Implementation of Qbd & AQbD approach in pharmaceutical formulation and analytical method development: A Comprehensive Research-Review

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ABSTRACT

In pharmaceutical terms, quality means a product free from any contamination and delivers the intended therapeutic benefit. The pharmaceutical sector is always seeking for new ways to guarantee and improve the product's efficacy, quality, and safety. Contrary to what recent medicine recalls, manufacturing failure costs, scale-up challenges, and regulatory burdens would imply, along with little knowledge of the process and important process parameters, the traditional Quality by Testing (QbT) strategy mostly relies on end-product testing to verify product quality and performance. QbD (Quality by design) is one of the in-process design experiments approved by the FDA to maintain the quality of the drug products before reaching into the market. QbD makes cost-efficiency and an easy production procedure a reality in the pharmaceutical business. QbD is a methodical, risk-based, proactive strategy to drug development that starts with predetermined goals and stresses product and process understanding as well as process control grounded on reliable research and high-quality risk management. QbD has its perspectives to contribute the drug design, development, and manufacture of high-quality drug products in the modern era of pharmaceuticals. The main aim of this review article to showcase a detail overview on QbD along with its elements (QTPP, CQA, CPP, CMA, Design space, control strategy and continuous implementation), tools (risk assessments, DoE and PAT), process of implementation (FDA and ICH guidelines), QbD role in different continents, opportunities in implementing QbD, future prospects of QbD and other features like Quality Risk Management, Pharmaceutical Quality System and Process Analytical Technology (PAT) guidelines are also being now introduced and involved into analytical method development processes. They are accepted as AQbD (Analytical Quality by Design) concepts by the industry.

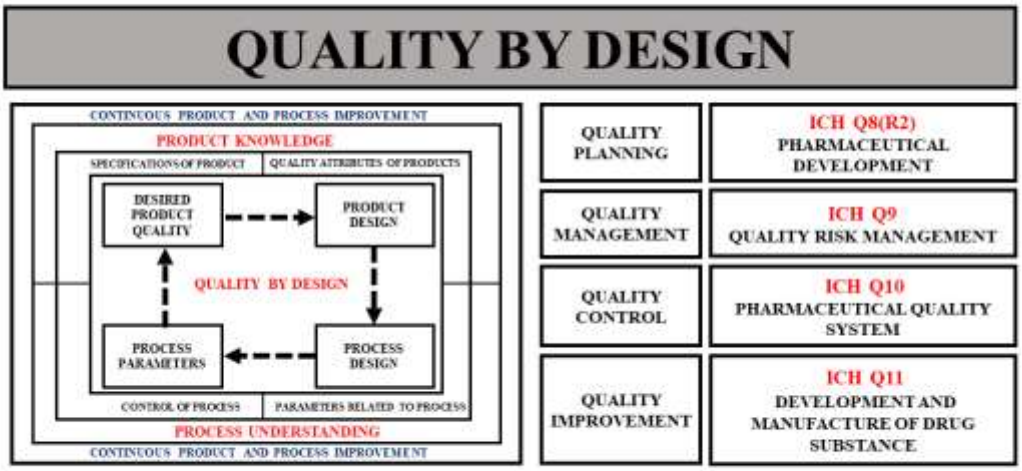
Keywords: Quality by Design (QbD), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Process Analytical Technology (PAT), Analytical Quality by Design (AQbD)

1. INTRODUCTION

Quality is one of the fundamental criteria in addition to safety and efficacy for any entity to be qualified and approved as a drug to give its desired therapeutic effects. Further, it is the foundation that allows patients and consumers to have confidence in the safety and effectiveness in their medications. For ensuring consistency of performance of pharmaceutical products and systems, emphasis has been made on building the "Quality" rather than testing it merely [1-2]. In pharmaceutical terms 'quality' means a product free from any contaminations and delivers the therapeutic effects specified on the label at a reproducible rate which can be assessed by carrying out *in-vitro* and *in-vivo* tests for performance evaluation [3]. Quality has been given a huge importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction with respect to service, product, and process. These quality related activities reflect the need for companies to excel in worldwide competition. Perfection in quality, reliability, low cost and timely performance are the major customer demands. Quality activities must try to detect the problems in quality early enough to permit actions without any compromise in cost, schedule or quality. The emphasis must be on the prevention rather than correction of problem occurring in the quality as error in the quality can be the leading cause of disturbance in other parameters. Therefore, quality has to be built in the product along with the services through appropriate planning, so, the upcoming failure can be avoided. Testing of the final product will not work but the quality must be design in the product [4]. In an attempt to curb rising development costs and regulatory boundaries to

innovation and creativity, the Food and Drug Association (FDA) and International Conference of Harmonization (ICH) have started promoting Quality by Design (QbD) in pharmaceutical industries [5-6].

