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Quality by Design: An Overview

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ABSTRACT

For the quality of pharmaceuticals, Quality by Design is the modern approach. Quality of pharmaceutical ensured by the use of Quality by Design approach. Quality is a prime factor of importance in today's competitive era. By the ICH guidelines, the principles of quality have been described: Q8 Pharmaceutical development, Q9 Pharmaceutical quality risk management, and Q10 Pharmaceutical quality system. The implementation of QbD performs by the use of various tools. The main objective of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality should be always built-in by design it cannot be tested in the product only. It includes the Quality target product profile, critical quality attributes, and key aspects of Quality by Design. And there are various challenges associated with the adoption of Quality by Design which is described here briefly.

INTRODUCTION:

Quality: In Quality by Design, Quality is an important word. So Quality is "standard or suitability for the intended use." This term includes such attributes of identity, potency, and purity.

Quality by Design: In the ICH Q8 guideline the concept of QbD was mentioned, which states that "quality cannot be tested into products, i.e., quality should be built in by design"**.** As per ICH Q8 QbD 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. QbD encompasses designing and developing formulations and manufacturing processes that ensure predefined product specifications.

The three ICH guidelines which are concern with quality-by-design and related aspects include Q8 Pharmaceutical development, Q9 Pharmaceutical risk management and Q10 Pharmaceutical Quality systems. The ICH guideline Q8 is sub-divided into two parts: part one deals with pharmaceutical development and Part two is the annex to the guideline which states the principles for Quality-by-Design (QbD) [1, 2, 3, 4].

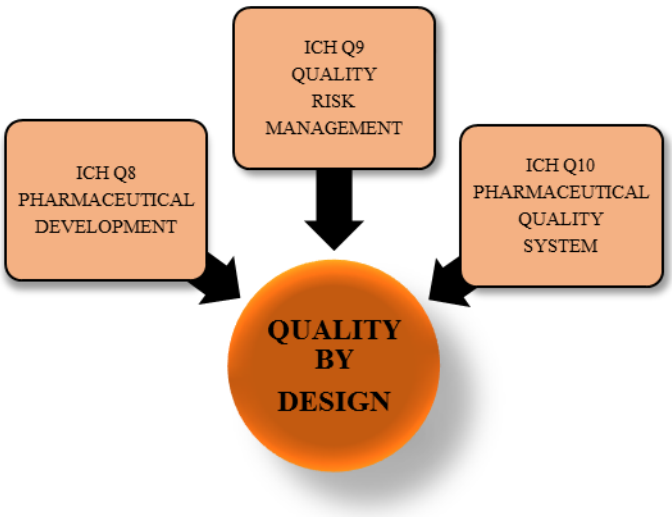

Figure No. 1: Content of Quality by Design [3, 4]

Advantages of QbD:

- Patient safety and product efficacy are focused on.
- Scientific understanding of pharmaceutical processes and methods is done.

- QbD involves product design and process development.
- Science-based risk assessment is carried.
- Critical quality attributes are identified and their effect on the final quality of the product is analyzed.
- QbD offers a robust method or process.
- Business benefits are also a driving force to adopt QbD.[4,5,6]

Opportunities of QbD:

- Efficient, agile, flexible system.
- Increase manufacturing efficiency, reduce costs and project rejections and waste.
- Build a scientific knowledge base for all products.
- Better interact with industry on science issues.
- Ensure consistent information.
- Incorporate risk management.[5,6,7]

Steps Involved in Quality by Design Products:

Table No.1: Steps Involved in Quality by Design Products [7, 8]

1. Development of new molecular entity	2. Manufacturing	3. Control Strategy
•Preclinical study •Nonclinical study •Clinical Study •Scale up •Submission for market Approval	•Design Space •Process Analytical Technology •Real time Quality Control	•Risk based decision •Continuous Improvement •Product performance

QbD has four key components:

