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QUALITY BY DESIGN BASED APPROACH FOR ANALYTICAL METHOD VALIDATION

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ABSTRACT

In the case of pharmaceutical processes, quality by design (QbD) is used to ensure a predetermined product quality. The International Conference on Harmonization (ICH) points Q8 (R1) (pharmaceutical development), Q9 (Quality risk management [QRM]), and Q10 (Quality risk management [QRM]) clarify the QbD concept unit of measurement (pharmaceutical quality system). According to the ICH Q8 (R1) guideline, "a systematic approach to development that begins with predefined objectives and stresses product and methodology understanding and methodology management, supported by strong science and QRM." The consequences of various input variables (e.g., methodological parameters and materials) of the merchandise development methodology on the end product were investigated using the QbD approach (active pharmaceutical ingredient or drug product). The late QbD method combines QRM principles with methodology and analytical technology (PAT). QbD paired with methodology analytical technology (PAT) tools improves methodology management and ensures that the unit of measurement for item quality attributes is regularly reached.

The QbD plan will also require an integrated and risk-based approach for reviewing the merchandise development methods in the future. Although using the QbD technique is not a legally binding requirement, regulatory authorities must provide flexibility in their pointers for producing the QbD-developed unit of measurement. Rising trends reflect an increased interest in quantifying and managing the impact of raw materials' features on methodology and product variability, as well as the emergence of retrospective QbD approaches in addition

to simple QbD. As a result, the QbD technique can be used to generate high-value, high-quality pharmaceuticals.

KEYWORD: Quality by Design, CQA, QTPP, Risk assessment, Design of Experiment, PAT analysis.

INTRODUCTION

Joseph M. Juran first proposed the notion of Quality by Design in a number of publications. Quality, he believed, could be planned. "To identify quality cannot be tested in products, i.e. Quality should be integrated in to product through design," according to the ICH Q8 criteria.[1] Quality refers to a drug substance's or a drug product's suitability for its intended application. This phrase encompasses qualities such as individuality, strength, and purity (ICH Q6A). Quality by Design is a methodical approach to development that starts with established goals and stresses product and process understanding and control, all while adhering to good science and risk management.[2]

QbD is more than just executing the science and risk-based work; it's also about clearly explaining the tale, both verbally and in writing. QbD connects patient needs to drug product and then drug substance. QbD usually begins in development and continues through manufacturing to produce a control plan for commercial-scale production. Small and big molecules, drug substance and drug product, vaccines, combination products, all or parts of a process, innovative pharmaceuticals or generics are all candidates for QbD. QbD entails gathering product and process knowledge, communicating it, and delivering it so that patients can continue to benefit from the drugs they are taking.[3]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for designing, assessing, and managing production by measuring important quality and performance attributes of new and in-process materials and processes in real time (i.e. during processing), with the purpose of assuring final product safety. The concept of "Quality by Design" (QbD) was defined as an approach that includes a better scientific understanding of critical process and product qualities during the development phase, designing controls and tests based on the scientific limits of understanding during the development phase, and using the knowledge gained during the product's life-cycle to work on a continuous improvement environment. QbD refers to a pharmaceutical development method that focuses on formulation design and development, as well as manufacturing procedures, to ensure that the

required product quality is maintained. Guidelines and mathematical models are used to ensure that knowledge on the subject is established and used in an independent and integrated manner.[4]

Advantages

- It allows for more freedom in decision-making.
- It enhances the likelihood of life cycle approval.
- Batch failure is minimised.
- It aids in the creation of designs for unmet medical needs.
- A better understanding of the process.
- The review was of higher quality.
- Allows for ongoing development till the method's conclusion.
- Reduce the number of deviations and the amount of money spent on research.
- It has an impact on product development and design.
- Improving method resilience by reducing variability in the analytical property.