The concept of Quality by Design (QbD) was introduced by the quality pioneer Dr. Joseph M Juran. Quality by Design (QbD) is defined by International Conference of Harmonization (ICH) Q8 (R1) guidelines 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" [7-9]. The primary goal of drug manufacturing is to provide a higher quality-based product and ensure that acceptable quality is reliably produced. Technological expertise is needed to access data collected from experimental studies and manufacturing to acknowledge design, specifications, and system control authenticity. Alterations in the manufacturing process, preparation and development are seen as opportunities to gain new knowledge or stimulate system design development. Quality by Design (QbD) is science of developing and building formulations and products lines that match the predestined criteria [10-15]. Like others regulatory guidelines, such as; International Conference of Harmonization (ICH) Q8, Q9, Q10, and current guidance documents, current good manufacturing procedures (cGMP), Food and Drug Administration (FDA), currently, the principles of QbD have gained popularity for several interventions in drug discovery in the 21st century. QbD model helps to avoid sampling errors and variability in investigations, escaping from prolonged experimentations, preventing complications with governing compliance, and enhancing production alternatives



[16-27].

Figure-1: Overview of Q bD system

1.1. Historical background and FDA's implementation

Joseph M. Juran, a well-known quality expert, was the first one to draw the idea of QbD. In later **1990,** an internal discussion began in FDA which concluded in the form of a conceptual paper in 21st century Good Manufacturing Practice (cGMP) which was published in the year **2002**. Initially, the application and understanding of QbD were explored by starting several pilot programs with the help of various pharmaceutical companies [28]. The pilot program intends consistent implementation of ICH guidelines Q8, Q9, Q10, Q11 between Europe and USA in the process of assessment and regulatory decisions to facilitate sharing on new regulatory concepts. Hence, regulatory bodies all over the world are showing curiosity for QbD [29-30]. Further, several programs were set forth by FDA including QbD Chemistry, Manufacturing, and Controls (CMC) pilot

programs (such as; Office of New Drug Quality Assessment (ONDQA) CMC pilot program started in July **2005** and FDA's office of biotechnology products pilot program in July **2008**) [31].

In **2007** FDA received an around 5000 supplements, it was actually a striking raise in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological License Applications (BLAs) and Abbreviated New Drug Applications (ANDAs). FDA recognized that there is an increase in lapse of NDA and ANDA submissions by the firms, huge number of supplemental applications for every manufacturing change were received. In both original applications and supplements the main focus of data was on chemistry and least attention was given on other important aspects of manufacturing such as product development, engineering [4].

In March **2011**, a pilot program was launched by EMA and FDA to assess certain qualities/Chemistry Manufacturing Control (CMC) section like design space, development and actual time release testing by both agencies in relevance to QbD. With industry sponsors and other FDA offices, ONDQA has been working to give confidence to use QbD in New Drug Application (NDA) and which has received attention for new drug entities. However, from FDA's perspective, there still exist challenges in the implementation of QbD [33-36].

1.2. Goals and Objectives of QbD

Pharmaceutical QbD is a systematic approach for the development that begins with a predefined objectives and emphasizes on product and process understanding and control based on sound science and quality risk management [37-38].

The goals of pharmaceutical QbD may include the following [39]:

1. To achieve meaningful product quality specification that is based on clinical activities.
2. To enhance process capability and reduce product variability and defects by enhancing product and process design, understanding and control.
3. To increase pharmaceutical product development and manufacturing efficiencies.
4. To improve post-approval change management and root cause analysis.

1.3. Characteristics of QbD

The characteristics of pharmaceutical QbD may include the following [40-41]:

1. It is an approach for development of efficient drug product.
2. It is a dynamic and systematic process/ approach.
3. This approach relies on the concept that quality can be built in as a continuum.
4. It is applicable to both drug product and drug substance development (chemicals biologics).
5. It is also applicable to analytical methods.
6. Can be used at any time in the life cycle of the drug.
7. Always encouraged by regulators.

