A Review on Quality by Design (QbD)

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Abstract: In this Review, we have done extensive literature on Quality by Design. ICH guidelines Q8 (pharmaceutical development), Q9 (quality risk management) and Q10 (quality systems) forms the basis of QbD. QbD defines the quality target product profile (QTPP), critical quality attributes (CQA), risk assessment and life cycle management to design and develops the formulation and process. This review provides overview of the modern pharmaceutical quality by design (QbD), clarifies the concept and describes its objectives. It is a cost and time efficient approach in design and manufacturing, with DoE, risk assessment, and PAT as its tools to achieve a better understanding on the materials and processes, which make the QbD approach available and feasible to the pharmaceutical field. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

Key Words: Critical Quality Attributes (CQA), Design Space (DS), Design of experiment (DoE), Process analytical technologies (PAT), Quality by design (QbD), Quality Target Product Profile (QTPP), Quality risk management (QRM)

INTRODUCTION

Quality comes from the Latin word "Qualitus," which meaning "distinctive feature" or "general excellence. " The ability to function as intended is the most basic definition of quality. What makes a drug substance or drug product suitable for its intended application is called its quality. Some characteristics that are included in this word are individuality, strength, and purity. High-quality pharmaceutical products are free from impurities and contaminants, provide the therapeutic and pharmacokinetic benefits as indicated on the label, and are reproducible. The three aspects of quality are durability, performance, and dependability. Planned quality is quality by design (QbD), which is included into the product. Dr. Joseph M. Juran first coined the term "quality by design," or QbD, and the automobile industry adopted it [(1)].

Quality: Quality is a key word in Quality by Design. Thus, "standard or suitability for intended use" is what quality is. Such characteristics as identity, potency, and purity are included in this term.

Quality by Design:

A lot of changes in the development of pharmaceutical products and their subsequent manufacture has been advocated by the US FDA and the International Council Harmonization (ICH).

"A systematic approach to development that begins with predefined objective and emphasizes product and process understanding and process control, based sound science and quality risk management" [(1)].

Quality by Design (QbD) ICH guidance Q8(R2) describes QbD as, “a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” [(2)].

The methodical approach to pharmaceutical development known as Quality by Design (QbD) places a strong emphasis on incorporating quality into processes and products from the beginning. The application of this methodology to analytical procedures has been growing in order to guarantee strong, dependable, and effective methods. Furthermore, software tools and approaches are essential for applying QbD concepts to the development and validation of analytical methods.

Initially, the concept of QbD was introduced for manufacturing processes, described in four steps: [(4)]

1. Determination of patient requirements, namely, the Quality Target Product Profile (QTPP).
2. Design and development of the manufacturing process.
3. Risk assessment and definition of the manufacturing Design Space (DS).
4. Implementation of a Control Strategy.

History of QbD:

Joseph M. Juran, a well-known authority on quality, established the idea of QbD. In 1986, W. Edwards Deming—who was then out of crisis—also fascinatingly used the example of illness to illustrate the idea of quality by design. A new program called cGMP for the 21st century: A risk based approach was introduced by the FDA in 2002. With this project, the FDA aimed to update its regulations regarding pharmaceutical quality and create a new framework that emphasized quality by design, risk management, and QbD. Understanding how process and product variables affect product quality is necessary for Quality-by-Design (QbD). Two significant guidelines were released as part of the international conference on harmonization (ICH) guidelines, in addition to the FDA's consideration of this novel idea in its cGMP initiative: Q8: Development of pharmaceuticals and Q9: Quality Risk Management [3].

Objectives of QbD:

The primary objectives of QbD can be summarized as follows: [4]

1. Achieving Quality Specifications: Establishing meaningful product quality specifications based on clinical performance to ensure that the final product meets the necessary standards for efficacy and safety.
2. Enhancing Process Capability: Improving the design and understanding of both products and processes to reduce variability and defects, thereby increasing the reliability of manufacturing operations.
3. Increasing Development Efficiency: Streamlining product development and manufacturing processes to enhance efficiency, which leads to faster time-to-market and reduced costs.
4. Facilitating Root Cause Analysis: Improving the ability to conduct root cause analysis and manage changes post-approval, which is crucial for maintaining product quality over time.
5. Continual Improvement: Establishing a framework for ongoing improvement in product and process design, ensuring that quality is not just a one-time achievement but a continuous goal.

