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# Quality By Design (QBD): A Modern Approach For Development of Quality Pharmaceuticals

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## ABSTRACT:

Quality by Design is the ultramodern methodical approach in development of new pharmaceuticals. It serves as link between industry and medicine non supervisory authority. The aim of this article is to discuss the quality by design and emphasize how it can be give pharmaceutical quality. It substantially defines and describe the quality by design, literal background behind the QBD, pillars of QBD similar as -product design thing, process design space, control space, operating space. It distinguishes between the traditional approach and enhanced QBD approach. It concluding the key elements of QBDincluding Quality target product profile (QTPP), critical quality attributes (CQAs) of drug product, Quality risk management, critical material attribute and critical process parameters, design space and control strategy along with various applications and benefitsof QBD.

**KEYWORDS :** Quality target product profile (QTPP), Critical quality attributes (CQA), Quality by design (QBD), Quality risk management (QRM), Critical materialattributes (CMA), Critical process parameters (CPP).

## INTRODUCTION:

Quality by design was first introduced by well known quality expert "Joshep Moses Juran". He believed that quality could be planned and that most quality associated problemshave their origin in the way which quality was planned in first place. His discovery of "designed in " concept, is used in quality by design for development of product.[11] The conception of quality by design was notified in the Q8 guideline of International conference on harmonization(ICH).

Quality by design is holistic approach which helps in the improvement of pharmaceutical product by ensuring the quality. It starts with the predefined objectives and process understanding and process control, based on sound science and quality risk management.[4]

**Quality:**

Quality is commonly referred to a parameter which decides the inferiority or superiority of product or service. It is a measure of goodness to know how a product meets its specifications.

Merriam Webster defines quality as a degree of excellence, or a distinguishing attribute. Managers endeavour for excellence in the organisation to improve customer satisfaction, increase the output in manufacturing while derogating defects, as well as making the company more profitable.

The term "quality" has a relative meaning. This is demonstrated by the ISO: "The totality of features and characteristics of a product or service that bear on its ability to satisfy statedor implied needs".[3]

**Design:[3, 10]**

The first aspect of QBD are an articulation of the design for the product

- Design a formulation to satisfy customers need and performance conditions.
- Manufacturing procedure is designed to always meet product quality attributes.
- Impact of critical process parameters and crude material attributes on product degreeof excellence are identified.
- The process is constantly examine and update to assure applicable product quality.

## Characteristics of QBD: [4, 7, 8]

- An approach for evolution of efficient drug substance.
- This approach depend on the conception that quality can be improved in as acontinuance.
- It is relevant to both drug product and drug substance development.
- It is also applicable to investigative methods.
- Can be used at any time in the life process of the drug.

## Objectives of QbD:[4, 9]

- To achieve purposeful product quality specifications that is based on clinical activities.
- To increase pharmaceutical product development and manufacturing efficiencies.
- To amplify root causes interpretation and post approval change management.

## Comparison Between Traditional and Enhanced Approach:

| Aspects | Current | QbD |
|---|---|---|
| Pharmaceutical Development | Empirical, Random, Focus optimization | Systematic, Multivariate experiments, Focus on control strategy and robustness |
| ManufacturingProcess | Fixed | Adjustable within design space, managed by company's quality system |
| Process Control | Some in-process testing | Process analytical technology (PAT) utilized, process operations tracked andtrended |
| Product Specification | Primary means of quality control, based onbatch data | Part of the overall quality control strategy, based on desired product performance |
| Control Strategy | By testing andinspection | Risk-based controlstrategy, real-timerelease possible |

**Table: Traditional approach and Enhanced QbD approach [5, 12]**

## Pillars of QbD : [3]

1) Product design goal
2) Process design space
3) Control space
4) Operating space