1.4. Role of QbD

The role of pharmaceutical QbD may include the following [35,42]:

1. QbD ensures that the designing of a product is made in a way to accomplish the needs of the patient and requirements for better performance.
2. Also, with QbD implementation, the designing of the process is done in a way to meet the Critical Quality Attributes (CQA) of the product consistently.
3. With QbD implementation, it becomes easy to attain the understanding of the influence of process parameters and starting raw materials on the quality of the product.
4. Critical sources of process variability are controlled and identified by means of suitable control strategies.
5. QbD ensures the continuous monitoring of the process and also it has to be updated constantly in order to maintain consistent quality over time.

1.5. Quality by Testing (QbT) v/s Quality by Design (QbD)

Pharmaceutical development and manufacturing by Quality by Design (QbD) can be explained against traditional/conventional or Quality by Testing (QbT) approach [1,43-44]:

Aspects	Conventional/traditional/ QbT approach	QbD approach
Definition	Quality assured by testing and inspection	Quality built into product & process by design, based on scientific understanding
Pharmaceutical development	Empirical; typically, univariate experiments	Systematic; multivariate experiments
Manufacturing process	Fixed process	Adjustable within design space; opportunities for innovation (PAT)
Process control	In-process testing for go/no-go; offline analysis with slow response	PAT utilized for feedback and feed forward at real time
Product specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; Control shifted upstream; real time release
Lifecycle management	Reactive to problems & OOS; Post-approval-changes needed	Continual improvement enabled within design space
Starting point	Start with hit and trial approach to meet method intent	Start with pre-defined objectives (ATP)
Type of process	Frozen process, discouraging changes	Flexible process within design space, allowing continuous improvement
Method performance	Method performance evaluated during validation	Focus on performance through establishment of ATP
Analytical variables	Limited understanding of analytical variables	Systematic evaluation of individual variables and interaction effects(s)
Method quality	Method quality based on method validation	Performance qualification is assurance of method quality
Method verification	Method verification and transfer are separate exercise	Performance qualification and verification are continuous exercise throughout life cycle
Changes	No regulatory flexibility with respect to changes	Working within MODR would not be considered as change, reduces post-approval changes
Focus	Focus on reproducibility-often avoiding or ignoring variation	Focus on robustness-understanding and controlling variation
specification	Specification based on batch history	Specification based on product performance requirements
Space for improvement	No space for further improvement	Flexibility to implement continuous improvement
Submissions	Data intensive submission- disjointed information without “big picture”	Knowledge rich submission-showing product knowledge and process understanding

Table-1: Quality by Test (QbT) v/s Quality by Design (QbD)

1.6. Advantages of implementing QbD

The QbD have numerous advantages. The various advantages of pharmaceutical QbD are [45-50]:

1. It involves both the patient safety and efficacy of the product.
2. The scientific understanding of the process involved in the manufacturing of the product can be done easily.

3. It includes both product design and process development.
4. The science-based risk assessment can be carried out by this approach.
5. It is a robust process.
6. Critical quality attributes are identified and their effect on final quality of product is analysed.
7. It offers an advanced assurance level of quality of drug product.
8. It is cost effective.
9. The transparency of the sponsors can be increased with QbD which results in better understanding of the control strategies for the drug product in order to achieve approval and finally commercialization.
10. The scale-up, validation and commercialization can become rational, transparent, and predictable with QbD implementation.
11. It increases the efficiency of pharmaceutical manufacturing processes.
12. It reduces high penalties and drug recalls.
13. It provides more efficiency for regulatory oversight.
14. It updates regulatory processes and post-approval manufacturing changes.
15. For first cycle approval, it enhances opportunities.
16. It assists in continuous improvement and reduces the computer (CMC) supplement.
17. It enhances the quality of Chemistry, Manufacturing and Control (CMC) and reduces the CMC review time.
18. Improves information in regulatory submissions.
19. Regulatory flexibility.
20. Reduces product variability.