QbD Applications in Analytical method Development:

Implementation of QbD helps to develop rugged and robust/strong method that helps to go with ICH guidelines hence for that reason pharmaceutical industries are adopting this concept of QbD. This approach facilitates continuous improvement in method.

1. Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceutical)

2. Karl Fisher titration for determination of moisture content

3. To Biopharmaceutical processes

4. Dissolution studies

5. Hyphenated technique like LC-MS

6. Advanced techniques like mass spectroscopy, UHPLC, capillary electrophoresis

7. Analysis of genotoxic impurity

Analytical QbD Method:

The validation of an analytical method over a variety of API batches is the AQbD method validation approach. It designs method validation for all types of API manufacturing changes without revalidation by utilizing both DoE and MODR expertise. In addition to providing information on interactions, measurement uncertainty, control strategy, and continual improvement, the technique also meets the requirements for ICH validation. This method preserves quality while requiring less resources than the conventional validation method [4].

Advantages of Analytical Quality by Design (QbD):

• Greater comprehension and management in February 2014 Compared to the conventional ICH method validation procedure

• Adaptability in analyzing API, contaminants in dosage forms, stability samples, and metabolites in biological samples

•Decreased variability in analytical attributes to strengthen the method robustness
To maintain the analytical attribute values inside the pharmacopoeia monographs and away from the boundaries of Out of Specification (OOS). Easy method transfer to the production level with no need for re-validation inside MODR.

Important attributes about QbD [14]

Quality Target Product Profile (QTPP):

The quality target product profile forms the basis of design for the development of the product. It mainly focuses on the safety and efficacy.

Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage forms, livery systems.
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance)
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

Critical Quality Attributes (CQAs):

A Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting:

• Product purity, strength,

• Drug release and stability.

CQAs for other delivery systems can additionally include more product specific aspects such as: • Aerodynamic properties for inhalational products,

• Sterility for parentrals,

• Adhesion properties for transdermal patches.

CQAs for drug substances, raw materials and intermediates include:

• Particle size distribution

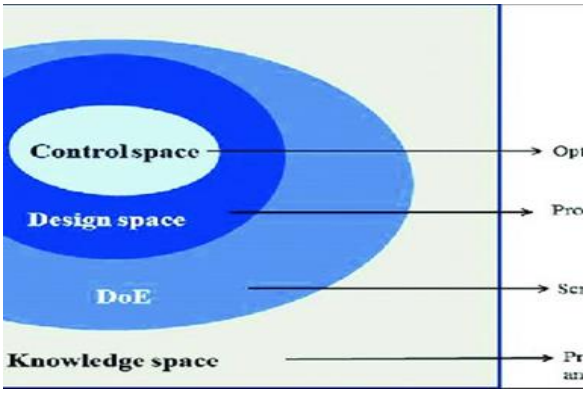
• Bulk density

Life cycle management:

In the QbD paradigm, process changes within the design space will not require review or approval. Therefore, process improvements during the product life cycle with regard to process consistency and throughput could take place with fewer post approval submissions.

Design Space:

The relationship between the process inputs (material attributes and process parameters) and Critical Quality Attributes can be described in the Design Space (Fig. 4). Working within a design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.



Control Strategy:

A control strategy can include:

• Control of input material attributes based on an understanding of their impact on processability or product quality. E.g., drug substance, excipients, primary packaging materials etc.

