition to supporting the creation of dependable and economical analytical techniques, AQbD offers the regulatory flexibility required to sustain these techniques over the course of a product's whole lifecycle. The acceptable range within which method parameters can be changed without affecting method performance is represented by the idea of the Method Operable Design Region (MODR). Analytical quality by design is not expressly covered by ICH Q11, despite the fact that it describes the QbD principles for the creation of active pharmaceutical ingredient (API) production procedures[3].

It is believed that the creation of medications depends on analytical sciences. Analytical methodology and product development are strongly linked throughout the whole life cycle of any pharmaceutical product. The typical technique to developing analytical methods is quite time-consuming because there is a lot of variation at every stage of the process. Analytical scientists are increasingly using a rigorous QbD-based strategy to reduce potential errors during method development. Analytical Quality by Design (AQbD) is a notion that emerged from applying QbD ideas to the development of analytical methods[4].

AQbD considers both an overall evaluation of scientific and regulatory skills and the requirements for quality control. Although most applications to date have focused on using design of experiments (DOEs) and statistical screening for method parameter operational spaces toward method robustness consideration, a methodical approach has also been advised. 7 "Six sigma" is a set of procedures designed to improve processes

methodically and get rid of statistically significant flaws[13].

Identifying possible failure modes and establishing a strong Method Operable Design Region (MODR), sometimes referred to as the design space, that complies with system suitability standards and facilitates ongoing lifecycle management are among the main objectives of AQbD. Establishing a robust MODR requires systematic multivariate experimentation to capture interactions among crucial method factors, as opposed to empirical or conventional univariate techniques like One Factor at a Time (OFAT)[4].

II. STEPS OF ANALYTICAL QUALITY BY DESIGN

1. ATP (Analytical Target Profile):

As the primary guiding component for method creation, validation, and lifecycle management inside the AQbD framework, the Analytical Target Profile (ATP) specifies the goal of an analytical method as well as the necessary performance criteria[40].

Method creation, validation, and lifecycle management are guided by it, the fundamental description of an AQbD-based methodology that specifies the method's intended purpose and performance criteria[26].

By establishing the ATP early on, analytical development is guaranteed to be both scientifically sound and compliant with regulations, which eventually supports consistent method performance throughout the lifecycle[41].

ATP should be fulfilled not just during method development but also throughout method transfer and lifecycle management. Additionally, ATP is not always restricted to a single method; several methods or analytical techniques can satisfy the same ATP[18].

The following is the general ATP for analytical procedures:

(a)selection of the target analyte (API and impurities),

(b) choosing a suitable analytical method (e.g., chiral HPLC, GC, HPTLC, ion chromatography, etc.),

(c) method requirements (assay, residual solvents, or impurity profile) selection

The analytical method's intended use includes additional specification tests like impurity profiling and residual solvent analysis in addition to standard assays including the identification, separation, and quantification of the active pharmaceutical ingredient. These assessments are necessary to verify the final drug product's safety, effectiveness, and general quality[19].