1.7. Disadvantages and challenges of implementing QbD

Basically, research has highlighted a number of difficulties that might arise in the application of QbD. These highlighted difficulties outline numerous areas that FDA may take into account to hasten the implementation of QbD. The actions that FDA takes become extra noticeable when applied to the subdivisions viz. type of drug and adoption level. The challenges for QbD implementation include the harmonization of terminologies and concepts, training and education of human resources for industries and regulatory agencies, and the need of guidelines regarding documentation of knowledge generate during pharmaceutical and/or method development [51-52].

The following are the challenges to generic drug and new drug development in implementing the QbD approach [53-56]:

1. Expectations for QbD-based submissions while addressing traditional requirements.
2. Training is also a major challenge, and therefore regulatory authorities and industry should conduct the training programme for the implementation of the QbD concept.
3. Establishing appropriate / expected level of detail in regulatory submissions (types and extent of data in future CMC submissions).
4. Achieving regulatory flexibility while assuring product quality.
5. Establishing balance between QbD-based versus traditional demonstration of quality.
6. Sharing proprietary information with regulatory groups.
7. Different strategies / approaches to accommodate diversity of drug products:
    - Small chemicals versus large biological
    - Oral solids versus complex / novel drug delivery systems (novel dosage form)
    - Drug versus combination products
8. A potential regulatory strategy–CMC Regulatory Agreement.
9. Lack of understanding and trust.
10. Associated costs to implement QbD into product development and manufacturing unit operations (business and marketing decisions).
11. Different regulatory processes (BLA, NDA, ANDA, follow-on and so on) and associated regulatory practices and culture; Integration of review and inspection
12. Workload
13. Resources for assessment; and Cultural changes needed in industry and FDA.

1.8. Limitations of implementation of QbD

The limitations of implementation Pharmaceutical QbD are as follows [57-58]:

1. QbD brings more questions and scrutiny and also delays in approvals.
2. Leads to pre-approval inspection which leads to approval delays.
3. Design of Experiments (DoE) and design space are identical.
4. "Criticality and Risk" means that the criticality of a parameter is controlled, when it is restricted

1.9. Applications of implementing QbD

The use of Quality by Design (QbD) tools during the creation of pharmaceutical goods is regarded as "the best" strategy to ensure product quality for the benefit of patients. QbD is therefore pervasive across the whole process of product development and may be seen as a flexible instrument for ensuring the safety and effectiveness of pharmaceutical goods in order to satisfy customer demand. Applications of Quality by Design are as follow [59-60].

1. For Chromatographic technique;
    a. In determination of impurity
    b. In screening of column used for chromatography
    c. In development of HPLC method for drug products substance
    d. In capillary electrophoresis
    e. In stability studies
    f. In UHPLC
2. For hyphenated technique; In LC-MS method development.
3. In bioanalytical method development.
4. In dissolution studies.
5. For spectroscopic measurement;
    a. In mass spectroscopy
    b. In IR spectroscopy
    c. In handling complex spectroscopic data
6. In modified release products.
7. In tableting process.
8. Nano-suspension preparation
9. In analysis of API and Excipients.
10. In Biopharmaceuticals

1.10. Future prospects of implementing QbD

QbD looks ready to become rapidly important for the pharmaceutical industry as more and more companies are looking to increase production output, reduce throughput times, and costs effective by shifting from batch production to continuous manufacturing. However, for these "always on" procedure, it's just isn't possible to perform quality testing within a series of continuous process steps in the same way as it is following each operation of a batch process. Additionally, as FDA, EMA, and other regulatory bodies further scrutinize production processes to ensure the highest levels of safety, QbD will make it easier for companies to demonstrate that they are operating within acceptable limits. As regulatory authorities start to insist that companies design quality into products at every stage of the pharmaceutical value chain, the use of QbD will become much more important [61]. Nowadays, several firms are starting to accept the concepts of QbD principle and designing frameworks to help it, as shown by incorporating one or even more QbD components into the production, indicating a positive move into QbD as the future development model. The foremost reason for QbD acceptance is regulatory criteria. The pharmaceutical as well as medicinal company needs regulatory enforcement in order to obtain the goods approved for distribution. Even so, the QbD solution produces a high-quality service by using cost-effective techniques. By offering a design space model, QbD eliminates the commonly utilized frizzed method to system development. Since it is not used among drug companies, it has a bright future when regulatory authorities require it. Due to the numerous benefits and flexibility of complying

with regulatory bodies, companies can voluntarily follow this principle. QbD enables the production of reproducible goods with the necessary quality regimen. It is a method of developing biological that is systemic in order to avoid errors and reduce uncertainty in product consistency. Creating new drug formulations is a difficult task that costs a lot of money. Utilizing QbD guarantees production performance from the start, reducing costs in producing the ideal composition. As a result, it has a lot of potential in producing high-quality pharmaceutical drug products [62-66].