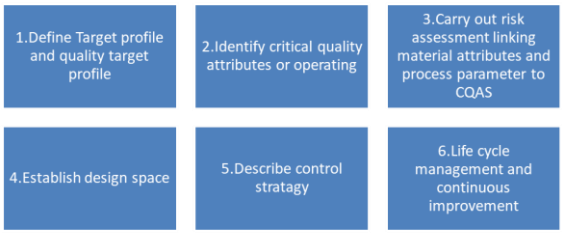
• Product specification(s)

• Controls for unit operations that have an impact on downstream processing or product quality. e.g., the impact of drying on degradation, particle size distribution of the granulate on the dissolution

• In-process or real-time release testing instead of end-product testing. E.g., measurement and control of CQAs during processing

• A monitoring program. e.g., full product testing at regular intervals for verifying multivariate prediction models.

Flow chart of QbD:



STEPS INVOLVED IN QUALITY BY DESIGN [5,6]

1. Development of new molecular entity
- Clinical study
- Nonclinical study
- Preclinical study
- Scale up
- Submission for market Approval

2. Manufacturing
- Design Space
- Process Analytical Technology
- Real time Quality Control

3. Control Strategy

- Product performance
- Risk based decision
- Continuous improvement

TOOLS OF QBD:

The manufacturing science and the design science are the two pillars of the QbD idea. Once the components of quality-based development (QbD) and its implementation procedures are understood, it is crucial to become familiar with the often utilized QbD tools, such as risk assessment, design of experiment (DoE), and process analytical technology (PAT) [7].

Risk assessment:

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. A risk assessment is useful for research and development, manufacturing, and the FDA's interactions with industry, as well as with the company's many manufacturing sites. It includes identifying the risks associated with exposure to certain hazards as well as analysing and evaluating those risks. It is the first phase in the quality risk management process; the other two are risk review and control. Reducing risk to an acceptable level is the goal of risk control, which involves making decisions to accept and/or minimize it [8]. The last step involves reviewing the output and results of the risk management process to incorporate the new information and experience.

Principles of quality risk management are;

- Scientific information is used to evaluate the danger to quality, which ultimately connects to patient protection.
- Sufficient effort is made; formality and documentation of the quality risk management procedure should be done in proportion to the degree of risk.

Risk assessment comprises three distinct components, namely risk identification, risk analysis, and risk evaluation.

1) Risk Identification: The methodical application of data, which may include stakeholder concerns, historical data, theoretical analysis, and educated opinions, to identify potential sources of harm (hazards) related to the risk question or problem description.

2) Risk Analysis: The estimation of the risk associated with identified hazards.

3) Risk Evaluation: The comparison of the estimated risk to given risk criteria using a qualitative or quantitative scale to determine the significance of risk. [9]

ICH Q9 offers a comprehensive list of nine common risk management tools, which include: [8]

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

2. Fault tree analysis (FTA)

3. Failure mode and effects analysis (FMEA)

4. Failure mode, effects, and criticality analysis (FMECA)

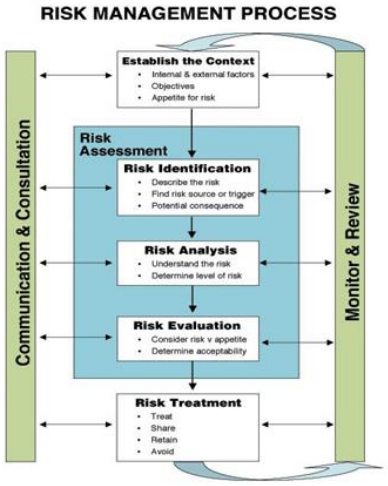
5. Hazard analysis and critical control points (HACCP)

6. Hazard operability analysis (HAZOP)

7. Preliminary hazard analysis (PHA)

8. Risk ranking and filtering

9. Supporting statistical tools.



DoE (Design of Experiments):

DOE is a statistical method to study the effect of multiple factors on a response variable. The process of designing and carrying out tests to obtain the most amount of information with the fewest analyses or experiments is known as DoE, or statistical experimental design. A tool, or combination of instruments, for obtaining test data is called a planned experiment

With the help of this fantastic technology, pharmaceutical experts may carefully alter the variables in accordance with a predetermined plan. Sound product knowledge and efficient process management throughout the production process are the cornerstones of a well-designed product. To improve our knowledge of products and processes, mechanism-based research and DoE studies collaborate [(9)].