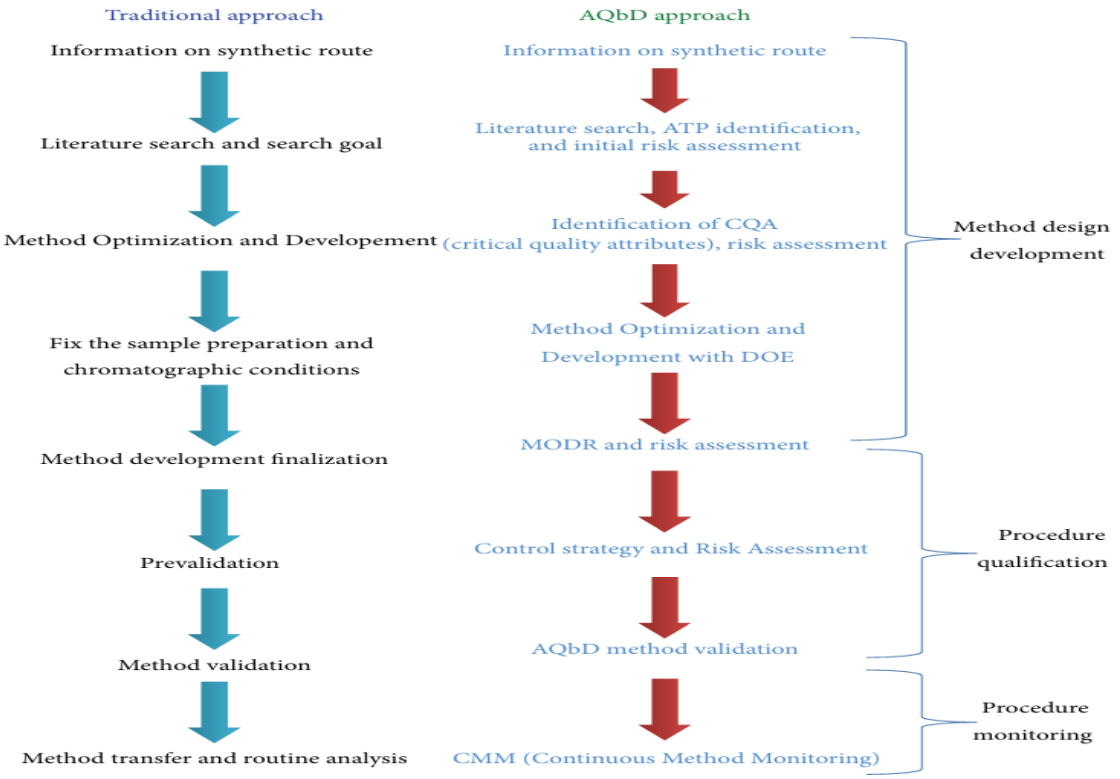

Fig 1: Difference between the traditional and AQbD approaches for analytical method development. 1

2. CQA (Critical Quality Attributes):
The physical, chemical, biological, or microbiological characteristics of a product that must stay within specified bounds to guarantee its intended safety, efficacy, and general quality within a QbD framework are known as Critical Quality Attributes (CQAs).35Controlling these CQAs throughout development and manufacturing is essential, as even small variations can influence the safety, stability, and therapeutic performance of the final pharmaceutical product[36].

The primary physicochemical or microbiological characteristics of a pharmaceutical product that must stay within predetermined acceptable bounds to guarantee its intended safety, effectiveness, and general quality during research and manufacture are known as Critical Quality Attributes (CQAs)[43].

Early CQA identification and control reduces variability and ensures consistent product quality by establishing a clear connection between material properties, process parameters, and product performance[44].

Critical Analytical Attributes (CAAs)
The physical, chemical, biological, or microbiological aspects of a product that must stay within specified bounds, ranges, or distributions to guarantee the intended level of product quality are referred to as Critical Quality Attributes (CQAs) in a pharmaceutical QbD framework[27].

CAAs are the measurable characteristics or outcomes of an analytical process that must be controlled to ensure the process meets its predetermined performance requirements. The performance of a method is directly impacted by these attributes, which include accuracy, precision, specificity, etc.

Examples of CAAs:
- Resolution between two peaks in chromatography
- Retention time (in HPLC/GC)
- Signal-to-noise ratio (in spectroscopy or chromatography)
- Peak symmetry
- Linearity(r^2)
- Detection limit (LOD) and quantitation limit (LOQ)

Critical Method Variables (CMVs)
CMVs are analytical method input characteristics or variables that can affect the method's variability or performance (i.e., the CAAs). During method development, it is necessary to comprehend and handle these controllable aspects.
Examples of CMVs:
- Column temperature (HPLC)
- Flow rate
- Mobile phase composition
- pH of the buffer
- Wavelength (in UV or fluorescence detection)
- Injection volume
- Sample preparation parameters