2. ELEMENTS OF QbD

In a pharmaceutical QbD approach for the product development, an applicant identifies characteristics that are critical to quality from the patient's perspective, translates them into the drug product critical quality attributes (CQAs), and establishes the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product with such CQAs to the patient. QbD consists of the following elements [9]:

1. A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) and Critical Process Parameters (CPPs) of the drug product.
2. Product design and understanding including the identification of critical material attributes (CMAs).
3. Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs.
4. A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process.
5. Process capability and continual improvement.

QbD means 'building in quality from the development phase and throughout a product's life cycle or designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains predefined quality at the end of the manufacturing process [67-68]. In order to address GMP's limitations, the FDA introduced cGMP in the year 2002. According to cGMP, the focus on "software" throughout the production phase, especially at the managerial level, precisely defines the transparency of workers. The ICH Q8 framework defines QbD as a systematic approach for development, which begins from predefined targets and emphasizes process and product evaluation with tracking, based on validated quality and process risk assessment. The various research studies of drug development and industrial experience offer knowledge and experiences that help create quality standards and controls [69-72]. QbD includes the following elements:

1. Quality Target Product Profile (QTPP)
2. Critical Quality Attributes (CQAs)
3. Critical material attributes (CMA)
4. Critical Process Parameters (CPP)
5. Design space
6. Control strategy
7. Continuous improvement

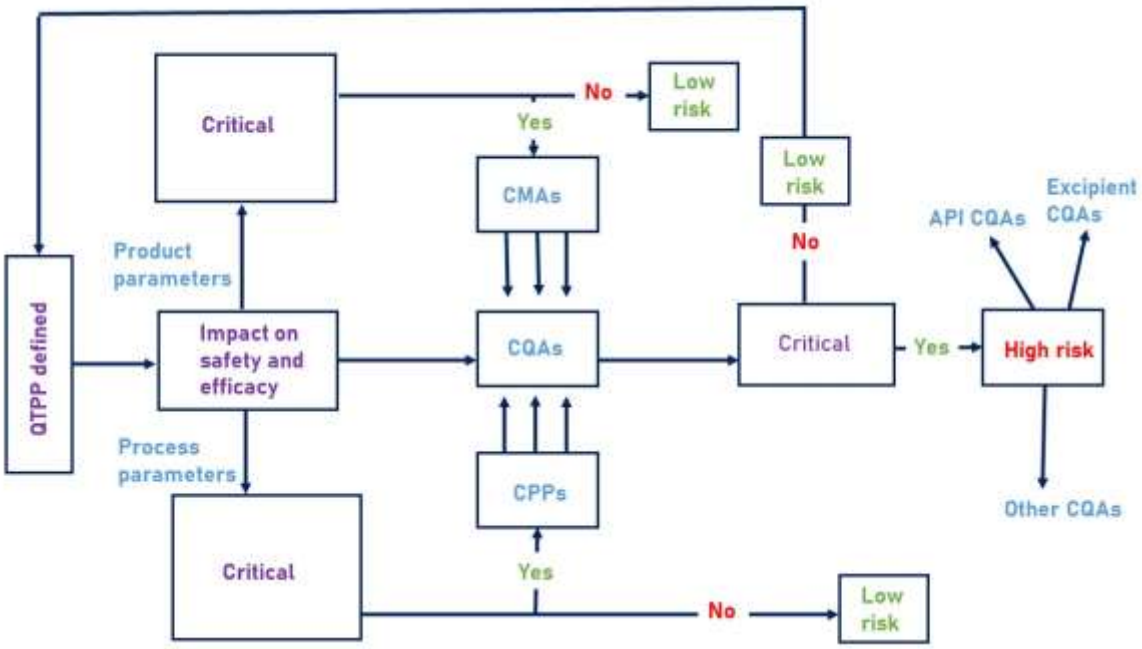


Figure-2: Fundamental elements of QbD

2.1. Quality Target Product Profile (QTPP)

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP forms the basis of design for the development of the product. Considerations for inclusion in the QTPP could include the following [9,37]:

1. Intended use in a clinical setting, route of administration, dosage form, and delivery system(s).
2. Dosage strength(s);
3. Container closure system;
4. Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed.
5. Drug product quality criteria (e.g., sterility, purity, stability, and drug release) suitable for the intended marketed product.