Through the establishment of mathematical models (y = f(xi)) in the studied process or phenomenon, a series of applied statistics tools are used in the experiment design process to systematically classify and quantify cause and-effect relations between variables or input factors (xi – independent variables) and output responses (y – dependent variables).

These connections enable the

- determination of the most prominent factors (CPPs) among the useful many;
- identification of optimum factor settings leading to better product performance and assuring CQA values lying within specifications with minimum variability;
- factors, elucidation of interactions between the an important advantage over the conventional way of experimentation, where each factor is studied independently of the others (One Factor-At-a-Time or OFAT experimentation).[(10)]

DoE is a useful technique for figuring out how a process's inputs and outputs relate to one another. The Design Space, as well as CMAs, CPPs, and ideal conditions, can all be found with its assistance. For the multivariate studies, it seems sense to create a Design Space using DoE. According to ICH Q8, the Design Space is the multidimensional combination and interplay of process parameters and input factors (such as material qualities) that have been shown to offer assurance of quality. [(10)]

Advantages of the DoE:

Design of Experiments (DOE) offers several advantages, especially in the fields of quality control, product development, and process optimization. Here are some key benefits

Precision in Effect Estimates: By comparing average s rather than individual data, DOE enables more pre cise evaluation of the effects of various factors.
This accuracy contributes to a more reliable identific ation of influential factors.

Factor Interactions: DOE can estimate interactions between factors, revealing how the effect of one factor may change depending on the level of another factor. This is crucial for understanding complex systems.

Optimization: It helps in determining the optimal levels of various factors to achieve the best possible outcome. This is particularly useful in improving product quality and process performance.

Variability Reduction: By systematically investigating and optimizing processes, DOE helps in reducing variability and waste, leading to more consistent and reliable outcomes.

DoE Software:

Regressive modelling is facilitated by good DoE software. In addition to validating unexplained residuals, it should advise them on how to properly select model terms based on graphical tools and statistics. It should also validate a model and its relevance based on statistical analysis. Make sure that your graphical tools offer an intelligent method for diagnosing, analyzing, predicting, and displaying the findings in two and three dimensions. Graphical tools are essential forcomprehending and presenting the results of statistical analysis.

There are 4 interrelated steps in building a design: [11]

1. Define the objective
2. Define the variable that will be controlled during experiment and their level /ranges of variation.
3. Define the variable that will be measured during experiment-Response variable
4. Choose among the variable standard design-the one that is compatible with the objective.

SCREENING DESIGNS

An experimental design known as a "screening design" can be utilized to find the most significant factors that could potentially impact one or more of the responses of interest when a multitude of potential causative factors need to be analyzed. As a result, fewer aspects will need to be looked into in the upcoming trials. Before spending money and time on a more involved experiment, it is necessary to rule out minor elements.

The strategy which is followed in all screening experiments is as follows:

1. Determining whether running a screening design is necessary.

2. Evaluating the number of runs' practicability by weighing the information obtained against the experiment's cost.

3. A feasibility study is conducted and all the factors are recorded. [12]

The screening design has several useful qualities, including:

- By identifying the upper and lower control limits of a given variable, it aids in improving the quality control process.
- A less expensive method of process refinement is to identify the contributing elements.
- Reduces the quantity of trials conducted while optimizing the amount of data obtained.
- An additional characteristic is that a methodical approach can enhance the calibre of the output while preserving the concepts and data in a comprehensible and legible manner.
- Because it is a mathematical expression, results can be checked quickly and accurately. The information gathered can also be utilized to maintain process repeatability and optimize a process. [12]

Plackett-Burman Designs:

Plackett-Burman designs are a type of experimental design used primarily in the field of statistics and experimental design to identify the most significant factors in a process or system. Named after the statisticians William J. Plackett and J. Burman, these designs are particularly useful for screening experiments where the goal is to find out which factors have the most impact on the outcome.

