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Pharmaceutical Quality by Design: An Overview

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Surya S*, Dr. Devi Damayanthi R, Dr. Daisy Chella Kumari S Valarmathy S, Amarnath S, Vaishnavi Durga G.K, Sri Vidhya P

Department Of Pharmaceutics, College of Pharmacy, Madras Medical College, India

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ABSTRACT

Regulatory agencies and the pharmaceutical sector are now focusing on applying quality by design (QbD) to the creation of pharmaceutical products. In their industry guidelines, the United States Food and Drug Administration (USFDA) and the International Conference on Harmonization (ICH) placed a strong emphasis on the concepts and uses of quality by design (QbD) in pharmaceutical development. The USFDA established a question-based review system for the chemical, manufacturing, and controls component of abbreviated new drug applications that address QbD qualities. When applied, QbD principles result in a successful product development process, swift regulatory approval, a reduction in the burden of laborious validation, and a considerable decrease in post-approval modifications. To comprehend the performance of dosage forms within design space, the essential components of QbD-Quality Target Product Profile (QTTP), critical quality attributes (CQA), critical material attributes (CMAs), critical process parameters (CPPs), risk assessments, design space, control strategy, product lifecycle management, and continual improvement—are discussed. The role of process analytical technology, risk assessment tools, and experiment design in QbD are also covered. This paper highlights the importance of QbD in promoting a science-based approach to pharmaceutical product development.

INTRODUCTION

The idea of quality by design, or QbD, was initially created by Dr. Joseph M. Juran, a pioneer in the field of quality. According to Dr. Juran, a product's design should incorporate quality, and the majority of quality-related issues and crises stem from the original design of the product.[1] According to Woodcock, a high-quality drug product is free of contaminants and consistently provides the customer with the therapeutic benefit that is stated on the label.[2]

The US Food and Drug Administration (FDA) promotes the use of QbD concepts and risk-based methodologies in the development, production, and regulation of pharmaceutical products. The FDA started putting more of an emphasis on QbD after realizing that more testing does not always translate into better products. The product needs to be engineered for quality. [3]

With the release of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System), QbD in the pharmaceutical industry has changed throughout time. [4,5]

The concept of QbD was mentioned in the ICH Q8 guidance, which states that "quality cannot be tested into products, i.e., quality should be built in by design". International conference on Harmonisation (ICH) Q8 (R1) guideline defines QbD 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". [6]

Figure. 1 Overview of Quality by design [1]

PRINCIPLE

QbD entails incorporating quality principles into the finished products, starting with industrial planning and ending with the supply of qualitative features to patients to guarantee total satisfaction with safety and efficacy. Since each quality by-product has predetermined goals that directly support its acceptance and success, the entire QbD process is built around a risk-based, holistic approach to improve overall quality features as best as possible while making the best use of various scientific tools.[7]

A prerequisite for guaranteeing the safety, effectiveness, and quality of products is the provision of sufficient proof and assurance regarding process alignment with QbD principles. Negligence in the monitoring and management of industrial processes using conventional methods not only negatively affects the commercial prospects of manufactured items but also attracts criminal penalties owing to the high likelihood of serious patient repercussions. A paradigm shift toward the adoption of QbD-based planning for delivery system design is required by the regulatory documents of product requirements and performances as mentioned in ICH guidance Q8 (R2) Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality Systems.[8]

Regulatory aspects [9,10]

To assist the industry in implementing quality by design (QbD) under Section 3.2.P.2 (Pharmaceutical Development) for drug products as described in the scope of Module 3 of the Common Technical Document (ICH guideline M4), ICH produced a guideline Q8 R (2) (Step 4) in August 2009. QbD (ICH Q8(R2)) is 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.” This is a more methodical approach to development that incorporates, among other things, knowledge management (ICH Q10), quality risk management (ICH Q9), results of research employing the design of experiments, and prior knowledge throughout the product's lifecycle.

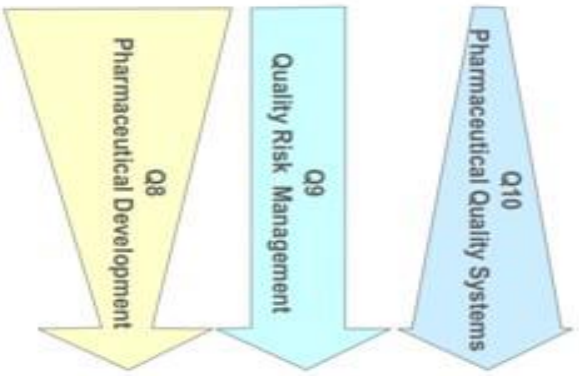

Figure. 2 Regulatory Aspects: ICH Q8, Q9, Q10 guidelines [9]

Objectives of Pharmaceutical Quality by Design (QbD) [11]

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and process understanding and process control, based on sound science and quality risk management. [6]

- To attain significant product quality standards that are grounded in clinical operations.
- To improve product and process design, understanding, and control to decrease product variability and flaws and increase process capabilities.
- To improve manufacturing and product development efficiency in the pharmaceutical industry.
- To improve change management after approval and root cause analysis.