Target Product Profile TPP is usually accepted as a tool for setting the strategic foundation for drug development planning with the end in mind. Recently, a broaden use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions and risk management has started to evolve. The target profile is a summary of the drug development process described in the context of giving information goals. TPP has also been defined as a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to evolve the desired quality and thus the safety and efficacy, of a drug product is known. It may also play a central role in the entire drug discovery and development process, in the following ways [9,67,73]:

1. Effective optimization of a drug candidate;
2. Decision making within an organization;
3. Design of clinical research strategies; and
4. Constructive communication with regulatory authorities.

TPP links drug development activities to specific statements intended for inclusion in the drugs label. It also leads to formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. For example, a typical TPP of oral suspension would include the following [67]:

a) Dosage form;
b) Route of administration;

c) Dosage form strength;
d) Oral suspension characteristics;
e) Identity; Assay and uniformity;
f) Purity / impurity profiling;
g) Stability;
h) Dissolution;
i) Pharmacological category;
j) Indication;
k) Contraindication;
l) Adverse reaction;
m) Precaution;
n) Overdose; and
o) Drug abuse and dependence.

The TPP of a generic drug can be readily determined from the Reference Listed Drug because a generic must contain the same active ingredients as the original formulation. According to the FDA, generic drugs are identical or bioequivalent to the brand name counterpart with respect to pharmacokinetic and pharmacodynamics properties. By extension, therefore, generics are identical in dose, strength, route of administration, safety, efficacy and intended use. The concept of TPP in this form and its application is novel in the QbD paradigm. The Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label [74-75].

2.2. Critical Quality Attributes (CQAs)

Once QTPP has been identified, the next step is to identify the relevant CQAs. The CQA element is very important and it is associated with the raw materials, intermediates as well as the drug products. It is studied that CQA is a subset of QTTP that changes with the change in the different formulation variables [76-77].

A Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be controlled within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with drug substance, excipients, intermediates and drug product. Drug product CQAs include the properties that impart the desired quality, safety and efficacy. The CQAs are commonly related to the drug material, inert components, intermediate inputs (additives or excipients), and the dosage form itself. CQAs typically effect the characteristics of drug products, like particle sizes, drug release, solubility, zeta potential, entrapment efficiency, product yield, and drug loading. CQAs of solid oral dosage forms are typically those aspects affecting product purity, potency, stability and drug release. CQAs for other delivery systems can additionally include more product-specific aspects, such as aerodynamic properties for inhaled products, sterility for parenteral and adhesive force for transdermal patches. For drug substances or intermediates, the CQAs may also include the properties such as, particle size distribution, bulk density that affect downstream process ability. A list of typical CQAs for drug substance, solid and liquid dosage form is mentioned below [52,79]:

For Drug Substance (chemical)	For tablets (solid dosage form)	For oral suspension (liquid dosage form)
Appearance	Appearance	Particle size and particle size distribution
Particle size	Identification	Density of drug substance and dispersion medium
Morphic forms	Hardness	Particle shape
Water content	Weight uniformity (API)	Polymorphic form
Residual solvents	Uniformity of dosage	Content uniformity
Moisture content	Physical form	Dissolution
Organic impurities	Dissolution	Order of addition of ingredients
Inorganic impurities	Degradation products	Viscosity (concentration of suspending agent)

Heavy metals	Water content	pH of suspension
Assay	Microbiological limits	Zeta potential of the drug substance
		Quality and quantity of the drug substance and excipients

Table-2: Typical CQAs for drug substance, solid and liquid dosage form

Identification of CQAs is carried out through the risk assessment as per the ICH Q9 guidance.

2.3. Critical Material Attributes (CMAs)

The mechanical, physical, microbial, or biological characteristics or qualities of raw materials are described as Critical Material Attributes (CMAs). CMAs are utilized during the context of a suitable range collection or production to assure that product content and excipients are consistent [17]. This information serves as a foundation for applying the CQA to the product's effectiveness. CQAs are concerned with production parts, while CMAs are concerned with raw resources, like drug products and inert materials used in the manufacturing process [9,17,81].