1. Defining the Product Design Goal

In this step, the Quality Target Product Profile (QTPP) define and identify all the critical quality attributes (CQA) for the product. The QTPP includes the factors that define the desired product and the CQAs include the product characteristics that have the most impact

on the product quality. These provide the framework for product design and understanding. The components are characterized and the compatibility of the components is evaluated. [8, 9]

2. Discovering the Process Design Space

Defining the design space is the key to understanding your processes. Design space defines by ICH Q8 "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to assure quality." By identifying critical process parameters (CPPs) the extent to which any process variation can affect the quality of the product is determined. By defining the design space, you can anticipate issues and plan how to control the process. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined. [9, 10]

3. Understanding the Control Space

On the process design space-based, a well-executed control space can be defined. This enables you to understand in a way that ensures product quality from known variability of the production process. By this disciplined approach will keep your complex production processes under control. To illustrate the concept of a control space study, think of a reference product data set with tightly clustered data points that represent the output of a tightly controlled process. Plotting the output of your process and comparing it to such a reference will give a clear indication of whether your process is in control. One technique to help avoid such a disparity is to conduct a Design of Experiments (DOE) study on your product in the development stage. Considerable wasted effort can be eliminated with such an approach as can any unexpected adverse outcome from the lack of control space understanding. [10, 11, 12]

4. Targeting the Operating Space

The operating space is the best set of parameters, determined statistically, which enable you to accommodate any natural variability in CPPs and CQAs. For generic products, the operating space should be within the control space and should allow a reference product to be tested with the same set of parameters.

For new products, the operating space should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing of formulations to truly refine their product. [13, 14]

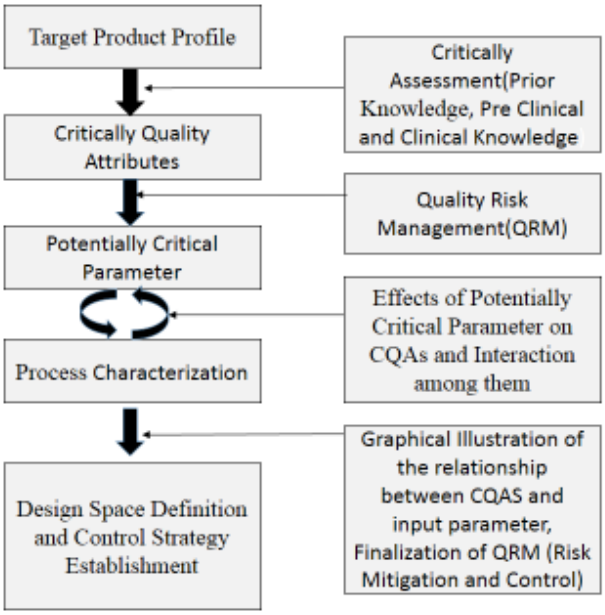

Figure No. 2: Elements of Quality by Design [13, 14]

Tools of Quality by Design:

A. Design of Experiments (DOE)

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. Application of DOE in QbD helps in gaining maximum information from a minimum number of experiments. When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors. [14, 15, 16]

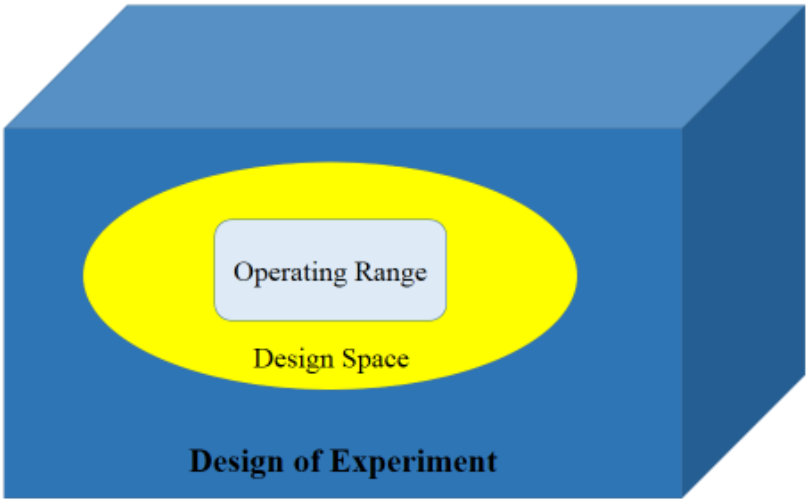

Figure No. 3: Design of experiment (DOE) [14, 15, 16]