Advantages of QbD [12]

- It offers a better degree of medication product quality assurance.
- It provides the pharmaceutical sector with efficiency and cost savings.
- It makes the sponsor more transparent and helps them comprehend the control approach needed to have the drug product approved and eventually go on sale.
- It creates rationality, predictability, and transparency in the scaling-up, validation, and commercialization processes.

- It encourages creativity in response to unmet medical requirements.
- It lowers production expenses and product rejections while improving the effectiveness of pharmaceutical manufacturing processes.
- It reduces or gets rid of expensive fines, medication recalls, and possible compliance actions.
- It increases the effectiveness of regulatory supervision.
- It simplifies regulatory procedures and production modifications after clearance.
- It concentrated more on CGMP inspections after approval.
- It lowers the CMC supplement and promotes ongoing improvement.

Table 1: Difference between the current approach and QbD approach [13]

S.No	Current approach	QbD approach
1	Inspection and testing ensure quality.	Quality is built into processes and products through design and is grounded in scientific knowledge.
2	Only submissions with a lot of data, such as fragmented material without a "big picture," are included.	It contains a knowledge-rich contribution that demonstrates comprehension of the process and product understanding.
3	Here, any specifications are derived from batch history.	Here, any specifications derived from product performance requirements.
4	This is a "frozen process," which consistently discourages modification.	This design space has a flexible process that enables continuous improvement.
5	The focus it places on reproducibility frequently prevents or minimizes variation.	It focuses on robustness, which recognizes and manages variation.

Key elements of Quality by Design

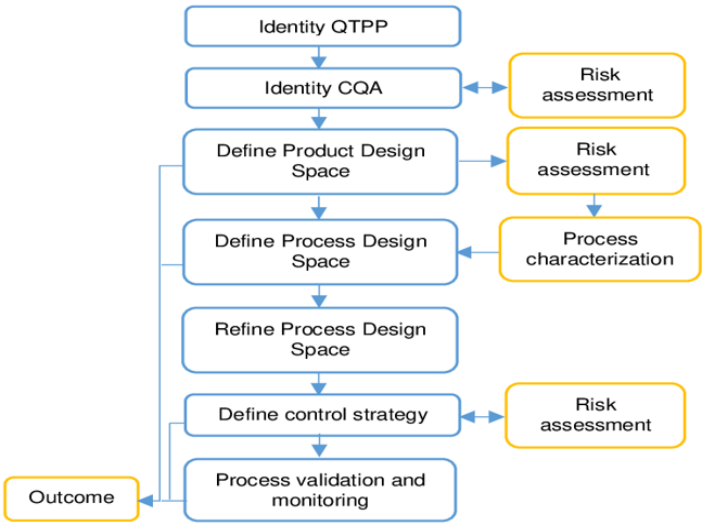

Figure. 3 Elements of quality by design [13]

Quality Target Product Profile [14]

The QTPP is the predetermined prospective summary of drug product characteristics essential to ensure desired quality concerning safety and efficacy and also helps in recognizing the CQAs of the product.

The QTPP for the development of nanocarriers includes the following: drug release behavior; pharmacokinetic characteristics; shelf life; quality criteria (purity and sterility); and container closure system. Dosage form (lyophilized powder or dispersion in the case of oral, injectable, gel or ointment in the case of topical preparation); dosage strength (as nanocarrier-based formulations have improved bioavailability, controlled release of drug).

Critical Quality Attributes [15,16]

CQAs are used to direct the development of processes and products and are developed from the QTPP. To guarantee the intended quality of the product, CQAs also determine the range or limit for acceptable quality products. The physical, chemical, biological, and microbiological qualities (CQAs) of a drug product are defined by ICH Q8 R2 as those that must fall within a given range to guarantee the intended level of product quality.

Critical Material Attributes [17]

The initial group of variables that can lead to CQA variability is called critical material attributes. CMAs, and they have to do with the preparation of the nanocarrier's composition. To guarantee the intended quality of the final product, the CMAs, which include the physicochemical, biopharmaceutical, or microbiological properties of the input materials, should be within an acceptable standard limit.

Surfactant concentration, type, volume, organic solvent concentration (in solvent evaporation technique), polymer/lipid concentration, and type and concentration of salts used, if any, for buffer preparation or to impart a charge on particles are some of the CMAs in nanocarriers.

Critical Process Parameters [17]

The second group of potential variables that could affect CQA variability is called critical process parameters (CPPs). And they have to do with how the nanoformulations are made. CPPs that contain the input variables that need to be kept within the designated ranges or limits in order to guarantee the product's high quality. A CQA and QTPP are impacted by input process factors. The sequence of phase addition, temperature, and batch volume are among the CPPs for nanocarriers, along with homogenization speed, homogenization time, sonication speed/amplitude, stirring time and speed, and others.

Quality Risk Assessment [18,19]

Determining the CPP of the drug product and assessing the influence of a single variable or critical features of excipients, packaging materials, active pharmaceutical ingredients (APIs), and raw materials are the primary goals of risk assessment. Each attribute is categorized into high, medium, and low-risk categories based on how it affects the product. To lower the likelihood of risk, high-risk qualities are further studied.