**1.Product design goal:**

The many key quality attributes (CQA) that must be included in the product must be acknowledged in the quality target product profile (QTPP), which must be developed.The QTPP includes elements that characterise the product,

such as dosage form, dose strength, delivery method, route of administration, and intended use, among many other elements. CQA refers to the physical, chemical, biological, or microbiological properties of a product that must fall within a given range, distribution, or limit in orderto guarantee that the product has the intended quality. Characterizing a substance's

solubility, stability, compatibility, etc. through tests is how to characterise its solubility,stability, compatibility, etc., and both QTPP and CQA provide a structure for the designing of the product and its understanding.[3, 13]

**2.Process design space:**

Internal and external batch variances are actually rather common in the pharmaceuticalindustry. The continuity of the design area can help to reduce these variations. A designspace is a "established multiscious combination and commerce of material qualities and process parameters exhibited to guarantee assurance of quality," according to ICHQ8.[14] Identification of crucial process parameters is aided by determining how mucha process variation may impact the quality of the final output (CPPs). When the designspace is specified, it becomes possible to anticipate issues and achieve greater processcontrol. With the use of product experience, validated experimental data, or literature assistance, the bounds of the sets of the parameter that is to be meliorated can be described.[3,15]

**3.Control space:**

A control space can be defined on the base of the process design space. It permit us tounderstand the processes in such a way that the quality of the product can be assured from the variability of the given product process, which permits a good control over multifarious product processes. This concept can be illuminated by thinking of dataset of a reference product having tightly varied data points representing the affair of a tightly controlled process. When the affair of this process is colluded and compared with a reference also it will show whether the process is in control or not. If a study ofDoE is conducted for a product right at the development stage, then several aberrations can be escaped on with the added advantages, which will lead to the elimination of various wasted efforts as well as the early determination of the root cause of accidentaladverse issues.[3, 15]

**4.Operating space:**

The best combination of statistically determined parameters, which can fluentlyaccommodate any variability being naturally in both CPPs and CQAs, is called as operating space. In case of generics, the operating space should lie within the boundaries of the control space allowing the testing of a reference product having a combination of same parameters, while in case of new products, the operating space should lie within the boundaries of the design space complying with nonsupervisory guidelines. A competitive advantage can be gained by the originators through a comprehensive disquisition of the design space carrying out tests on multiple formulation batches with the objective of refining their product.[15].