3.Risk Assessment:
Risk assessment is a methodical procedure for identifying, analyzing, and evaluating quality risks over the course of a product's lifecycle. It forms the basis for setting control priorities and making sure that important criteria are maintained within a QbD framework[28].
A hazard in risk assessment is typically characterized as a mix of the probability of an unfavorable occurrence happening and the seriousness of its repercussions. Fishbone diagrams and cause-and-effect diagrams are two examples of tools that can be used to discover the different aspects that could affect an analytical method's performance. These possible hazards are arranged into categories like materials, techniques, measurements, equipment, and other pertinent sources of variability in a fishbone diagram [8].
In our example, possible method inputs are mapped out using a fishbone diagram (Figure2), which can subsequently be ranked using systematic risk assessment techniques such a failure-mode-effects analysis (FMEA) or a more straightforward cause-and-effect analysis (CEA)[15].
ICH Q9 does not particularly handle risk assessment in product development, even though it mainly offers an organized framework for quality risk management. To identify possible risks and enhance process comprehension throughout product development, the same risk assessment instruments and concepts outlined in ICH Q9 can still be successfully used[17].

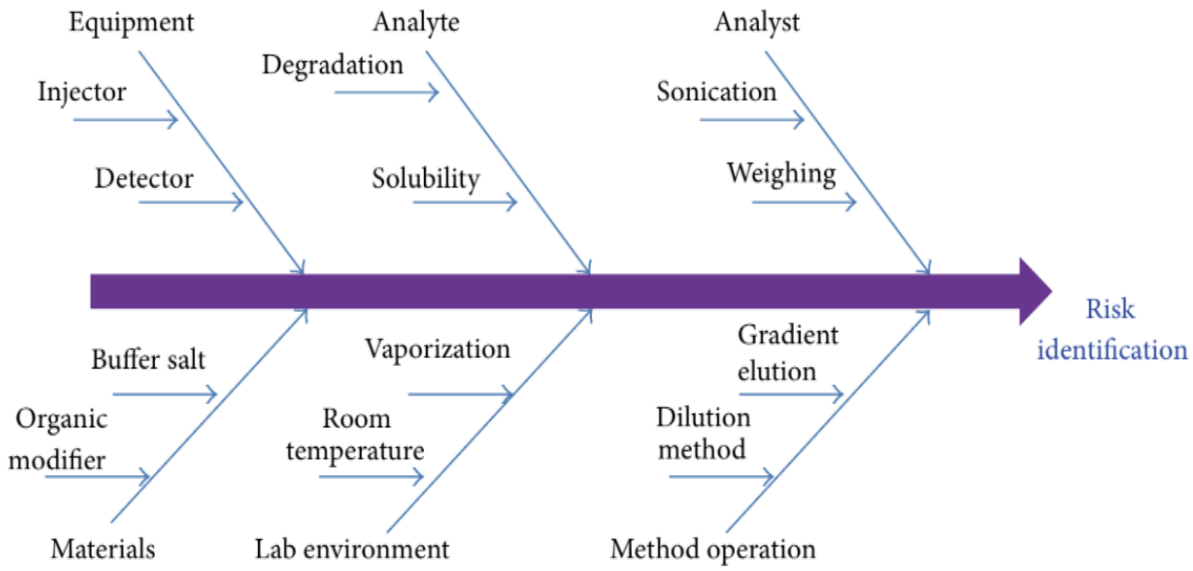

Fig 2:FishboneforRiskidentification.

4. DoE: Design of Experiments (Method Optimization and Development):

After an initial risk assessment has identified the important variables that need to be addressed, Design of Experiments (DoE) is used to improve and validate crucial technique parametersBy examining the chosen parameters separately or in combination, it is possible to assess both the primary impacts and the interaction effects determining method performance. Several experimental settings can be effectively explored with a comparatively short number of trials thanks to this methodical methodology. Finding the variables that have a major impact on the procedure and figuring out the ideal operating ranges required to create a flexible and dependable performance region require statistical analysis of the generated data[1].

A simultaneous multi-variant approach for the four components employed under DoE is referred to as "multi-variation at a time." In these experiments, an orthogonal and balanced FFD was employed to determine the main effects[10].

Screening designs

The most frequently used screening designs are Placket-Burman models, fractionate factorial designs, and two-level complete factorial designs given their inexpensiveness. Those methods allow the examination of many input factors with fewer experiments. It essential to consider these constraints in order to gain a better understanding of how elements of input influence output reactions.

The main drawback of two-level entire factorial designs is the large quantity of experiments involved when compared to fractionate factorial designs and Plackett-Burman designs[2].