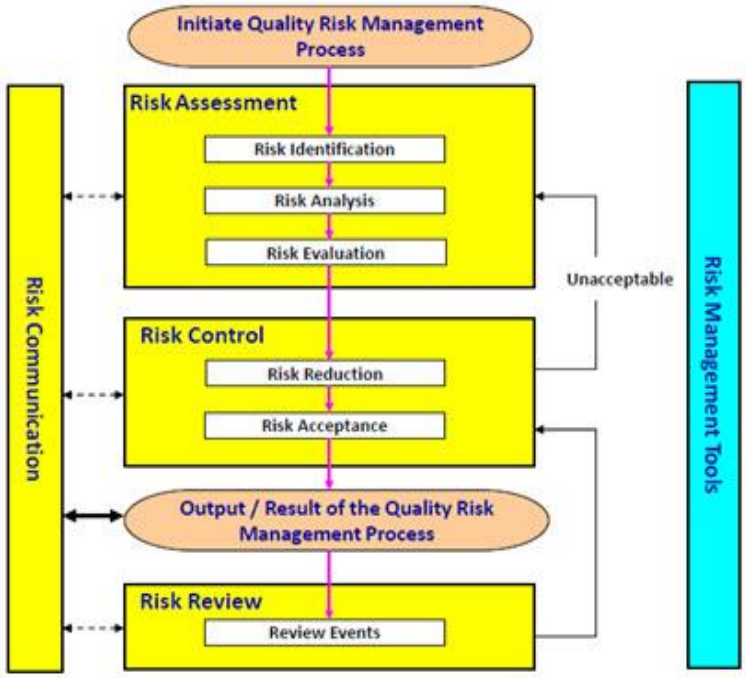

Figure 4. Quality Risk Management

ICH Q9 has summarized a non-exhaustive list of common risk management tools as follows:

(1) Basic risk management facilitation methods (Ishikawa fishbone diagram, flowcharts, check sheets, etc.)

(2) Fault tree analysis

(3) Risk ranking and filtering

(4) Preliminary hazard analysis

(5) Hazard analysis and critical control points

(6) Failure mode and effects analysis (FMEA)

(7) Failure mode, effects, and criticality analysis (FMECA)

(8) Hazard operability analysis

(9) Supporting statistical tools.

Basic risk management facilitation methods

Flow charts, check sheets, process mapping, cause and effect diagrams, etc., are the most commonly used simple methods for RA and management.[20]

Process mapping is a method that connects crucial material properties, vital procedure parameters, and/or critical product quality to a response surface generated from experimental data. For example, the development of product specifications to ensure bioequivalence within the limits of acceptable dissolution specifications.[21]

A cause-and-effect diagram, also known as an Ishikawa diagram or a fishbone diagram, shows every factor that could affect a crucial product quality. A horizontal line with its end pointing in the direction of the impacted product quality will be seen in the diagram. Then, diagonal lines are used to represent the main impacting elements. Sublines for the diagonal lines then show the influence of the critical material attributes and critical process parameters. [20, 23] A simple Ishikawa diagram is shown in Figure 5.

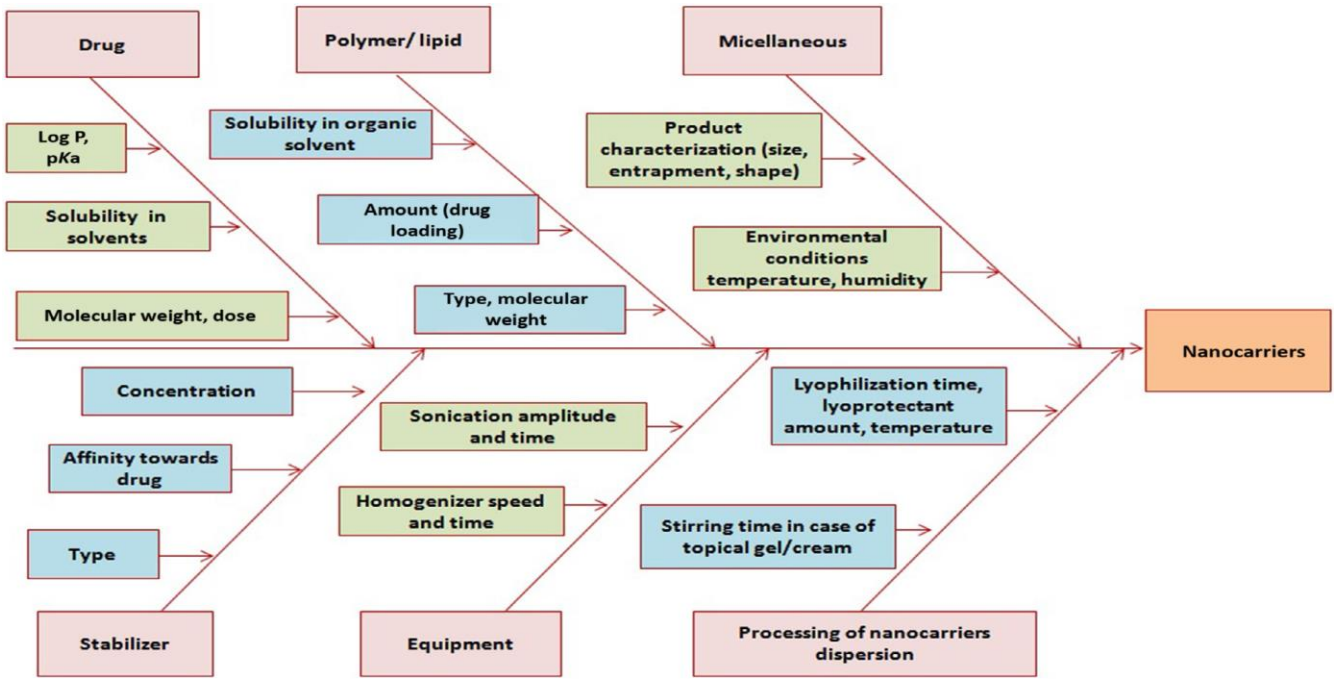

Figure 5 Potential formulation and process parameters that influence the CQAs of Nano formulation