Opportunities

- System that is effective, quick, and adaptable.
- Reduce expenses, project rejections, and waste by improving production efficiency.
- For all items, establish a scientific knowledge basis.
- Improved collaboration with the scientific community.
- Ascertain that every data is consistent.
- Risk management should be included.[3,4]

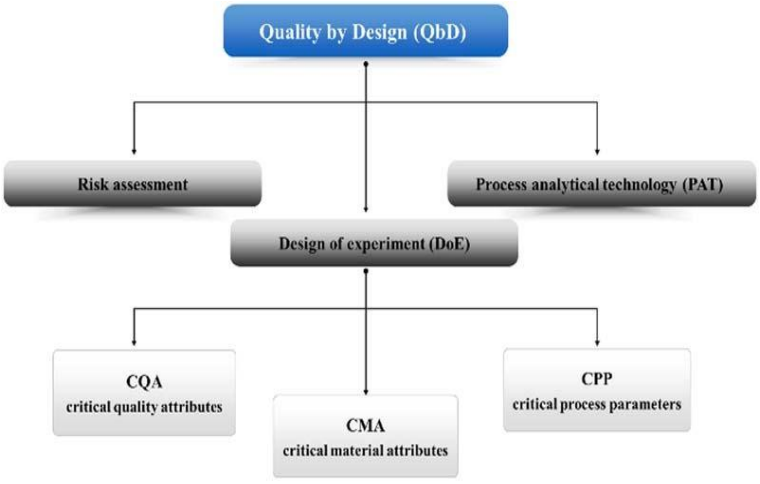

Fig. 1: Quality by Design: Tools and Elements.[5]

Table 1: Difference between Conventional approach and QbD approach.[6]

Parameters	Conventional approach	QbD approach
Approaches	Based on empirical approaches	Based on systemic approaches
Quality	QA including final product testing and inspection	Quality is maintained throughout the method development phase
Method	Fix process,changes not supported	Flexible process, it allou continuous improvement
Reliability	Based on batch trial and Validation report	Based on method performance to ATP criteria
Submission	Submission of data only	Submission with product designing and knowledge
Cost	If any change to occur in the process involve hug lose incost	Cost effective Method

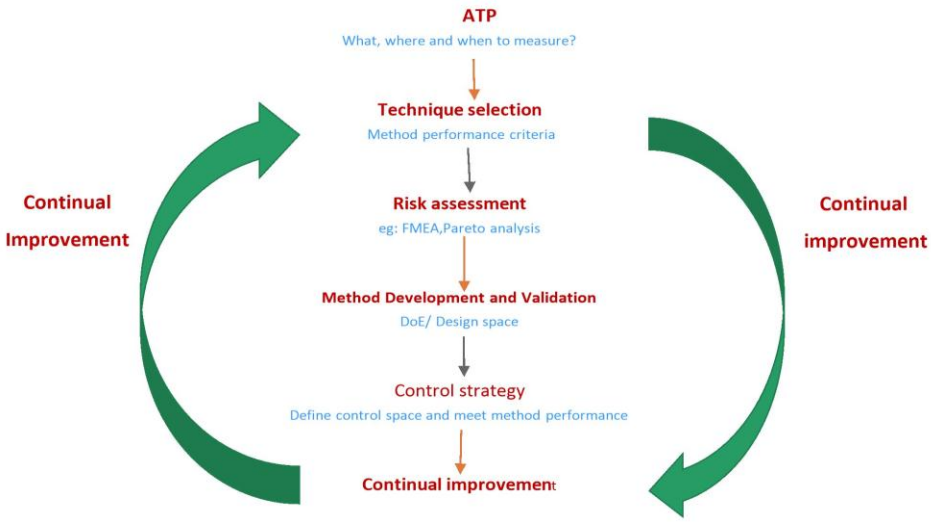

Fig. 2: Analytical method development in QbD.[7]