The screening trials should indicate the CMP segregation that needs to be either regulated or exposed to DOE techniques in MODR optimization[14].

The most popular DoE-based screening techniques are the Plackett-Burman Design (PBD), Fractional Factorial Design (fFD), and Full Factorial Design (FFD), according to a number of findings in the literature[23].

- Full Factorial Design (FFD)

A two-level Full Factorial Design (FFD) is frequently used during the screening stage to methodically assess both main and interaction effects, enabling quick identification of the critical variables that need additional optimization[37].

During the screening phase, a Full Factorial Design (FFD) is used to find the significant variables and their interactions that could affect the analytical method's overall performance and accuracy. This methodical assessment aids in identifying the most important variables, offering a solid basis for further method improvement and optimization[30].

When dealing with two to five variables, Full Factorial Design (FFD) is extremely helpful for comprehending the main effects of individual factors as well as their interconnections. Because it is affordable and simple to use, the two-level FFD is frequently the first option during the screening stage. Each factor in this design is denoted by a capital letter, with +1 denoting the high level, –1 denoting

the low level, and 0 denoting the middle or intermediate level. For studies with two, three, or four components, the two-level factorial matrices show every potential combination of these levels. The precise number of factors and levels included in the investigation determines the overall number of experimental runs needed for the design.(Figure3).

2^2 Design Matrix			2^3 Design Matrix				2^4 Design Matrix				
No.	X_1	X_2	No.	X_1	X_2	X_3	No.	X_1	X_2	X_3	X_4
1	−1	−1	1	−1	−1	−1	1	−1	−1	−1	−1
2	−1	+1	2	−1	−1	+1	2	−1	−1	−1	+1
3	+1	−1	3	−1	+1	−1	3	−1	−1	+1	−1
4	+1	+1	4	−1	+1	+1	4	−1	−1	+1	+1
			5	+1	−1	−1	5	−1	+1	−1	−1
			6	+1	−1	+1	6	−1	+1	−1	+1
			7	+1	+1	−1	7	−1	+1	+1	−1
			8	+1	+1	+1	8	−1	+1	+1	+1
							9	+1	−1	−1	−1
							10	+1	−1	−1	+1
							11	+1	−1	+1	−1
							12	+1	−1	+1	+1
							13	+1	+1	−1	−1
							14	+1	+1	−1	+1
							15	+1	+1	+1	−1
							16	+1	+1	+1	+1

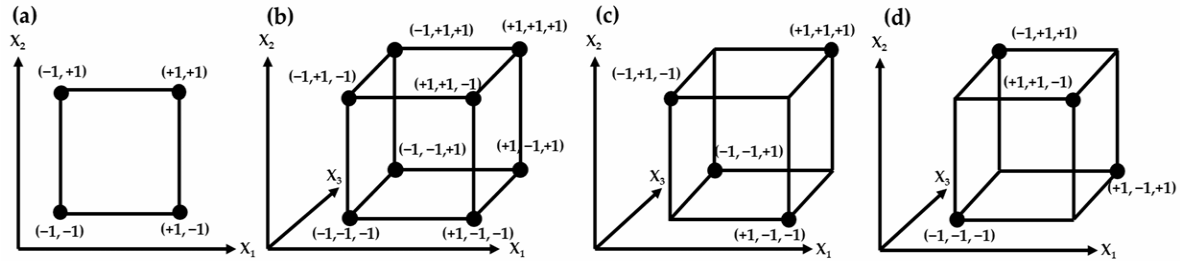

Fig3: illustrates a two-level FFD matrix for two factors (22), as well as for three factors (23) in parts (a) and (b) matrix with 3 factors, and (c) and its complementary design matrix (d)

- Fractional factorial design(fFD)

A popular screening method is fractional factorial design (fFD), especially when more than four experimental elements need to be investigated. This approach is useful because it makes it possible to evaluate several variables with comparatively few experiments. The total number of experimental runs in a fractional factorial design is denoted as 2^{k-p}, where p is the number of generators used to minimize the full factorial design and k is the number of factors being studied.