Fault tree analysis

Fault tree analysis (FTA) is a structured, graphical, quantitative assessment tool that makes modeling of complex systems easy. FTA is a great method for assessing various aspects that influence the quality of a product. It is beneficial for both monitoring and RA. Here, the method is regarded as the logic tree's root. There will only be one top event (root). A sequence of logic statements for each critical process parameter or critical material characteristic is added to the tree. Fault trees can be used to compute failure probabilities using software. FTA primarily depends on the experts' comprehension of the procedure used to determine the causal factor.[20]

Risk ranking and filtering

It is used for comparing and ranking risks. Numerous different quantitative and qualitative parameters are assessed for each risk. Here, a fundamental risk question is dissected into its constituent parts to pinpoint the causes of that risk. These variables yield a single relative risk score, and the hazards are ordered. Filtering is done using weighting variables or risk score cut-offs. This is helpful for regulators or businesses to prioritize production facilities for inspection or audit. Risk ranking can be used to evaluate risks that have been analyzed both quantitively and qualitatively.[20]

Preliminary hazard analysis

When there is limited knowledge available about operating methods or design details, this can be employed in the early stages of product development.[20] Using additional RA tools, hazards found in the preliminary hazard analysis (PHA) are often evaluated in further detail.

PHA consists of:

1. Identification of the possibility of a risk event.

2. A qualitative assessment of the potential risk's magnitude.

3. The danger's relative ranking.

4. Determining potential solutions.

Hazard analysis and critical control points

Rather than relying just on finished product inspection, Hazard Analysis and Critical Control Points (HACCP) is a methodical, proactive approach to ensuring product quality, reliability, and safety. Physical, chemical, and biological dangers (including microbial contamination) can be identified and managed using HACCP. It is an organized strategy against the risk resulting from design, development, and production, and it is founded on technical and scientific principles.

HACCP is based on the following seven principles or steps:

1. Carrying out a risk assessment.
2. Determining critical control points.
3. Determining each important control point's critical limits.
4. Determining the need for monitoring crucial control points.
5. Establishing corrective actions.
6. Creating protocols for maintaining records.
7. Creating protocols to guarantee the HACCP system is operating efficiently.

When knowledge of the product and process is sufficiently deep, HACCP works best. Monitoring of crucial stages in the manufacturing process and other stages of the product life cycle is made easier by the results of an HACCP analysis. [20, 24]

Failure mode effects analysis

You can use this tool to find any shortcomings in the product's development. The process detects, ranks, and methodically evaluates risks in order to avert failure. Failure mode effects analysis (FMEA) can also be used to reduce the risk associated with process changes. Understanding the product and process is essential for FMEA. Once failure modes have been identified, the risk reduction can be used to manage possible failures. [20, 23]

Failure mode, effects, and criticality analysis (FMECA)

This evaluation of FMEA takes into account the consequences' level of severity, likelihood of occurrence, and detectability. Thus, the frequency of failure modes is plotted against the seriousness of their repercussions in this instance using criticality analysis. The most common use of failure mode, effects, and criticality analysis is for risks and failures related to industrial processes.[20]

Hazard operability analysis

Hazard operability analysis (HAZOP) is a widely used method of hazard analysis in the process industries. It evaluates the risks brought on by alterations to the design or the intended operation. It finds possible deviations by applying "guide words" (such as no, more, other than, part of, etc.) to pertinent metrics. HAZOP can be used in the pharmaceutical product manufacturing process.[20]

Supporting statistical tools

These are utilized for efficient data evaluation, figuring out the data's importance, and making decisions. Control charts (weighted moving average, cumulative sum, Shewhart, arithmetic average, warning limits, acceptance control charts, etc.), histograms, Pareto charts [23] (a pictorial representation used to separate significant factors among many, thereby identifying the factors of most concern affecting the desired product quality), process capability analysis, and other tools are included. A Pareto chart displaying the standardized effects for factors may be found in Figure 6. The effects or components that cross the dotted line are regarded as important and as having a major impact on the response; these may even be several components of a single factor, such as its linear, quadratic, or combination effects with other factors. In figure 6 effects, A, B, and C are significant, whereas C and D are not.