Plackett-Burman designs are useful for screening factors because they provide a great method for studying numerous components in small tests.
The commonality among them is that 4n tests are conducted, with n = 1, 2, 3,... Only seven factors can be examined in an eight-experiment Placket-Burman design since the maximum number of factors that may be evaluated is 4n_1.

Plackett–Burman 8-Run Matrix

Treatment Combinations	Factors A	B	C	D	E	F	G
1	+	-	-	+	-	+	+
2	+	+	-	-	+	-	+
3	+	+	+	-	-	+	-
4	-	+	+	+	-	-	+
5	+	-	+	+	+	-	-
6	-	+	-	+	+	+	-
7	-	-	+	-	+	+	+
8	-	-	-	-	-	-	-

Factorial design:

Factorial design is an experimental setup used to evaluate the effects of multiple factors simultaneously and their interactions on a response variable. Unlike one-factor-at-a-time experiments, factorial designs allow you to study the effect of each factor and the combined effects of multiple factors in a single experiment. This can lead to more efficient and informative results.

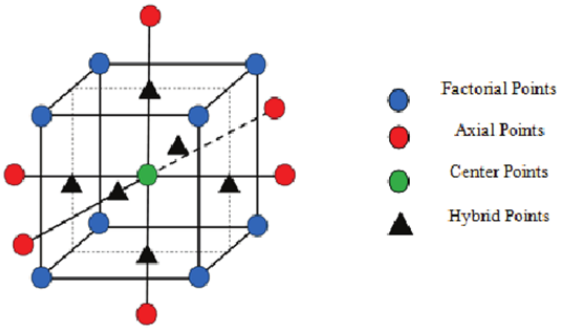
The 2K complete factorial designs are the most basic of these designs, evaluating k factors at two levels, typically ―low and high levels. Therefore, for a two-factor, two-level factorial design, there will be four experiments; when the factors rise to three, four, five, and six, there will be eight, sixteen, thirty-two, and sixty-four experiments.
The symbols for the levels of the factors are (+) plus for a higher level and (-) minus for a lower level. Occasionally, a zero level is incorporated to symbolize the variable's mid-value or centre.

		Independent Variable 2	
		Level 1	Level 2
Independent Variable 1	Level 1	Dependent Variable	Dependent Variable
	Level 2	Dependent Variable	Dependent Variable

Central Composite Design:

The central composite design is the most commonly used fractional factorial design used in the response surface model. In this design, the center points are augmented with a group of axial points called star points. With this design, quickly first-order and second-order terms can be estimated.

Box and Wilson created the five-level fractional factorial design known as the central composite design. Typically, the design comprises of m central designs, 2 × n axial designs, and 2n complete factorial designs. With the exception of one component, which will have levels either above or below the high and low levels of the two-n complete factorial design, the axial design is the same as the central design.

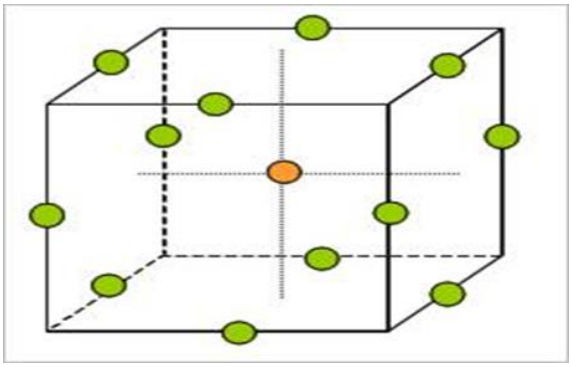


Box-Behnken Design:

The BoxBehnken design is a fractional factorial design with three levels that was created by Box and Behnken.The design can be compared to an incomplete block design combined with a two-level factorial design. While certain factors are preserved at the central levels, a specific number of factors are run thr-ough all possible combinations for the factorial design in each block.