Analytical method development strategies

The notion of building quality into an analytical technique during its development is the principal application of quality by design (QbD) principles for analytical method development. As a result, the real method development process for an analytical quality by design (QbD) technique should be organised. The goal of the QbD method development is to meet predetermined goals. Using HPLC as an example, the goal of QbD method development may be demonstrated. The purpose of the HPLC method for API is to separate and quantify the primary ingredient as well as any key quality attributes (CQA0) that may affect the therapeutic product's quality. Specificity, linearity, accuracy, precision, robustness, and ruggedness are all regulatory standards that must be met.[6]

Steps of QbD approach in analytical method development

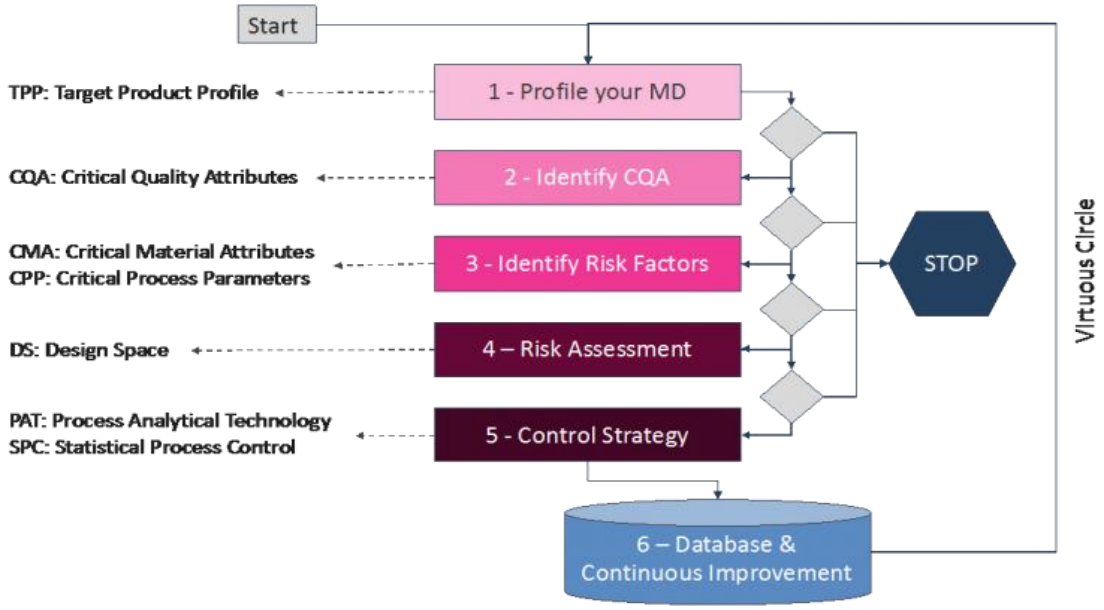

Fig. Steps in QbD.[8]

Components of QbD

1. Quality target product profile (QTPP)

The quality attributes associated to the product's safety and efficacy are defined by the FDA as QTPP. Route of administration, dosage form, delivery systems, dose strength(s), container closing system, pharmacokinetic considerations, and medication product quality criteria are some of the things that can be included (e.g., sterility, purity, stability, and drug release). It's critical to remember that QTPP should only include product performance elements that are relevant to patients. Tablet density or hardness, for example, may be included as a standard for process monitoring but not in QTPP. In addition, if particle size is important for a solid oral product's dissolution, the QTPP should include dissolution but not particle size. The QTPP for an NDA is still being developed, whereas the QTPP for an ANDA product is fully established, based on the qualities of the drug substance (DS), characterization of the reference listed drug (RLD) products, RLD label, and targeted patient group. As a result, a generic drug product should have the same QTPP as a brand-name or reference product. [9]

2. Process Analytical technology (PAT)

"Tools and systems that use 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 a final product that consistently conforms to established quality and performance standards," according to the definition of

PAT. The usage of PAT is identified in ICH Q8 as a way to verify that the process stays inside a defined Design Space. The concept stems from regulators' aim to move product quality control to a science-based approach that openly attempts to limit patient risk by controlling manufacturing based on a thorough understanding of the process. A process is deemed well understood from a PAT standpoint when:

i) All significant causes of variation have been found and explained.

ii) The process manages variability

iii) Product quality attributes can be predicted accurately and reliably.