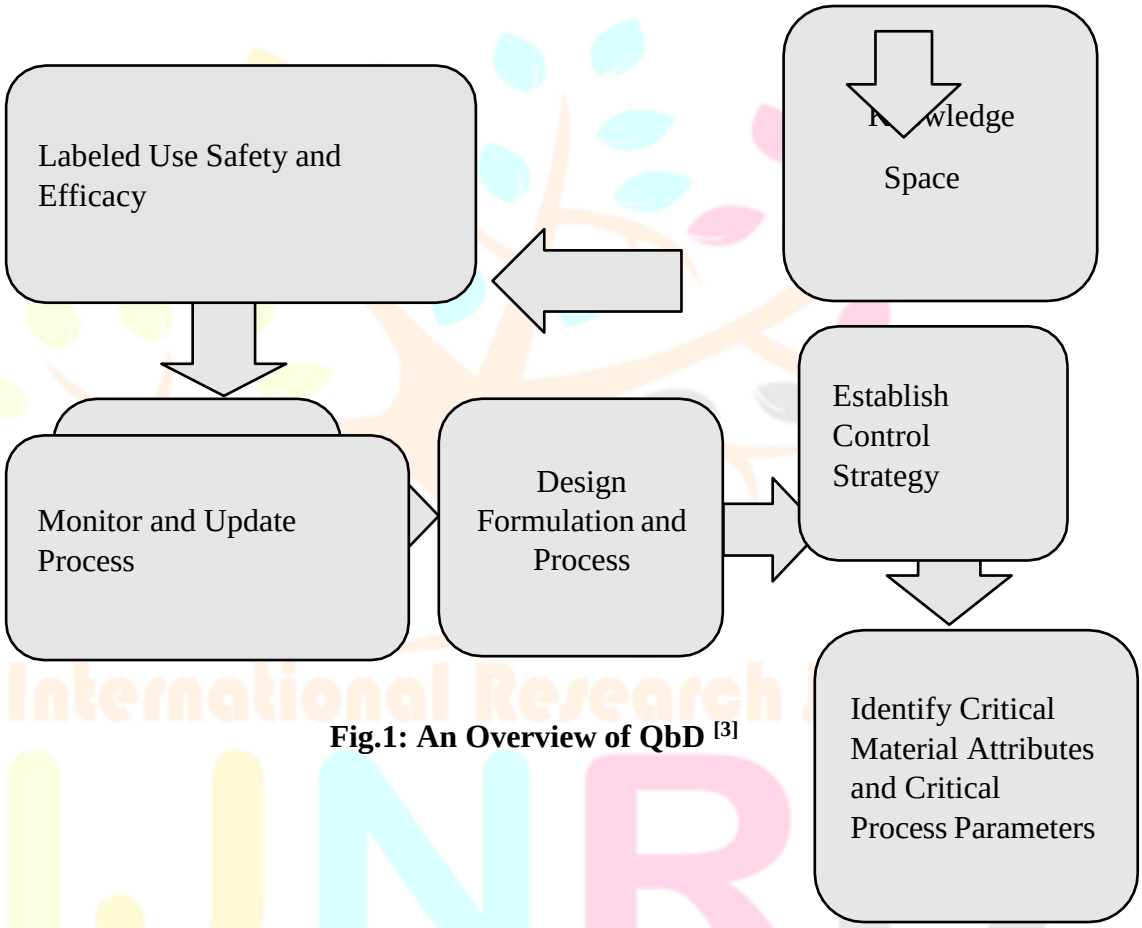


**Fig.1: An Overview of QbD [3]**

## Key Elements of Quality By Design:

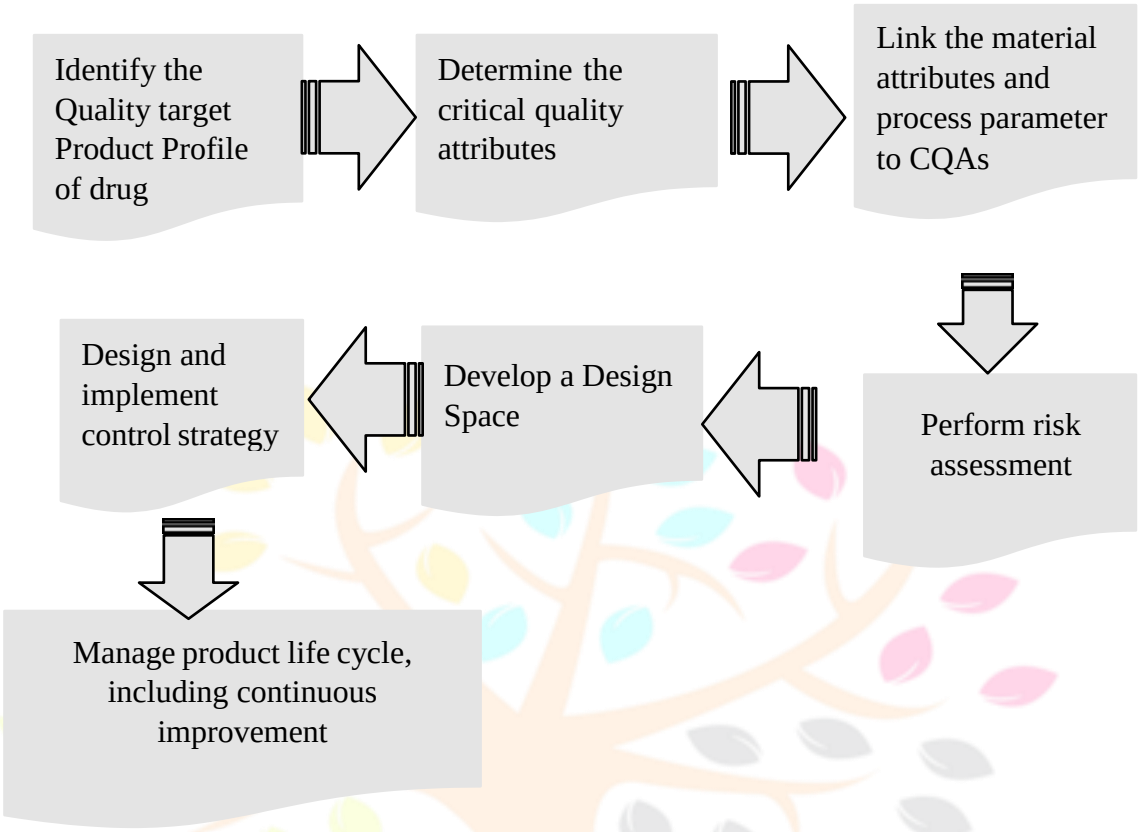


**Fig.2: Flow diagram of key elements of QbD [1]**

### 1) Quality Target Product Profile (QTPP):

Quality Target Product Profile (QTPP) is defined by ICH Q8 (R2) as "Expected summary of quality characteristics of a drug product that should be reached to establish the intended quality, taking into account safety and efficacy of the medicinal product." It plays a crucial role in the entire process of finding new drugsand developing them. Additionally, it aids in the efficient optimization of drug candidate decision-making within a regulatory body. The drug product must have certain qualities in order to consistently provide the therapeutic benefit stated on thelabel. It facilitates identification of what's needed for the in the patient in the Quality

Target Product Profile. The QTTP should be performance based and notmechanism based.[3, 13]

- Identifies risks and best approaches to manage.
- Uses tools in an optimised fashion
- Generates and enables knowledge sharing.

Quality Target Product Profile (QTPP) includes , but not limited to:

- Dosage form
- Route of administration

- Strength
- Release of delivery of the drug
- Pharmacokinetic characteristics

e.g., dissolution, aerodynamic performance

- Drug product quality characteristics for intended use

e.g., sterility, purity.[1]

**2) Critical Quality Attributes (CQA):**

Finding the pertinent CQAs is the next step after identifying the QTPP. Physical, chemical, biological or microbiological tests are considered CQAs. A quality or traitthat should fall within the specified range, limit, or distribution to guarantee the intended product quality.[6, 17]

Critical Quality Attributes(CQA) connected to materials are referred to as critical material attributes(CMA), and those related to processes are referred to as critical process parameters(CPP). Materials used to make pharmaceutical product, such as drugs and excipients, are known as critical material attributes(CMA). A thorough assessment of the drug ingredient should be done to its physical, biological, chemical and mechanical properties, such as its solubility, polymorphism, particle size, stability and flow property, as well as its compatibility with excipients.[6, 18] Example CQA for HPTLC method is TLC plates, mobile phase, Injection concentration and volume, plate development time, a reagent for colourdevelopment and detection.[5]