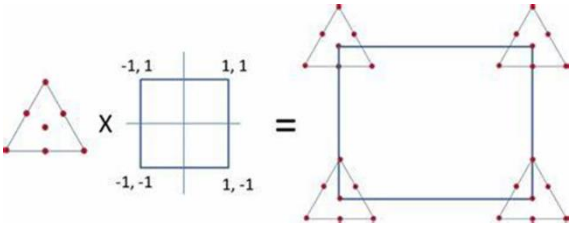
- Each factor, or independent variable, is placed at one of three equally spaced values, usually coded as −1, 0, +1. (At least three levels are needed for the following goal.)
- The design should be sufficient to fit a quadratic model, that is, one containing squared terms, products of two factors, linear terms and an intercept.
- The ratio of the number of experimental points to the number of coefficients in the quadratic model should be reasonable (in fact, their designs kept in the range of 1.5 to 2.6).
- The estimation variance should more or less depend only on the distance from the centre (this is achieved exactly for the designs with 4 and 7 factors), and should not vary too much inside the smallest (hyper)cube containing the experimental points

Even though Box-Behnken design covers a very small portion of the nonlinear design space, it is nevertheless regarded as the most effective and powerful design when compared to other designs like the three-level full factorial design, central composite design (CCD), and Doehlert design.



Mixture Designs:

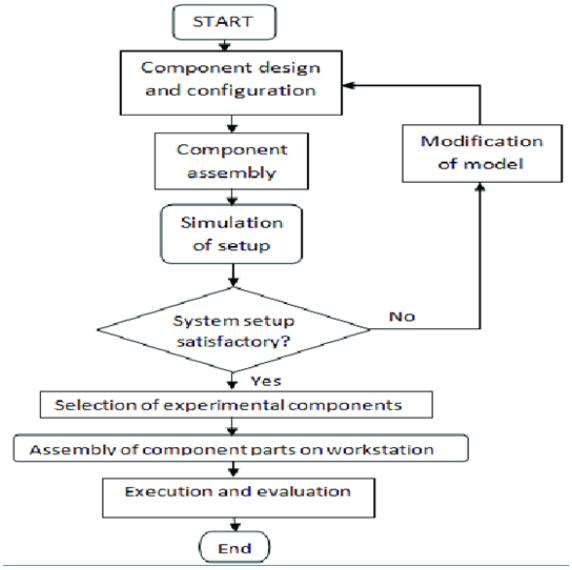
One type of response surface experiment is the mixture design, in which each ingredient's function is seen as a response and the mixture's constituents as the factors.The constant total that results from adding all the elements is 100% or 1. A limitation on the mixed trials that shows independence among all elements is represented by the constant total.The formulation factors or mixture elements whose proportions need to be changed in theexperiments and which have an effect on the formulation.



Taguchi Design:

A Taguchi design, also known as an orthogonal array, is a method for designing experiments to investigate how different process factors affect the mean and variance of a process performance characteristic1. It involves using orthogonal arrays to organize the factors and their levels12. Developed by Japanese engineer Genichi Taguchi, these designs aim to choose products or processes that function more consistently in the operating environment.

Taguchi methods are statistical methods, sometimes called robust design methods, developed by Genichi Taguchi to improve the quality of manufactured goods, and more recently also applied to engineering, biotechnology, marketing and advertising. Professional statisticians have welcomed the goals and improvements brought about by Taguchi methods, particularly by Taguchi's development of designs for studying variation.