B. Process Analytical Technology (PAT)

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during the processing of critical quality and performance attributes of raw and in-process materials and processes, to ensure final product quality". PAT aims to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." The design space is defined by the key and critical process parameters identified from process characterization studies and their acceptable ranges. These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness. NIR act as a tool for PAT and useful in the RTRT (Real-Time Release Testing) as it monitors the particle size, blends uniformity, granulation, content uniformity, polymorphism, dissolution, and monitoring the process online, at the line, and offline, thus it reduces the release testing of the product. [17, 18,]

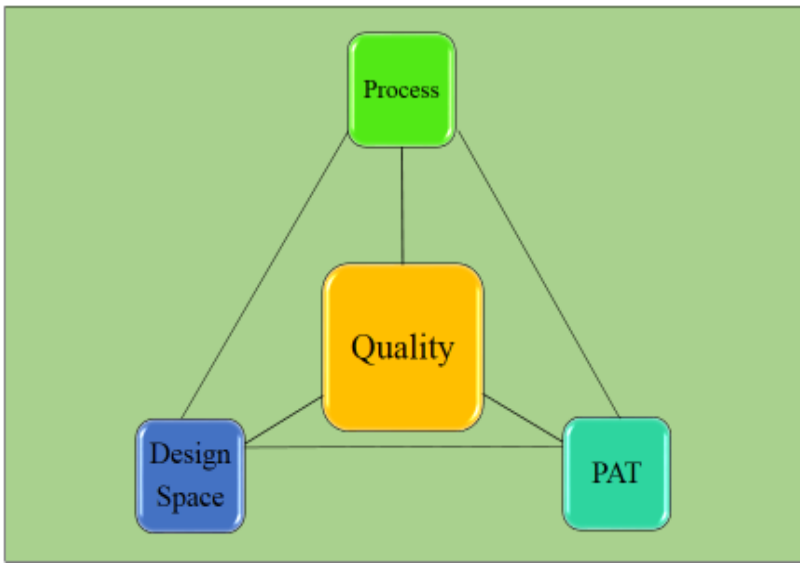

Figure No. 4: Interrelationships between PAT and QbD [17, 18]

C. Risk Management Methodology

Quality Risk Management is defined as "A systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. Risk assessment tools are used to identify and level parameters (e.g., process, equipment, input materials) with the potential to have an impact on product quality, based on prior knowledge and primary experimental data. The early list of potential parameters can be fairly broad but can be modified and prioritized by additional studies (e.g., through a combination of design of experiments, mechanistic models). Once the considerable parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.[17, 18]

Figure No. 5: Basics of Risk Management [17, 18]

The Challenges of Adopting QbD:

Despite the many financial and operational benefits of QbD, and even with the FDA new recommendations, not all companies have adopted the QbD approach." By an organization implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment. Understanding the effort necessary to implement QbD is a key component for successful adoption. Some of the most common barriers to adoption include:

• Insufficient understanding of the process and its benefits

• Competing priorities

• Organizational resistance to change

• Lack of resources and expertise in QbD. [19]

SUMMARY

In today's era Quality by design is an important tool as far as pharmaceutical industries are concerned. The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and post-approval change management. Considering this ICH has also specified guidelines for

using QbD in daily practices of the industry. This approach allows the establishment of priorities and flexible boundaries in the process. As such QbD is becoming a promising scientific tool in quality assurance in the pharmaceutical industry.

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