CHAPTER 1

Introduction to Quality by Design

In pharma, **quality** means that a medicine is **safe, effective, pure, and consistent**, so that every dose a patient takes works as intended without causing harm. Like human race, pharmaceutical manufacturing and quality systems have evolved from primitive dispensing of powders to novel drug delivery systems and testing by organoleptic and gravimetric methods to advanced process analytical technology. The traditional pharmaceutical quality relied on end product testing for defined specifications to control quality and is called "Quality by Testing (QbT)". About 10-20 tablets are tested from a batch of 0.1 million to 1 million tablets to assure the quality of the entire batch, which is statistically inefficient to prove the results. In addition, the failure to meet specified quality attributes of end product lead to severe loss to the industry and re-processing of failed batches was also considered till they meet the desired specifications.

The reasons for failure of a batch to meet set specifications are unknown since the product development and manufacturing process were not investigated scientifically thoroughly to understand the effect of the material attributes, process variables and process controls on *quality* of finished product. Dr. Joseph M. Juran, a pioneer in quality management, introduced the term Quality by Design (QbD) in the 1980s. His philosophy is that *quality* should be planned and built into the product rather than testing the end product. The idea of "designing quality into products" originated outside pharmaceuticals, particularly in manufacturing and engineering industries.

In 1990s and early 2000, pharmaceutical industry has understood the significant of building quality into the product instead of testing the finished product. This shift is from Quality by Testing (QbT) to quality by design (QbD). Frequent failure of drug product quality, recalls from the market and unwanted side effects from drug products have been the focus of regulatory authorities across the globe. The USFDA has launched the initiative *"Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach"* in 2004, promoting science- and risk-based regulation. The Europe, Japan and other countries had series of meetings to address the quality issues and led to the formal incorporation of QbD into pharmaceutical regulations via the

International Council for Harmonisation (ICH). A series of ICH guidelines were issued from 2004.

- **ICH Q8 (2004, revised 2009):** *Pharmaceutical Development* – introduced QbD concepts like QTPP, CQAs, and design space.
- **ICH Q9 (2005):** *Quality Risk Management* – emphasized risk assessment tools.
- **ICH Q10 (2008):** *Pharmaceutical Quality System* – lifecycle approach to quality management
- **ICH Q11 (2012):** *Development and Manufacture of Drug Substances* – extended QbD principles to Active Pharmaceutical Ingredients (APIs).

"Quality by Design (QbD) is a systematic, science-based, and proactive approach to pharmaceutical development and manufacturing. It emphasizes that product quality should not be tested into the product at the end, but built into the product and process from the beginning**"** is the definition used.

Currently, QbD is not an option but the need to achieve high quality drug products development, scale up, manufacturing and continuous improvement. Pharmaceutical companies started applying QbD in:

- Formulation development (defining design space for excipients and processes).
- Analytical methods (Analytical QbD, or AQbD, for robust, reliable testing methods).
- Biologics and biosimilars, where complex processes require greater control.
- Continuous manufacturing and real-time release testing (RTRT).

Quality by Design (QbD) is not a process but it is a philosophy where the scientists apply their knowledge, literature, experimental data, statistical analysis, and risk assessment to understand the material attributes of excipients used, process parameters applied and their impact on quality attributes of product. The objective is to build the quality into the product and hence, the first step is to define the quality target product profile (QTPP). QTPP is nothing but list of specific characters of a dosage form that ensure safety, efficacy and quality. These QTPPs of finished product can be summarized into few Quality Attributes called Critical Quality Attributes (CQAs).

A drug product contains drug and excipients and they are subjected for processing to convert them into a suitable dosage form. For example, a drug, diluent, dry binder, glidant and lubricant are blended and compressed into an immediate release tablet. These materials have some attributes based on their

functionality that would affect the tablets quality. For example, the surface area of lubricant is a critical character that affects the lubrication process and hence, the surface area of lubricant is called critical material attribute (CMA). One excipient may contain more than one CMA and all the materials critical attributes have to be identified so that systematic experimentation can be carried out to study their impact on CQAs. Apart from composition of formulation, the process used is also important for achieving desired quality. Pharmaceutical manufacturing comprises of several unit operations arranged in order. In direct compression example, blending of excipient, lubrication of blend in a blender followed by compression are the simple unit operations for the production of tablets.

The CMAs of drug and excipients are important for the blending and lubrication processes, and the output is the lubricated blend for compression. The lubricated blend characters such as assay of drug in blend, uniformity of drug in blend and blend flow properties are the CQAs of the lubricated blend. The blend CQAs are not only influenced by CMAs of materials used but also by the process parameters and hence, identification of critical process parameters (CPPs) of the blending operation is important so that proper control of CPPs can be used to produce blend with desired CQAs. It should be noted that the CQAs of lubricated blend are now CMAs to the next operation of tablet compression and the CPPs of compression process impact the CQAs of tablets.