For instance, a half-fraction factorial design (24 1=8 experimental runs) might be used for an experiment with four experimental factors, while a quarter-fraction factorial design (25 2=8 experimental runs) might be used for an experiment with five experimental factors. Table 2

The related fractional factorial matrices get more complicated when three, four, or five factors are involved. Complete interpretation of the design becomes more difficult as the number of variables increases since it is harder to assess all individual effects and interactions[6].

2^{3-1} Design Matrix *A				2^{4-1} Design Matrix *B					2^{5-2} Design Matrix *C					
No.	X_1	X_2	X_3	No.	X_1	X_2	X_3	X_4	No.	X_1	X_2	X_3	X_4	X_5
1	−1	−1	+1	1	−1	−1	−1	−1	1	−1	−1	−1	+1	+1
2	−1	+1	−1	2	+1	−1	−1	+1	2	+1	−1	−1	−1	−1
3	+1	−1	−1	3	−1	+1	−1	+1	3	−1	+1	−1	−1	+1
4	+1	+1	+1	4	+1	+1	−1	−1	4	+1	+1	−1	+1	−1
				5	−1	−1	+1	+1	5	−1	−1	+1	+1	−1
				6	+1	−1	+1	−1	6	+1	−1	+1	−1	+1
				7	−1	+1	+1	−1	7	−1	+1	+1	−1	−1
				8	+1	+1	+1	+1	8	+1	+1	+1	+1	+1

*A $X_3 = X_1 \times X_2$; *B $X_4 = X_1 \times X_2 \times X_3$; *C $X_4 = X_1 \times X_2$; $X_5 = X_1 \times X_3$.

Table2: Two-levelfFDmatrixforthree(23 1),four(24 1),andfive(25 2)experimentalfactors.

- Plackett-Burman design (PBD)

Originally presented by R.L. Plackett and J.P. Burman in 1946, the Plackett–Burman Design (PBD) is a two-level screening method built as multiples of four studies.

Because PBD focuses on estimating just main effects and not interactions, it is suitable for swiftly narrowing down essential variables before going to more comprehensive optimization designs. [41]

Although it does not capture interactions between variables, the Plackett–Burman Design (PBD) is very useful for preliminary screening because it enables assessment of the main effects of numerous factors using a small number of experiments. Because of this, it is frequently used to determine the most important factors early on in fields like medicinal plant research. The additional columns serve as dummy variables when the number of elements being assessed beyond the design's structural capacity (N–1). Instead of representing any actual experimental condition, these fake components alternate between –1 and +1 levels to quantify experimental error and increase the screening process's dependability[6].

No.	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}
1	+1	−1	+1	−1	−1	−1	+1	+1	+1	−1	+1
2	+1	+1	−1	+1	−1	−1	−1	+1	+1	+1	−1
3	−1	+1	+1	−1	+1	−1	−1	−1	+1	+1	+1
4	+1	−1	+1	+1	−1	+1	−1	−1	−1	+1	+1
5	+1	+1	−1	+1	+1	−1	+1	−1	−1	−1	+1
6	+1	+1	+1	−1	+1	+1	−1	+1	−1	−1	−1
7	−1	+1	+1	+1	−1	+1	+1	−1	+1	−1	−1
8	−1	−1	+1	+1	+1	−1	+1	+1	−1	+1	−1
9	−1	−1	−1	+1	+1	+1	−1	+1	+1	−1	+1
10	+1	−1	−1	−1	+1	+1	+1	−1	+1	+1	−1
11	−1	+1	−1	−1	−1	+1	+1	+1	−1	+1	+1
12	−1	−1	−1	−1	−1	−1	−1	−1	−1	−1	−1

Table 3: ThematrixofPlackett-Burmandesign(PBD)forelevenexperimentalfactors

Optimization designs:

- Full Factorial Design (FFD)

Within DoE, Full Factorial Design (FFD) can be used for both optimization and screening. When optimization is necessary, the three-level FFD is generally favored because it enables modeling of complex response surfaces by evaluating all combinations of factor levels (−1, 0, and +1). Because this method necessitates testing every potential combination of levels, it becomes particularly helpful when just a limited number of factors—typically two or three—are being researched. However, the number of experimental runs increases dramatically as more components are introduced. The number of factors and their corresponding levels determine the total number of experiments in a three-level FFD.