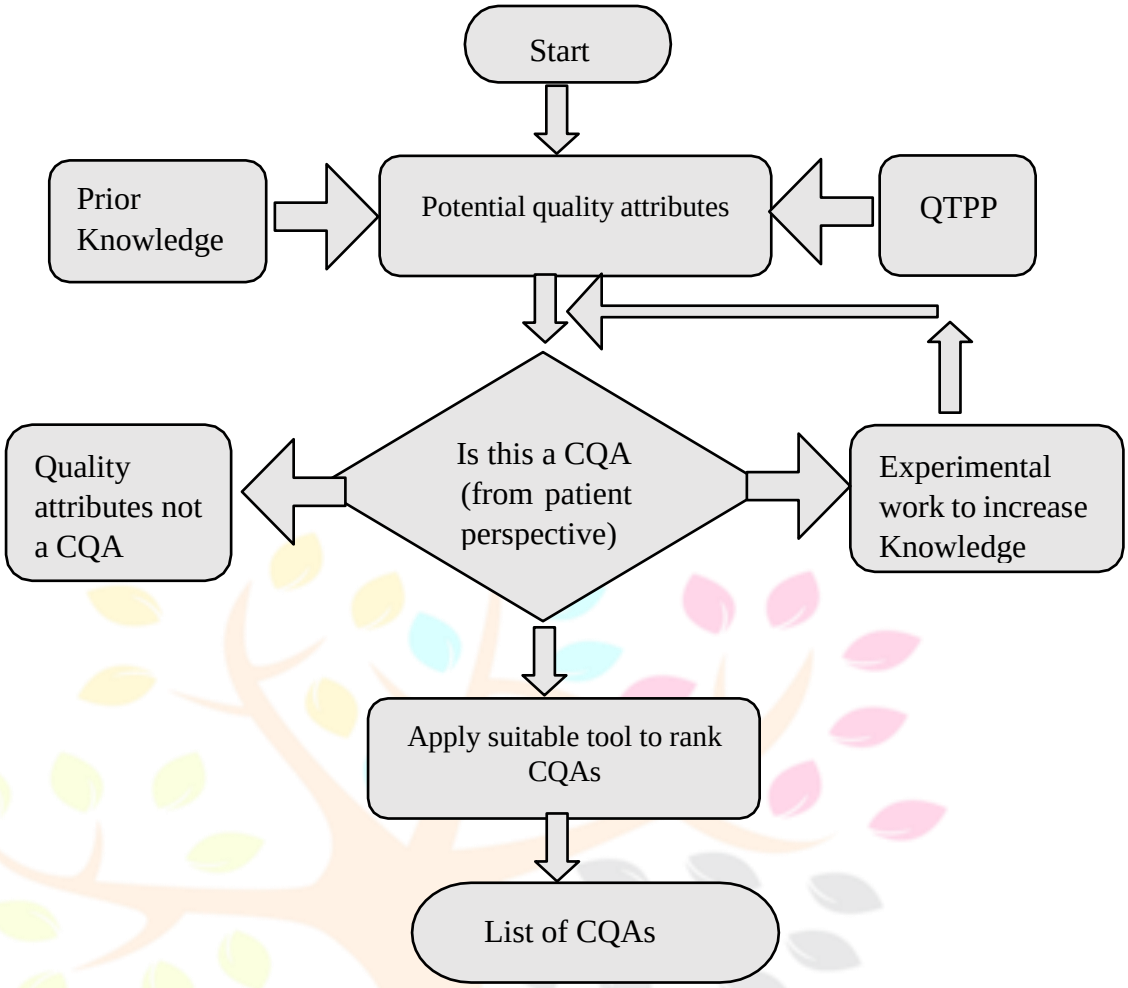


**Fig.3: Decision Tree to Decide CQAs [1, 16]**

**3) Critical Material Attributes (CMA) and Critical Process Parameters (CPP):Material attributes:**

Materials: packaging labelling materials, processing aids, reagents, solvents,starting materials, intermediates, and raw materials.

The examination of the relationship between drug substance and drug product is necessary for the identification of CQAs for drug products. It is crucial to performance to comprehend the functional properties of excipients. Important quality qualities are also influenced by the choice of salt, solid forms, particle size,and morphology.[2, 9]

The characteristics of a material can be measured, are normally fixed, but occasionally they can change with subsequent processing.[2, 18]

Examples include sterility, porosity, specific volume, and impurity profile.

**Critical process parameters**

Crucial quality qualities are impacted by a critical process parameter, or shoe. In order to guarantee that the process yields the desired quality, it should be watched over or managed. A pharmaceutical production process often entails a succession ofunit activities (such as mixing, milling, granulation, drying, etc.) to create a productof the specified quality.[2, 19]

CPPs are in charge of ensuring the CQAs, and a list of prospective CPPs is used toidentify them. Three types of parameters are available:

I. **Unclassified parameters:** It is unknown what criticalities apply to undeclared parameters. the additional information required to label a parameter that hasn'tbeen designated as critical or non-critical.

II. **Critical parameters:** When a parameter's realistic modification can result in the product failing to receive the QTPP, that parameter is considered to be critical.

III. **Non-critical parameters:** In the potential working space, no QTPP failure was noticed, and no interactions with other parameters were found within thestated, acceptable range.