Various QbD tools such as Ishikawa diagram or failure mode effect analysis (FMEA) are used for risk identification, risk analysis and risk management of quality. Risk identification is a systematic process to identify potential risks to product quality throughout the product lifecycle. Identified risks are now subjected for thorough analysis with respect to probability of occurrence, severity of harm and detectability of risk. Risk evaluations consider the strength of evidence for probability, severity, and detectability.

After identification of CMAs and CPPs, the next step is to carryout Pareto analysis of them to short list the most important CMAs and CPPs. Systematic study of impact of short-listed CMAs and CPPs on CQAs is carried out by the application of Design of Experiments (DoE). Design of Experiments (DOE) is a systematic and statistical approach for planning, conducting, and analysing controlled tests to understand how multiple input variables (factors) affect an output or response variable. Its core purpose is to determine which factors are most influential, optimize process settings, and achieve desired outcomes efficiently, saving time and resources compared to traditional one-factor-at-a-time experiments.

Design of experiments is carried out with the help of DoE software for screening the short-listed CMAs and CPPs that impact CQAs. The results from screening experiments are used to identify most impactful factors (CMA and CPP) on CQAs of the drug product. Optimization of these most influential factors is achieved using response surface methodology-based experiments such as full factorial designs, central composite design, mixture design, D-optimal etc. The results of these experiments are used to build mathematical models that relate the factors (CMAs and CPPs) and CQAs so that desired CQAs can be achieved using optimum factors. The experimental data allows the creation of design space for CMAs and CPPs within which the CQAs are met. A design space is defined as the multidimensional region of input variables (like process parameters and material attributes) that have been shown to consistently deliver a product meeting its quality requirements. Working within the established design space is considered normal process operation and is not a regulatory change, while operating outside it is a change that requires further review.

The measurement of CQAs can be in-line, on-line, at site or off-line. Measurement of specific characteristics of raw material, blend, or process parameter in-line or on-line using proper instruments enables continuous quality control, provides deep process understanding, optimizes processes for efficiency and cost-effectiveness. Process Analytical Technology (PAT) is used to design, analyse, and control manufacturing processes in real-time by measuring critical quality and performance attributes of raw materials and in-process materials to ensure final product quality. The data is inspected, transformed, and modelled using multivariate, artificial intelligence (AI) and machine learning methods to detect trends, predict outcomes, and enable immediate process adjustments or real-time release testing. Key goals include enhancing process understanding, improving operational efficiency, reducing reliance on offline testing, and ensuring product quality throughout the manufacturing lifecycle.

During the drug product development, the composition of a dosage form is finalized and the manufacturing process is optimized using the laboratory equipment. In general, the pharmaceutical composition is fixed and is *scale independent*. But the commercial production of drug product utilizes bigger equipment than those used in laboratory. Therefore, there is a need for systematic and scientific investigation to scale up the manufacturing process from laboratory scale to commercial scale. The CPPs are divided into scale independent and scale dependent. Scale independent process parameters are those process parameters that remain constant across the size of the batch. However, scale dependent parameters have to be optimized based on the commercial batch size using sound scientific principles and scale up techniques.

Once the scale up of the process at the commercial scale is established, there is a need to develop a control strategy to ensure batch to batch consistency in the quality of product. As per the USFDA a control strategy "is a planned set of controls, derived from an in-depth understanding of the product and process, designed to ensure process performance and product quality." Once the optimization of composition and process completes with design space, the controls for each critical process parameter are placed including CMAs. These controls would ensure the quality of drug product during the manufacturing of commercial batches.

All the QbD principles explained with the help of formulation development, process optimization and process validation are equally applicable to various analytical methods used to measure the attributes of raw materials, drug, packing material and finished product. The analytical method development, verification, optimization of critical method parameters (CMPs) and method validation should follow QbD principles including DoE. Creation of design space or method operable design region (MODR) for analytical method are highly useful for flexibility during regular analysis.

The drug product is supplied into the market upon receipt of marketing authorization from regulatory authorities by manufacturing the drug product at commercial scale regularly. The QbD frame work continues to measure the process capability and strives for continuous improvement in the quality of the product. The purpose of process capability is to provide statistical data on performance, identify areas of poor quality, set a baseline for improvement, and reduce defects and costs. The purpose of continuous improvement is to use this data and other feedback to constantly refine processes, eliminate waste, enhance quality, and boost efficiency and profitability over time.

Quality by Design is a philosophy that focus on building quality to into the product by studying the impact of variables with most advanced scientific principles on critical quality attributes, creating design space, monitoring process capability and engaging in continuous improvement in quality of the product. Quality should be built into the product but not test for. QbD is a journey throughout the life cycle of the product not a destiny.