For instance, a two-factor study arranged at three levels requires nine experimental runs (3^2), while a design involving three factors at three levels expands to twenty-seven runs (3^3)[6].

Table and Figure describe the 3-level FFD matrix for three factors.

In unusual circumstances, FFD can be performed without CP because the factors' characteristics prohibit CP from being set[20].

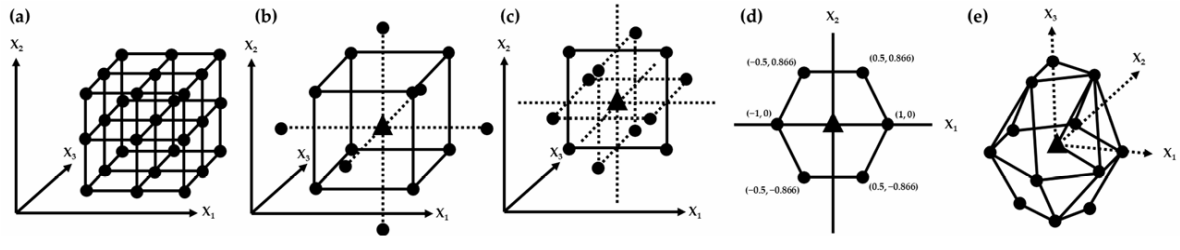

Figure 4: Illustration of 33-Full factorial design (a), Central Composite Design with 3-factors (b), Box-Behnken design with 3-factors (c), and Doehlert design for 2-factors (d) and 3-factors (e).

3^3 – Full Factorial Design				Central Composite Design				Box – Behnken Design			
No.	X_1	X_2	X_3	No.	X_1	X_2	X_3	No.	X_1	X_2	X_3
1	−1	−1	−1	1	−1	−1	−1	1	−1	−1	0
2	−1	−1	0	2	+1	−1	−1	2	+1	−1	0
3	−1	−1	+1	3	−1	+1	−1	3	−1	+1	0
4	−1	0	−1	4	+1	+1	−1	4	+1	+1	0
5	−1	0	0	5	−1	−1	+1	5	−1	0	−1
6	−1	0	+1	6	+1	−1	+1	6	+1	0	−1
7	−1	+1	−1	7	−1	+1	+1	7	−1	0	+1
8	−1	+1	0	8	+1	+1	+1	8	+1	0	+1
9	−1	+1	+1	9	−1.68	0	0	9	0	−1	−1
10	0	−1	−1	10	+1.68	0	0	10	0	+1	−1
11	0	−1	0	11	0	−1.68	0	11	0	−1	+1
12	0	−1	+1	12	0	+1.68	0	12	0	+1	+1
13	0	0	−1	13	0	0	−1.68	13	0	0	0
14	0	0	0	14	0	0	+1.68	14	0	0	0
15	0	0	+1	15	0	0	0	15	0	0	0
16	0	+1	−1	16	0	0	0				
17	0	+1	0	17	0	0	0				
18	0	+1	+1	18	0	0	0				
19	+1	−1	−1	19	0	0	0				
20	+1	−1	0	20	0	0	0				
21	+1	−1	+1								
22	+1	0	−1								
23	+1	0	0								
24	+1	0	+1								
25	+1	+1	−1								
26	+1	+1	0								
27	+1	+1	+1								

Table 4: The matrix of 33-Full Factorial Design (33-FFD), Central Composite Design(CCD),and Box-Behnken Design(BBD)

- Central Composite Design (CCD)

By integrating factorial points, axial points, and center points to represent curvature,it is a well-liked response-surface design, efficiently optimizes key variables within a QbD framework[33].

Equation (1) is used in Central Composite Design (CCD) to calculate the total number of experimental runs (N), where C_0 is the number of center-point replications. The two-level factorial section, the axial or "star" points, and the center points are the three primary parts of CCD. The response surface's curvature may be well modeled thanks to this structure. CCD is frequently used in optimization studies because of its adaptability and effectiveness, particularly in research employing materials originating from plants[21].

$$N=2^{\text{factors}}+2\text{ factors}+C_0.$$

The central composite design (CCD), which employs five stages of any input component and necessitates fewer tests than the three-level complete factorial design, is one of the most widely used optimization designs. The elements of this design are as follows:

a) the factorial design points (black dots);
b) the axial points (grey dots); and
c) the center point (white dots)[2].