Ex: Temperature, addition rate, cooling rate, pH, agitation.[18]

**4) Risk assessment:**

Risk is defined as the likelihood that harm will occur, regardless of its severity. It improves the standard of the method.[2, 20]

The ICH Q9 guidelines state that risk assessment is a systematic method for evaluating, controlling, communicating, and reviewing risk to quality throughout the product life cycle. Three steps are involved in risk assessment: risk identification, risk analysis, and risk evaluation. Identifying and ranking potential risks is a crucial initial step in the risk assessment process. Risk evaluation is the next phase in the risk assessment process. Risk assessment, commonly known as Ishikawa, is carried out using a fishbone diagram. The risk factor is classified into three groups in accordance with these approaches: high-risk factor, noise factor, andexperimental factor.[5]

**Risk Assessment Methods :[6]**

The risk assessment can be determined by various methods which are as follows:

i. Failure Mode Effect Analysis
ii. Failure Mode Effect And Criticality Analysis
iii. Fault tree Analysis
iv. Hazards Analysis and Critical Control Point
v. Hazards Operability Analysis
vi. Preliminary Hazard Analysis
vii. Risk ranking and Filtering.

**5) Design Space:[4]**

The multidimensional combination and interaction of input factors (such as material qualities) and process parameters that have been shown to give assurance of qualityare referred to as Design Space by ICH Q8 R2. Moving outside the Design space isregarded as a change and typically starts a regulatory postapproval change process.

Working inside the Design space is not regarded as a change. The recognised rangeof formulation features and process parameters that have been shown to provide assurance of quality is known as the design space. It serves as the connection between manufacturing design and development.

For a single unit operation, a number of unit operations, or the full process, a designspace may be built. A method of securing the FDA's approval is through submittinga design space.

**Use of Design Space:**[3, 21]

- Linkage between process inputs such as inputs variables and processparameters and critical quality attributes (CQAs).
- Use for more than one-unit operations or upto complete process.
- Can be implemented prior or after MA.
- Presented by Applicant.
- Working between the design space.
- Subject to regulatory approval and evaluation.