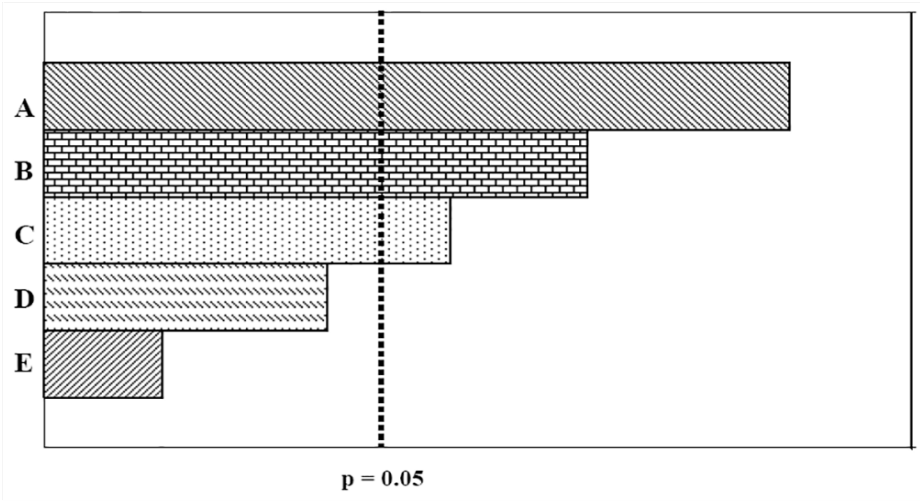

Figure 6 Pareto chart A, B, C, D, and E represent different factors or effects of factors that are evaluated for a particular response

Design of Experiments [24,25]

Fisher introduced DOE to the agricultural industry, and ever since, it has permeated almost every sector of the economy, particularly the pharmaceutical industry. Since the production of pharmaceuticals is an expensive endeavor, the industry can save a significant amount of money by applying experimentation with caution and rationality. Mathematical models based on computer-aided process design and simulation make up DOE. The DOEs that are most frequently used in the creation of pharmaceutical products are full factorial, fractional factorial, Plackett-Burman, Box-Behnken, central composite, Taguchi, mixture design, and surface design.

Formulations have always involved interactions between different ingredients and processes, making them difficult and complex procedures, especially when using novel technologies. When building an optimal formulation that can produce a cost-effective product quickly and with the fewest number of experiments, DOE is crucial.

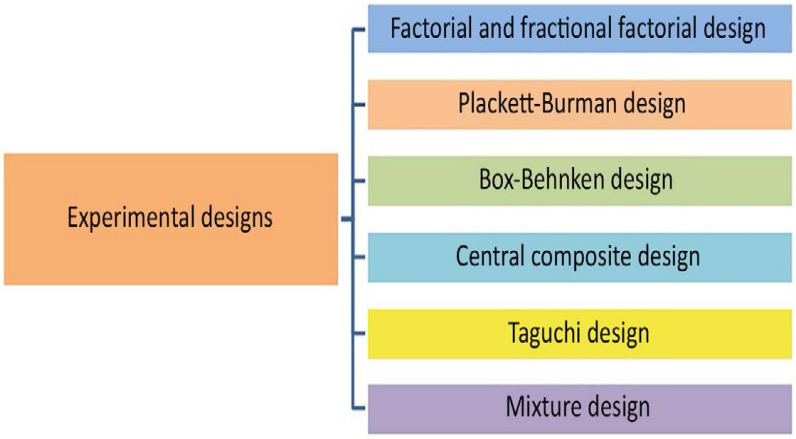

Figure. 7 Experimental designs

Factorial Design

The levels of components are changed independently at two or more levels in a factorial design. The components' effects can be identified, and it is possible to evaluate their interactions effectively. The 2K complete factorial designs, which assess k factors at two levels, typically "low" and "high," are the most basic of these designs. As a result, for a two-factor, the two-level factorial design will comprise four experiments; for factors three, four, five, and six, the number of experiments increases to eight, sixteen, thirty-two, and sixty-four. The symbols for the levels of the factors are (+) plus for a higher level and (-) minus for a lower level. Sometimes a zero level is added to show the midway or center of the variable values. A study design of two factors, the two-level design will include:

Study 1: Both factors at their lower levels (notation ‘1’).

Study 2: First factor at a higher level and second factor at a lower level (notation ‘a’).

Study 3: First factor at a lower level and second factor at a higher level (notation ‘b’).

Study 4: Both factors at their higher level (notation ‘ab’).

All four experiments are carried out simultaneously, the responses are measured and the results are analyzed. Apart from the aforementioned, the primary motives for determining the center points are to reduce the possibility of overlooking nonlinear correlations and to create a confidence interval through multiple experiment runs.[27] The major impacts of each variable and all potential interaction effects between two variables as well as between all the

elements in a study model are included in the mathematical model related to the design. Tables 1 and 2 provide examples of factorial designs with two and three variables. [28, 29]

Table 2 factorial design with two variables

		variables	
Experiment number	X1		X2
1	-		-
2	+		-
3	-		+
4	+		+

Table 3 Factorial design with three variables

		variables	
Experiment number	X1	X2	X3
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+
9	0	0	0

The equation has been inserted as experiment 9 in the design with three variables, but an additional experiment can be added to evaluate the probability of nonlinearity. If there is a discernible discrepancy between the centre point's reaction and the mean value, b0, then quadratic terms must be included in the model and more trials must be conducted.

The experiments are evaluated to fit a polynomial model for two-level, the two-factor model is $y = b0+b1x1+b2x2+b3x3$.