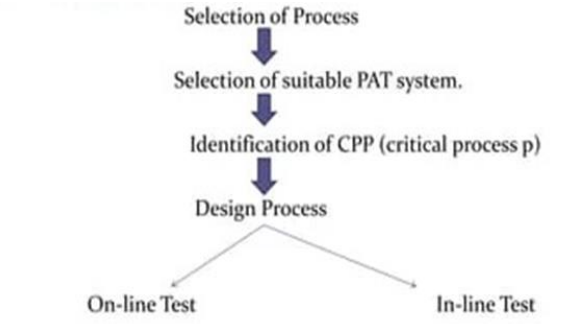


Factor	A	B	C	D	E	F	G
Experiment 1	1	1	1	1	1	1	1
Experiment 2	1	1	1	2	2	2	2
Experiment 3	1	2	2	1	1	2	2
Experiment 4	1	2	2	2	2	1	1
Experiment 5	2	1	2	1	2	1	2
Experiment 6	2	1	2	2	1	2	1
Experiment 7	2	2	1	1	2	2	1
Experiment 8	2	2	1	2	1	1	2

PAT (Process Analytical Technique):

Process Analytical Technology (PAT) is a framework developed by the United States Food and Drug Administration (FDA) to enhance pharmaceutical manufacturing processes. The main goal of PAT is to design, analyse, and control manufacturing processes through the measurement of Critical Process Parameters (CPP) that affect Critical Quality Attributes (CQA) of the final product.

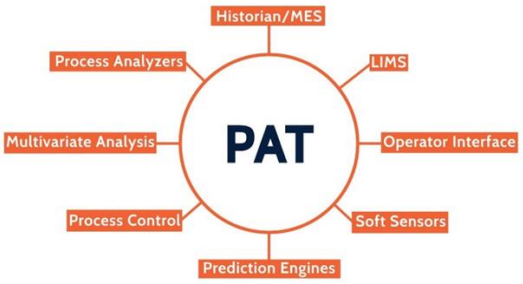
PAT is defined as “Tools and systems that utilize real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce final product that consistently conforms to established quality and performance standards”. To make sure that the process stays inside a predetermined Design Space, ICH Q8 specifies the usage of PAT. The idea came about because the regulators wanted to move the power to control product quality in the direction of a scientific approach that tries to limit patient risk by regulating production based on clear knowledge of the process. By applying technical and scientific concepts, it is helpful in the design, analysis, and control of the production process. [13] Procedure Analyses (PAT) are used to identify process factors that impact product quality. Online tracking of some CQAs is required for increased robustness and process control. The focused beam reflectance measurement, infrared, near infrared, Raman, and infrared are a few typical PAT instruments.



Atline: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream

Online: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream

In-line: Measurement where the sample is not removed from the process stream and can be invasive or non-invasive.



Process Analytical Technology (PAT) offers several advantages, especially in the pharmaceutical and manufacturing industries. Here are some key benefits:

1. Improved Product Quality: PAT ensures consistent product quality by monitoring and controlling critical process parameters in real-time.
2. Reduced Costs: By minimizing waste and rework, PAT helps in reducing overall production costs.
3. Enhanced Efficiency: PAT allows for faster process development, scale-up, and technology transfer, leading to more efficient manufacturing processes.
4. Increased Safety: Continuous monitoring and control improve the safety of both the process and the final product.
5. Regulatory Compliance: PAT facilitates easier regulatory acceptance and compliance by providing detailed process understanding and control.
6. Reduced Downtime: Automated, real-time monitoring reduces the need for manual interventions, leading to less downtime. (13)

CONCLUSION

In this Review, we have done extensive study on QbD, it's history, objectives and applications. In this study, the important attributes of Qbd are included like Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Life Cycle Management, Design Space, Control strategy. The tools of Qbd like Risk Assessment, Design of experiment (DOE), Process Analytical Technique (PAT) are also studied. Finally, the screening designs which includes Plackett-Burman Designs, Factorial Design, Central composite design, Box-Behnken Design, Mixture Design, Taguchi Design have been studied. From the above study, we conclude that the QbD is to minimise product variability and defects, thereby enhancing product development and manufacturing efficiencies and post-approval change management. QbD is quality system that builds on past and sets the potential regulatory expectations. QbD becomes important in the area of pharmaceutical processes like drug development, formulations, analytical methods and biopharmaceuticals. This new QbD process offers the opportunity for much greater regulatory flexibility in the future.

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