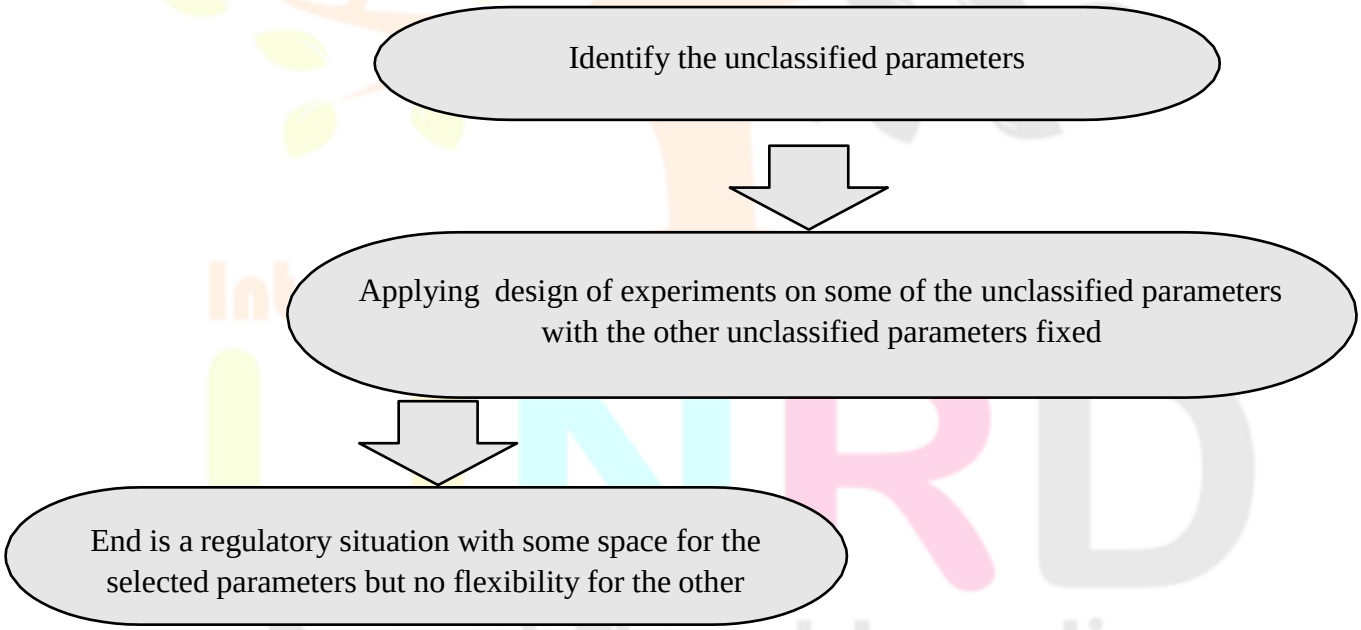


**Fig.4: Steps to Design Space** [1]

### 6) Control Strategy :[2]

"A designed set of controls, generated from current product and process informationthat insures process performance and product quality" is the definition of a control strategy. To make sure that the material and process are within the anticipated lowerand upper limits, a control plan is needed. It aids in fault avoidance and upholds target quality. Design space should contain the control space. The reproducibility and robustness of a process are traced by QBD, together with the process capacity index expression.

Control strategies that are used to guarantee consistent quality may include input material control, process controls, and monitoring, design space to end product specifications.

**Elements of control strategy[2]**

- Procedural control
- In-process controls
- Batch release testing
- Process monitoring
- Comparability testing
- Constancy testing

The risk assessment used to determine the control plan in the QBD standard carefully considers the CQAs. Example: Impurity date mapping (IFM), which mapsthe destiny of impurities throughout the process by identifying their sources in rawmaterials and processes. Impurity removal is a crucial component of a control approach.[2, 22]

### 7) Product life cycle and continuous improvement:[2, 23]

The quality of a product can be enhanced over the course of its existence. Businesseshave the chance to assess contemporary approaches to enhance product quality. Toensure quality consistency, process performance can be tracked. Within the company's internal quality system, routine maintenance can be carried out.

A crucial component of a contemporary quality system is continuous improvement.QBD emphasises product quality as well as ongoing process improvement and variability reduction.

Pharmaceutical Quality System is the foundation for ongoing improvement (PQS).It aids in identifying and putting into practise relevant process, variability, and product quality improvements, boosting the ability to meet quality standards.