PAT Tools: Many tools are provided in the PAT framework for comprehending scientific, risk-managed pharmaceutical development, production, and quality assurance. According to the PAT guidelines, they are divided into four categories.

i) Design, data collecting, and analysis multivariate tools

ii) Analyzers of processes

iii) Instruments for process control

iv) Tools for continual development and knowledge management.[5]

3. Analytical target profile (ATP)

The first step in QbD is to create an analytical target profile that is linear to QTPP. The goal of the analytical method development process is defined by the analytical target profile, which links the method's results to the QTPP. The technique requirements, which are assumed to be the measurement, are described by ATP. The analytical target profile is defined using the analytical process' knowledge and scientific reasoning. The ATP specifies the level of measurement required (i.e., operating level attributes such as precision, accuracy, range, and sensitivity) as well as the parameters that the method must measure (i.e. acceptance criteria).[5] In general, an ATP for an analytical procedure includes a target analytic (API and impurities), analytical technology (HPLC, HPTLC, gas chromatography, ion chromatography, and so on), and method requirements (assay and impurity profile).[6]

Table 2: Method performance characteristics as per ICH Q2.[10]

Performance characteristics	Definition	Categorisation
Accuracy	Closeness of agreement between the value	Systemic variability
Specificity	Ability to assess unequivocally the analyte in the presence of components which may be expected to be present	
Linearity	Ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample	
Prescision	Closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions	Inherent random
Limit of detection	Lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value	
Limit of quantitation	Lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy	
Range	Interval between the upper and lower concentration (amounts) of analyte in the sample	NA
Robustness	Measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage	NA

4. Critical Quality Attributes (CQA)

Physical, biological, microbiological, and chemical properties are used to ensure that the product obtained meets the necessary quality, safety, efficacy, and stability standards. That, too, can be defined, quantified, and constantly monitored to ensure that final product outputs remain within acceptable quality norms. Clinical safety and efficacy, manufacturing an attribute, and parameter boundary approach edge of failure are all quality attributes. The criticality for the APT manufacturing process may differ, and the level of criticality increases the risk. CQA analytical techniques can vary from one to the next.

a. The temperature of the oven and its programme, injection temperature, gas flow rate, sample diluents, and concentration are all CQA for the GC technique.
b. Mobile phase buffer, mobile phase pH, column selection, organic modifier, and elution method are CQA for the HPLC method.
c. TLC plats, mobile phase, injection concentration and volume, plate development time, and colour development and detection reagent are the CQA for HPTLC method.[11]

5. Risk assessment

To get the most out of a risk assessment, the analysts who created it should collaborate with the analysts who will use it in production. A walk-through is recommended to thoroughly grasp the process, which entails all analysts watching one analyst use the procedure in a production environment from start to finish. The method's steps can then be broken down into individual steps and mapped out (e.g., sample preparation, dissolution, extraction, chromatographic separation, data analysis). A priority matrix and failure mode effect analysis (FMEA) can be used to identify where variability in a factor or failure of an element of the system may pose a risk to the method's capacity to meet the design goal.

Before any experimentation, the process must be enhanced as much as feasible by using the FMEA output. After the method has been examined by DOE, the FMEA may be used to assess the risk associated with using the method and to determine the demonstrated acceptable ranges for the method factors. The analytical technique design space is a documentation of the statistical studies' outcome. A measurement systems analysis (MSA) design is used to conduct a ruggedness investigation. This research tries to test the strategy by giving it as much time as feasible to reveal any flaws.[12]

6. Method operation Design region

Method operational design region: After determining the method development and risk assessment, the next stage is to determine the method operational design region. MODR is a way for developing an operating region for day-to-day operations. MODR is a risk-based, multivariate strategy to analysing the effect of numerous factors on method performance that is based on science. It's also how crucial method controls like system appropriateness, RRT, and RRF are put up.[6]