The main effects of x1 can be calculated as the difference between the average response when x1 is at a high level and the average response when x1 is at a lower level. Interaction or lack of additivity of factor effects can be synergistic or antagonistic. It is the difference between the effects of x1 at two levels of x2. If the effects of x1 are the same in the presence of low and high levels of x2, then it is additive or there is no interaction. [30,31]

In the case of a two-level, three-factor, the model consists of b0, which is the mean, a constant, three main variables b1x1, b2x2, b3x3 and four interactions (b12x1x2, b13x1x3, b23x2x3, b123x1x2x3). The model is represented by the equation:

$$y = b0 + b1x1 + b2x2 + b3x3 + b12x1x2 + b13x1x3 + b23x2x3 + b123x1x2x3$$

Since the center point is not utilized in the impact's computation, it is eliminated. Multi-linear regression can also be used to estimate the model's coefficients b1. The next stage is to determine which of the seven computed effects is significant. If the effects are replicated, analysis of variance (ANOVA) can be used. One popular technique is to create a normal probability plot of the effect values' distribution. Upon identification of the significant impacts, the minor effects can be eliminated to create a simplified model. Even though they are not significant, the corresponding main effects should be included in the equation if an interaction has been found.[32]

Given the time and costs involved in conducting the trials, a factorial design with a high number of factors or different levels of factors will require an enormous number of experiments, making it impractical. A fractional factorial design, which allows for the execution of a portion of the initial number of tests, can be used in these circumstances. In screening designs where a lot of variables are involved, these designs are especially crucial. We identify and look into the aspects that have greater effects.[33]

Plackett-Burman Designs

The mathematicians R.P. Placket and J.P. Burman created the fractional factorial designs that comprise the Plackett-Burman designs in 1946 while they were employed at the British Ministry of Supply. When full system knowledge is not available, these designs are utilized to determine the most crucial formulation or process parameters early in the testing process. When it is anticipated that there would be little two-way interactions, these designs should be utilized to investigate the principal consequences. Plackett-Burman designs are useful for

screening factors because they provide a low number of experiments needed to explore a wide range of factors. The commonality among them is that 4n experiments (n = 1, 2, 3…, n) are involved. Only seven factors can be examined in an eight-experiment Placket-Burman design since the maximum number of elements that may be evaluated is 4n_1. [34, 35]

Central Composite Design

It is used in response surface design and optimization and is a development of factorial design. It is also referred to as the Box-Wilson central composite design. As part of the design, it comprises trials at the center, experiments at the axes (axial points), and factorial or fractional factorial design.[36]

If the distance between the fractional point and the center point in the central composite design is equal to 1. Then, for each axial point, the distance from the central point will be more than or equal to one; if the value is less than or equal to one, the axial point is inside the cube. Extremely high and low values are dealt with in central composite design. Orthogonally blocked designs are used in conjunction with independent block effect estimation to minimize variances in regression results. The number of orthogonal blocks is determined by the number of factors, number of experiments, and selected proportion.[37]

The desired feature of constant prediction variance is made possible by rotatable designs, which enhance prediction quality at all places equally spaced from the design center.[38] They are be particularly handy for consecutive experiments. Axial and center points can be added to prior factorial trials to change them. Three categories primarily distinguish central composite designs:

- Central composite circumscribed (CCC),
- Central composite inscribed (CCI), and
- Central composite face-centered (CCF).

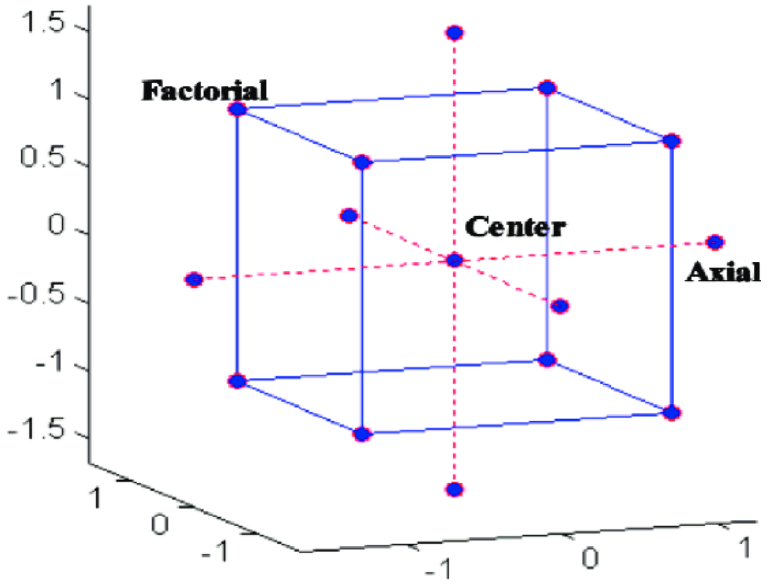

Figure 8 Central Composite Design

If a central composite design is chosen, it is important to confirm that the factor values can be understood at the axial points in a cubical or traditional square design even if they are out of range. While some factors have a minimum and maximum value, few factors can have a value of zero. Prior to experimenting, careful consideration must be given to the location of the center and the size of the experimental unit, including the factorial points, which must fall inside the bounds of each variable. [39,40, 41]