CMAs are the pivotal elements that directly influence the CQAs. These are defined as the physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of drug products. Initially, the material attributes (MAs) influencing the CQAs are screened first on the basis of their criticality, where only vital few material attributes are identified as the CMAs. These primarily include active and inactive input raw materials or excipients, which possess direct link with drug product CQAs [4,60,82].

2.4. Critical Process Parameters (CPPs)

Like CMAs, the CPPs are related to the intended process(es) used for manufacturing of drug products and possess direct influence on the CQAs. In different circumstances, these are the key variables which can affect the process performance and variability in product quality. A traditional risk assessment approach is used for identifying the criticality of process parameters. With the screening approach in place, only the vital few process parameters are identified as CPPs from the possible few process parameters. Apart from CPPs, the process parameters without having any variability of its impact on CQAs are discriminated as non-Critical Process Parameters (non-CPPs) [83-84]. Critical Process Parameters (CPP) are defined as any measurable input such as input material attribute or output such as output material attribute of a process step that should be controlled to achieve the desired product quality as well as process uniformity [85]. A realistic change in CPP can cause the product to fail or to meet the QTPP, which can affect the scale-up process and for process design and understanding [32,86-87].

For example, a material attribute, such as moisture content, should consist of the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

For a given unit operation, there are four categories of parameters and attributes:

1. Input material attributes;
2. Output material attributes;
3. Input operating parameters;
4. Output process state conditions.

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. Unit operations may be executed in batch mode or in a continuous manufacturing process. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when [9,88];

(1) All critical sources of variability are identified and explained;
(2) Variability is managed by the process, and
(3) Product quality attributes can be accurately and reliably predicted.

Process parameters are also known as the input operating parameters (e.g., speed and flow rate) or process state variables (e.g., temperature and pressure) of a process step or unit operation. A process parameter is critical when its variability has an impact on a critical quality attribute and therefore should be look after or controlled to ensure the process produces the desired quality [9,88].

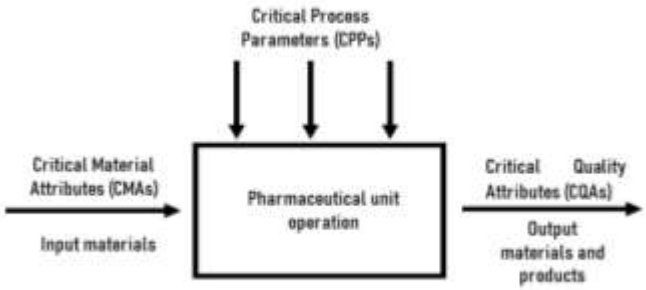


Fig-3: Link between input critical material attributes (CMAs) and critical process parameters (CPPs) to output critical quality attributes (CQAs) for a unit operation. [9]

2.5. Design space

To ensure product quality, in the existence of interacting critical process parameters, a “design space” is one approach. The “design space” is “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality”. FDA acquiescence of a design space is a path obtaining the capacity to function contained by that design space without additional approval from the regulatory bodies. There are various steps included in design space, and these are [5, 89-90]:

- Identify the unclassified parameters then.
- Applying design of experiments using the unspecified parameters by means of the further fixed unclassified parameters.
- Selection of selected parameters.

Design space is defined in the ICH Q8 guidelines (November 2007) as ‘the multidimensional and interaction of input variables (for example, material attributes) and process parameters that have been demonstrated to provide assurance of quality’. The definition itself is not self-expanding, and needs further elaboration by industry and regulators before it can be implemented in daily practice. A design space for a certain product proposed by the applicant is subject to regulatory assessment and approval [67,78]. This definition arises from early ICH Q8 drafts where design space was defined as, “The established range of process parameters that has been demonstrated to provide assurance of quality”. Methods for determining design space involves; one variable at a time experiments, statistically designed experiments, and modeling approaches. Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations, and models. Alternatively, the design space can also be explained mathematically through equations describing relationships between parameters for successful operation [91-93].