7. Control strategy

A control approach ensures that a high-quality product is consistently produced. The following are examples of control elements that contribute to the quality of the finished product:

- Controls implemented during the manufacturing process
- Input materials (drug substance and excipients)
- Intermediates are all under control (in-process materials)
- System for sealing containers
- medication (Drug products)

- In-Process Control (or Process Control): Inspections carried out during production to monitor and, if necessary, change the process, and/or ensure that the intermediate or API meets its specifications. (Q7) Applies to the drug product in a similar way.
- In-Process Tests: Tests that are carried out during the manufacturing of a drug substance or a drug product, rather than as part of a formal battery of tests carried out prior to release (Q6A)
- Control strategy is derived from risk management and should result in the assurance of consistent product quality in accordance with the Quality Target Product Profile (QTPP).

The following is the control strategy

- This isn't a novel notion.
- It's not simply about specifications.
- Understanding of the product and process, as well as risk management
- Control approach is not optional, but design space is.

- A control plan is associated with each process and product.
- For each product, there is a single overall control approach.
- For unit operations, there exist control strategies.
- It may include some site-specific features.

- These controls should be based on a thorough understanding of the
- Product
- Formulation
- Process.[13]

8. Lifecycle Management

Lifestyle management: The final step in QbD is lifecycle management. The ultimate outcomes of risk assessment, assumption-based anterior knowledge, MODR, control strategy CQA, and analytical target profile are all part of a continuous process of sharing knowledge gained during the method development phase. QbD techniques have a different lifetime management than traditional approaches.[14]

Design of Experiment

Design of experiments (DOE) is a time-saving method for planning tests so that the results can be examined to produce reliable and objective findings. An experiment is a structured,

organised strategy for determining the relationship between elements affecting a process and the outcome of that process. In experiments, we purposefully change one or more process variables (or factors) in order to see how the change affects one or more response variables. The design of experiments (DOE) is a time-saving method for organising tests and analysing the results to arrive at reliable and objective findings. Choosing the process parameters for the study and identifying the experiment's goal are the first steps in DOE. An experimental design is the creation of a detailed experiment plan prior to conducting the experiment. Maximize the amount of data that can be gathered for a given amount of experimental effect.

Benefits of Design of Experiments: Experimental design entails tinkering with the independent variable to see how it affects the dependent variable. This allows a cause-and-effect relationship to be established. The experimenter tries to reduce undesired extraneous variables in addition to manipulating the independent variable. Extraneous variables are frequently better controlled than in other research approaches. The experimenter can set up the experiment again and replicate or confirm their results because of the stringent circumstances and control. Replication is critical because when similar results are produced, it increases confidence in the findings.

Use of Design of experiment: The design of experiments is used to establish the reasons for response variance, find conditions under which the optimal (maximum or lowest) response is attained, compare responses at different levels of controlled variables, and construct a model for forecasting response.

Key steps for Design of experiments

Obtaining good results from a Design of experiments involves those seven steps:

1. Set objective
2. Select process variables
3. Select an experimental design.
4. Execute the design.
5. Check that the data are consistent with the experimental assumptions.
6. Analyze the results.
7. Interpret the results.[15]

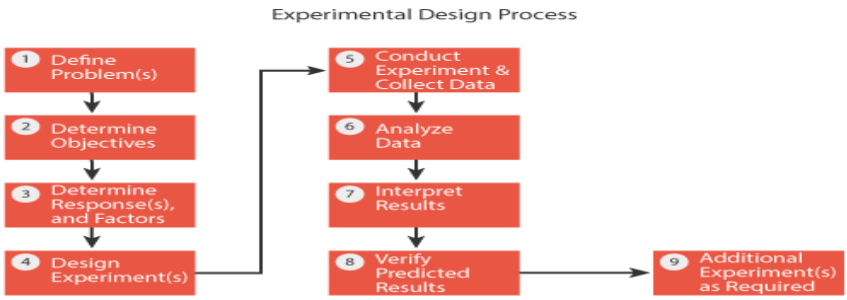

Fig: Design of Experiment process.[16]