Box-Behnken Design

The BBD is a class of rotatable or nearly rotatable designs that was created in 1960 by George E. P. Box and Donald Behnken. Each factor has a maximum of three levels, and the domain is contained inside the initial factorial shape. As seen in Fig. 9, the design is represented as a cube, but instead of being at the corners and centers of the faces, or $\sqrt{2}$, or 1.414 e.u. from the center, the experimental points are at the midway of the process space's edges. The coding method is applied to factors, which are then expressed in experimental units, or e.u. A comparable process that puts all the variables in the same range is coding. For instance, in a two-level experiment, the range for a factor is 2 e.u. since the lower level is denoted as -1 and the upper level as +1. By using this, the central point (0,0) in the design can be allocated and interpolated. Therefore, one e.u. will be the focal focus. [40]

N=2k (k-1) +C0 defines the number of experiments required for the BBD as an optimization technique, where

N is the number of experiments,

C0 is number of central points,

k represents the number of factors.

Table 3 provides the values of the experimental points for the BBD. With the third element having a value of 0, every combination of extreme values for the first two factors is investigated. The BBD does not cover the entire cube, in contrast to a traditional three-component design, because the cube's corners are not assessed. The domain of a three-factor design is 8 e.u.3, whereas the domain volume of a central composite design is 20 e.u.3. In contrast, the domain of a BBD design is just 6 e.u.3. The BBD was shown to be even more efficient than the three-level full-factorial design and somewhat more efficient with central composite when compared to other response surface designs. The efficiency of these models is calculated by dividing a number of coefficients in the estimated model with number of experiments. [41,42,43]

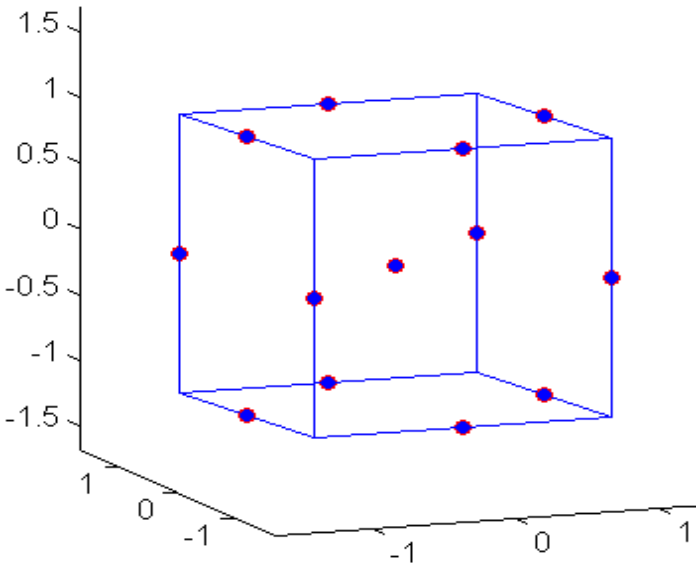

Figure 9 Box Behnken Design

Table 4 BBD for three factor experiment

	Factor X1	Factor X2	Factor X3
Center point	0	0	0
	_1	_1	0
	+1	_1	0
	_1	+1	0
	+1	+1	0
	_1	0	_1
	+1	0	_1
	_1	0	+1
	+1	0	+1
	0	_1	_1
	0	+1	_1
	0	_1	+1
	0	+1	+1

Mixture Designs

Mixture designs are one of the response surface experiments where component of mixture are the factors and the function of each ingredient is considered as a response. All elements added together result in a constant total of 100% or 1. A limitation on the mixed experiments that denotes the independence of all components is represented by the constant total. The formulation factors, or mixture factors, whose proportions need to be changed in the experiments and which affect the formulation.[35]

Taguchi Design

These experimental designs, proposed forth by Japanese engineer Genichi Taguchi, use a variety of statistical methodologies to guarantee a process's dependability and enhance product quality.[44] Fractional factorial designs at the two, three, and mixed levels are used. The underlying premise of these systems is that not every variable can be managed. Noise

factors are variables that are not subject to control (uncontrollable). Finding controllable parameters or control factors that reduce the impact of noisy elements is made easier with the use of Taguchi designs.[45]

During experimentation, noise factors are varied forcing variability to occur. The best control factor settings are chosen based on this, producing a reliable process or product. Taguchi's design is highly helpful in making experiments cost-effective and completed in the least amount of time. Taguchi focuses largely on the main effects when estimating the factors influencing response mean and variation. It makes use of an orthogonal array to balance equally weighted factor levels. Because orthogonal arrays ensure that the estimation of one element is unaffected by another, every factor in this architecture is evaluated separately from every other factor.[46]

Design Space

ICH Q8 (R1) defines design space as, the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to assure quality. This definition evolved from early ICH Q8 drafts where design space was defined as “the established range of process parameters that has been demonstrated to provide assurance of quality”. The schematic representation of the design space is shown in figure 10.