- Box-Behnken Design (BBD)

An incomplete three-level factorial structure is used in the Box–Behnken Design (BBD), a second-order response-surface methodology that is intended to be rotatable or nearly rotatable. Equation (2) is used to get the total number of experimental runs (N), where C_0 is the number of replicated center points. For instance, the design calls for fifteen experimental runs when three components are examined and the center point is repeated three times[6].

$$N = \{2\text{ factors (factor 1)}\} + C_0$$

In pharmaceutical optimization, the Box–Behnken Design (BBD), a three-level response-surface tool, is especially useful since it effectively assesses quadratic interactions between variables and requires a lot fewer experimental runs than a full factorial design. Because of this, it is a useful and economical tool for creating and improving formulation and analytical procedures[38].

- Doehlert Design

Efficient and balanced exploration of multidimensional factor spaces is made possible by the Doehlert design, which produces an evenly spaced experimental arrangement where each point is positioned at an equal distance from the others. Compared to many conventional response-surface designs, this structure allows for a thorough

assessment of variable effects with fewer experimental runs[39].

In a Doehlert design, the experimental points are arranged so that each point is uniformly spaced from the others across the experimental region. The total number of runs (N) is determined using Equation (3), where *k* represents the number of replicated center points. For example, a two-factor Doehlert design consists of seven points—six located at the vertices of a hexagon and one at the center—while a three-factor design comprises thirteen points arranged in a dodecahedral configuration with a central point[6].

$$N=factors^2+factors+k$$

For Two Experimental Factors			For Three Experimental Factors			
No.	**X_1**	**X_2**	**No.**	**X_1**	**X_2**	**X_3**
1	0	0	1	1	0	0
2	1	0	2	0.5	0.866	0
3	0.5	0.866	3	0.5	0.289	0.816
4	−1	0	4	−1	0	0
5	−0.5	−0.866	5	−0.5	−0.866	0
6	−0.5	−0.866	6	−0.5	−0.289	−0.816
7	−0.5	0.866	7	0.5	−0.866	0
			8	0.5	−0.289	−0.816
			9	0	0.577	−0.816
			10	−0.5	0.866	0
			11	−0.5	0.289	0.816
			12	0	−0.577	0.816
			13	0	0	0

Table 5: The matrix of Doehlert design with two and three factors.

5. METHOD OPERABLE DESIGN REGION (MODR)

The operable design region, also known as the analytical design space, is the nonlinear composition and relationship of analytical circumstances (input elements, including chromatographic settings) which must be demonstrated to ensure the performance of the analytical technique.Two The MODR, or design space, is the set of method parameter ranges (at least, but not necessarily, all essential parameters) that have been evaluated and verified to meet both the ATP criteria and the specific method performance criteria. A particular approach is always intimately linked to the MODR. While multiple applications may employ a common approach, the MODR is made to meet ATP specifications. The project criteria make it difficult to transfer the MODRs of shared methods, and as a result,the ATP criteria are different[5].

The MODR may be more helpful for enhancing the data package enabling traditional modifications or for facilitating the use of more limited ongoing verification data by comparing real-world data with prediction models[16].

The statistical results from the DoE study are used to create a multidimensional design space. As long as it produces satisfactory and reliable analytical performance, any method modification made within this MODR can still satisfy the ATP requirements. The design space's center point method is typically completed and validated; also, revisions made within the pre-existing design space are not regarded as alterations, and revalidation of those changes is not necessary[8].

The multidimensional space where analytical technique parameters can change while still reliably satisfying the predetermined Analytical Target Profile (ATP) is known as the technique Operable Design Region (MODR). Understanding how the Critical Analytical Procedure Parameters (CAPPs) and Critical Analytical Procedure Attributes (CAPAs) interact to ensure that the analytical method maintains dependable performance within acceptable bounds defines this region[22].