Applications of Design of Experiments In QBD And AQBD

The FDA approved the Quality by Design approach in 2004 and detailed it in "pharmaceutical cGMPs for the twenty-first century—a risk-based strategy." The Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system of the International Conference on Harmonization (ICH) establish precise requirements for pharmaceutical product quality. Implementing ICH/Q8 and ICH/Q9 is easier using QbD and DoE techniques. DoE has been widely used since the FDA approved the QbD approach in order to provide a thorough understanding of the product and its production process. The literature has numerous examples of DoE applications for screening and optimization of pharmaceutical goods and production processes. Several input components (independent variables) can be tested and optimised using DoE, including excipient concentrations, stirring time, stirring speed, temperature, and pressure, among others. Particle size, entrapment efficiency, and dissolution rate were among the output responses studied (dependent variables). Table VII contains some examples of DoE applications. Screening designs are used in pharmaceutical QbD to find critical material attributes (CMAs) and critical process parameters (CPPs) (independent variables) that influence critical quality attributes (CQAs) (dependent variables) and, as a result, the quality target product profile (QTPP). Furthermore, improving design and surface response methods, as well as multiple response optimization, allows for the creation of a design space region where CQAs and QTPPs are addressed. Because changes inside the design space area do not require previous regulatory permission, the adoption of a design space region based on product and process understanding allows regulatory flexibility. Particle size, entrapment efficiency, and dissolution rate were among the output responses studied (dependent variables). Table VII contains some examples of DoE applications. Screening designs are used in pharmaceutical QbD to find critical material attributes (CMAs) and critical process parameters (CPPs) (independent variables) that influence critical quality attributes (CQAs)

(dependent variables) and, as a result, the quality target product profile (QTPP). Furthermore, improving design and surface response methods, as well as multiple response optimization, allows for the creation of a design space region where CQAs and QTPPs are addressed. Because changes inside the design space area do not require previous regulatory permission, the adoption of a design space region based on product and process understanding allows regulatory flexibility.[17]

Challenges

1. A lack of understanding of the pharmaceutical process is the root of the problem and a fundamental impediment to Qbd adoption. Pharmaceutical corporations have generally placed greater emphasis on the end result, with little regard to a scientific understanding of the process involved.
2. Collaboration and consensus on how to address QbD between field inspectors and the FDA review and compliance sectors remains an unresolved issue.
3. The majority of pharmaceutical businesses believe that more concrete guidelines on how to really adopt QbD are needed. Companies asked the FDA to clarify QbD nomenclature, authorise procedures, criteria for selecting and deselecting essential quality attributes, control sufficiency standards, and criteria for analytical method substitution.
4. For efficient QbD adoption, there is a need for better collaboration across many disciplines inside the organisation, including process development, production, and quality control.
5. Pharmaceutical companies believe that QbD may lengthen the time it takes to file an approval application or that it will disclose unneeded information to the regulatory authorities, thereby causing delays in the approval process.

CONCLUSION

Quality by Design is based on current guidelines and reference papers and is meant to improve process understanding. QbD is a quality system that builds on previous regulatory expectations while also setting new ones; it may be thought of as a process described by a series of document requirements. These documents structure and demonstrate understanding of the process. Legacy and modern products can both use QbD, although the supporting document bundle may differ. The documents in the QbD suite are "living." As the knowledge base evolves, they can and should be revised. It ensures reliable commercial manufacturing processes for consistent drug manufacturing. It guarantees that therapeutically comparable

generics are produced each and every time. The QbD technique aids in the identification and justification of target product profiles, as well as product and process comprehension. Strong and well-funded research initiatives are required to develop new pharmaceutical manufacturing platforms.

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