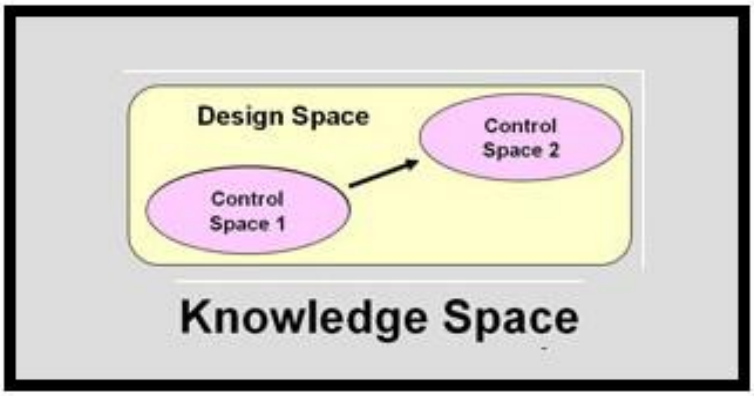

Figure. 10 Schematic representation of Design Space

Design space is proposed by the applicant and is subject to regulatory assessment and approval. Because design space is potentially scale and equipment-dependent, the design space determined at the laboratory scale may not be relevant to the process at the commercial

scale. Therefore, design space verification at the commercial scale becomes essential unless it is demonstrated that the design space is scale-independent. [47]

Steps for the Design Space [48]

- Identify the unclassified parameters.
- Using an experiment design where certain unclassified parameters are applied while the other unclassified parameters are fixed.
- Finally, there is a regulatory situation with some space for the selected parameters but no flexibility for other parameters.

Implications of Design Space [49]

- Increased process and product understanding.
- Increased assurance to regulators i.e., regulatory flexibility.

In some cases, boundaries will be identified that are known to be an edge of failure. In these situations, it may be important to set boundaries at acceptable tolerance intervals around.

Control Strategy [50]

Control strategy is intended to guarantee that a product of the necessary quality will be produced consistently, according to ICH Q11. Among the possible control strategies are:

- Control of the characteristics of input materials that affect processability or product quality, such as raw materials, packaging materials, and in-process materials.
- Complete product specification.
- Controls for unit operations (e.g., the effect of size-reducing technology, particle size on medication release) that affect downstream processing or product quality.
- Instead of testing the final product, use in-process or real-time release testing (e.g., measurement and control of CQAs throughout processing example: temperature).

Product lifecycle management and continual improvement

A product's quality must be maintained throughout its life cycle through effort. To accomplish this goal, the pharmaceutical quality system consists of four distinct components. Product development can benefit from the findings of exploratory and clinical development research. The foundation for ongoing process and product improvement is formed by the information acquired through technology transfer efforts, which offer helpful inputs for manufacturing processes, control strategies, and process validation. The pharmaceutical quality system ought to recognize and assess areas for improvement during commercial manufacturing. It is also important to apply the information gained from commercial manufacturing to ongoing product development. If a product is discontinued, ongoing evaluation of the product is necessary to handle complaints and ensure stability. Regulations demand that samples of discontinued items and associated documentation be kept on file. It is always important to assess opportunities for creative methods to raise the quality of a product based on where it is in its life cycle.[51]

A process performance and product quality monitoring system are used to identify possible areas for continuous improvement and to obtain products of the desired quality. This system's prompt feed-forward or feedback should support corrective and preventive measures (CAPAs). Statistical and data management tools are invaluable for implementing the control plan. The CAPA system identifies and prevents product or process variability by taking corrective action. Overall, this system should lead to improvements in both the product and the process over the course of a product's life cycle, and CAPA should be maintained even in the event of a product discontinuation.[52]

Process Analytical Technique (PAT)

The FDA has taken the initiative to involve process analytical technique (PAT) in formulation process it believes “quality cannot be tested into products but it should be built in or should be designed.” PAT uses engineering and scientific ideas to design, analyze, and control production processes. PAT is used to identify process variables that have an impact on the quality of the final product. Online monitoring of some CQAs is required to increase process control and robustness. Near-infrared, infrared, Raman, focused beam reflectance measurement, and turbidity probes are a few of the common PAT instruments. Multivariate

data acquisition and processing techniques are required for the analysis of multidimensional spectral data produced by PAT. [53]

PAT Tools as Per the FDA Guidelines [54]

Multivariate tools for design, data acquisition, and analysis:

➢ Identification and evaluation of product and process variables which are CQAs and performance.

➢ Identification of failure modes and mechanisms on product quality along with quantifying the failure modes.

Advantages of PAT [53]

❖ Improving process safety by detecting unstable intermediates during the process.

❖ The robustness and quality of the product can be enhanced.

❖ Prevent batches from being rejected.

❖ Minimize expenses by drastically cutting back on collection and analysis.

❖ Increase automation of the process for better control during the process.

CONCLUSION

Quality by design is a novel approach to pharmaceutical quality and a crucial component of the contemporary, dependable idea. The establishment of QTPP, which lays out the quantitative target for QbD, the identification, and establishment of a mechanistic link between critical material attributes and critical process parameters, and the choice of a control strategy for the incremental implementation of QbD elements in corresponding processes within design space are some of the ways that this session intensifies the benefits of QbD. Additionally, the study explains how to apply QbD to establish raw material specifications, create risk-reduction plans, and minimize quality control testing. The principles of quality-by-design (QbD) aid in the creation of high-quality goods and their evaluation at every stage of their lifespan, which eventually leads to increased patient compliance.

This contemporary paradigm may represent important advantages that result in the creation of high-quality pharmaceutical products that are continuously improved over the course of their lives. Building quality into the product and production process, together with continual process improvement and variability reduction, are the main points of QbD's conclusion.

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