6. Control Strategy:

To continuously maintain product quality and guarantee a state of control throughout manufacturing, the control strategy in a QbD

framework combines material characteristics, process parameters, and monitoring plans[32].

Product AQbD's control strategy is designed to guarantee that the analytical technique continuously satisfies or surpasses the ATP's requirements. Statistical results from DoE, data from the MODR, robustness evaluations, forced degradation tests, stability assessments, compatibility studies, and verification results are among the insights acquired throughout method development that have shaped this approach. When taken as a whole, these datasets aid in determining if the technique can consistently produce the desired results. Often, the control strategy only involves emphasizing important factors like the proper grade of reagents, the method's sensitivity to pH changes, or the necessary organic solvent ratio in the mobile phase, rather than requiring significant departures from standard laboratory procedures[8].

Automated systems are used in level 1 control to continuously monitor CQAs and make real-time adjustments to process settings to keep them within acceptable bounds. Compared to traditional end-product testing, this level offers the greatest flexibility and can even allow real-time release testing through predictive models, offering a higher assurance of product quality.

Level 2 control involves fewer end-product tests and functions within the defined design space. Controls can be moved upstream by applying QbD principles to identify sources of variability, which lessens reliance on final testing and enhances overall process comprehension and consistency.

The conventional method is represented by level 3 control, which entails stringent requirements for raw materials and process parameters as well as rigorous end-product testing. Any deviations require regulatory scrutiny because the sources of variability and how they affect CQAs are not completely understood. This increases the burden and resource requirements for both industry and regulators[9].

In order to ensure smooth coordination between pharmaceutical development, manufacturing operations, and the engineering controls applied to processing equipment, developing an efficient control plan necessitates an organized approach including a multidisciplinary team[12].

A control strategy can be improved and modified at several points during the lifecycle of the analytical technique; it is not a static, one-time task restricted to method creation[24].

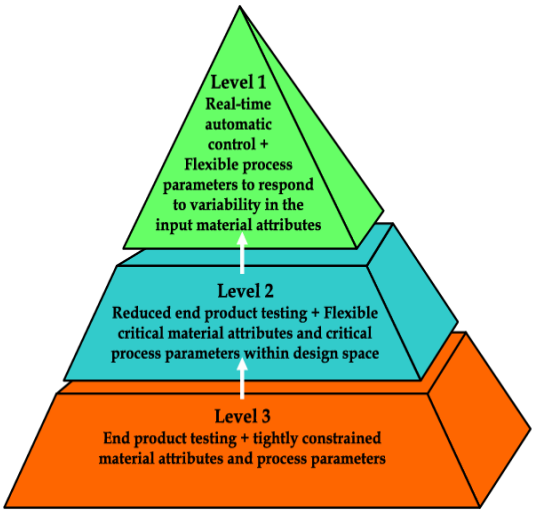

Fig 5: Control strategy implementation options

7. Process Capability and Continual Improvement

Process capability is a crucial indicator for robustness and control in a QbD-driven pharmaceutical quality system. It measures how well a controlled manufacturing process consistently generates output within predetermined standards[29].

When there are no systematic trends or patterns and all observable variability in the data is simply random and intrinsic to the process, the process is said to be in statistical control[25].

Continuous improvement refers to a series of actions undertaken to enhance the capability of a process or system to consistently meet predefined requirements. It is generally carried out through five key phases that structure and guide the improvement effort:

• Clearly state the issue and specify the project's goals.

• Measure the important components of the current procedure and collect all pertinent information required for assessment. Examine this data to find and confirm any possible cause-and-effect connections that might affect how the method is carried out.

Examine how the variables relate to one another and make sure that all pertinent elements have been fully taken into account. Additional study should be carried out to uncover any underlying concerns that may be contributing to the condition[9].

Index	Description
$C_p = \frac{(USL-LSL)}{6\widehat{\sigma}}$	Estimates process capability when the data mean is centered between upper and lower specification limits.
$C_{pkl} = \frac{(Mean-LSL)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of a lower limit only.
$C_{pku} = \frac{(USL-Mean)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of an upper limit only.

Table. Process Capability Indices and Their Measures

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