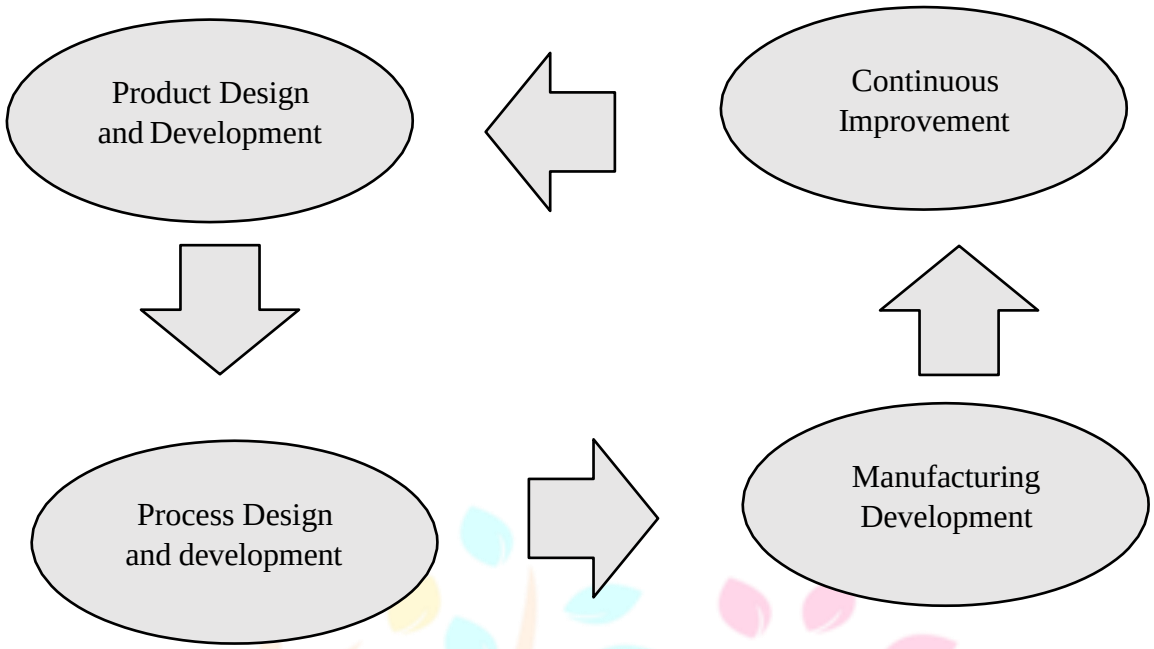


**Fig.5: Product Lifecycle Management[6]**

## Tools of Quality By Design:[6]

### 1.Design of Experiments (DOE):

Design of trials (DOE) is a useful method for organising trials so that the collecteddata can be analysed to produce reliable and impartial results. "Design of experiments". refers to a planned, systematised method for figuring out howelements influencing one process and its outcomes relate to one another. Choosing the process parameters for the study and choosing the right trial design are the firststeps in DOE.

### 2.Use of Design of experiments:

• Design of experiments is used to identify the variables that affect response variability, to identify the circumstances that produce the best (maximum or lowest) responses at various levels of controlled variables, and to create a modelfor predicting response.

• The first step in DOE is to choose the study's process parameters and experiment's objective. A complete experiment is laid out according to a design.

### 3.Process Analytical Technology (PAT):

Numerous tools are provided in the PAT framework to help with understandingscientific, risk-managed pharmaceutical development, manufacture, and qualityassurance. The PAT guidelines state that these tools can be divided into four classes.[3, 13]

1) Multivariate tools for design, data acquisition and analysis;
2) Process analyzers;
3) Process control tools;
4) Continuous improvement and knowledge management tools.

As defined by FDA's PAT guidance document whether to remove the sample ornot, process analysis can be divided into three categories as:

i. Atline Measurement

ii. Online Measurement

iii. In-line Measurement

## Advantages of Quality By Design:[6]

- It provides a higher level of assurance of drug product quality.
- It offers cost savings and efficiency for the pharmaceutical industry.
- It makes the scale-up, validation and commercialization transparent, rational andpredictable
- It reduces potential compliance actions, costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It more focused post approval CGMP (Current Good Manufacturing Practices)inspections.

## Applications of Quality By Design:[3, 24]

1. For Chromatographic technique

a. In determination of impurity

b. In screening of column used in chromatography

c. In method Development of drug product substance using HPLC

2. For hyphenated techniques like LC-MS

3. In bioanalytical method development with precision and accuracy

4. In dissolution studies for testing release of drug 5. For Spectroscopicmeasurement

a. In mass spectroscopy

b. In IR spectroscopy

c. In handling complex spectroscopic data

6. In modified release products

7. In tablet processing

8. In compatibility study analysis of API and Excipients

9. In Biopharmaceuticals

10. In Biotechnological Products

11. In formulation and processing of protein liposomes

## CONCLUSION:

An essential component of the contemporary approach to pharmaceutical quality is quality by design. If correctly implemented and viewed in conjunction with the currentglobal harmonisation of regulations and risk, QbD should be viewed for what it has togive as opposed to what it raises concerns about. Establishing a trustworthy method that can be used with a high degree of assurance to create data that consistently meetsstated criteria when operating within defined bounds is the aim of a well-characterizedmethod development endeavour. With DoE and risk assessment as its tools to better understand the materials and processes, QbD is a cost- and timeeffective design and manufacturing approach. This makes QbD available and practical for the pharmaceutical industry.

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