2.6. Control strategy

A control strategy is intended to consistently ensure product quality. Control strategy describes and justifies how in-process controls and the controls of input materials (drug substance and excipients), the container closure system, intermediates, and end products contribute to the final product quality. These controls should be based on product, formulation and process understanding, and should include, at a minimum, control of the critical parameters and attributes [67,78]. ICH Q10 characterizes a control technique as "an arranged arrangement of controls got from current item and procedure understanding that guarantees procedure execution and item quality. The controls can incorporate parameters and ascribes identified with medication substance and medication item materials and segments, office and hardware working conditions, in procedure controls,

completed item determinations and the related techniques and recurrence of observing and control." A control methodology typically incorporates information material controls, process controls and observing, structure space around individual or numerous unit activities, as well as definite item determinations used to guarantee reliable quality [32, 52, 94].

ICH Q8 (R2) also defines a control strategy as a "A planned set of controls, derived from current product and process understanding that assures process performance and product quality" [37]. The control strategy may include the following elements [5,9,37,89,95]:

- Control of characteristics of the raw material (e.g., drug substance, excipients and primary material for packaging) on the basis of an understanding of their influence on product quality or process ability.
- Procedural controls;
- Specifications of product;
- Control of facility like operating conditions, environmental systems and utilities;
- Controls for unit operations having an effect on end-product quality or downstream processing;
- A monitoring program for verifying multivariate prediction models;
- In-process controls;
- Lot release testing;
- Process monitoring;
- Characterization testing;
- Compatibility testing and;
- Stability testing.

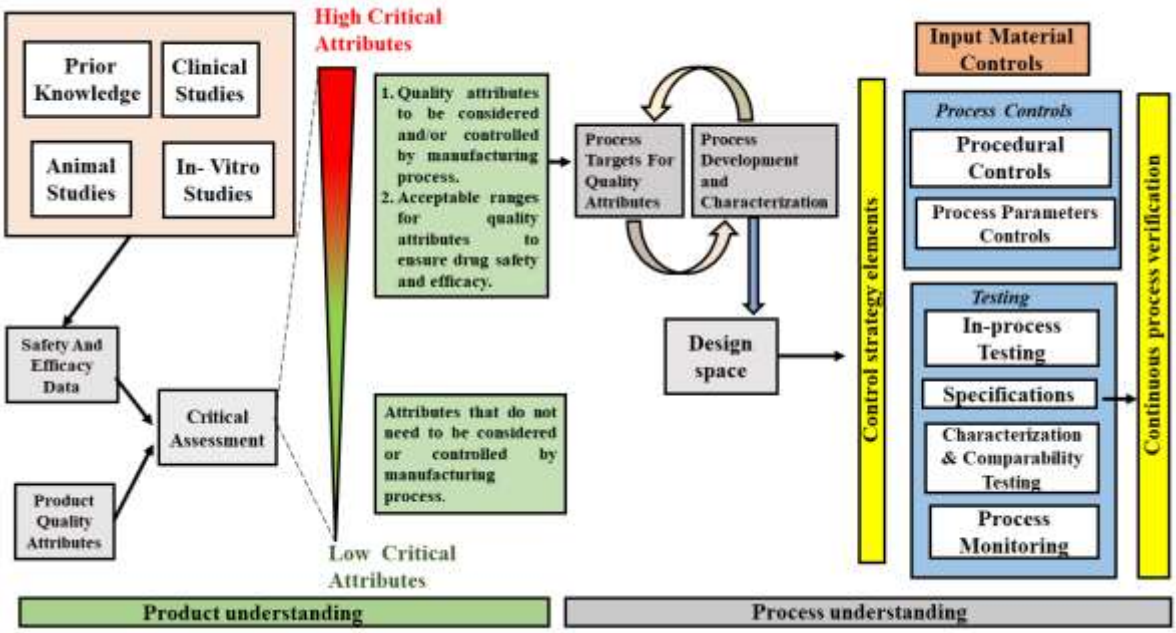


Figure-4: Control strategy: link between product and process understanding

2.7. Continuous improvement

With the implementation of QbD, the quality of the product can be improved throughout the life-cycle of the product. With this approach, the companies may have an opportunity of opting creative approaches for improving product quality, monitoring the performance of the process to ensure consistent quality. Maintenance can be done on periodic basis within the internal quality system of the company without making any changes in the design space [4,89].

Process capability can be used to measure process improvement through continuous improvement efforts that focus on removing sources of inherent variability from the process operation conditions and raw material quality. Ongoing monitoring of process data for C_{pk} and other measures of statistical process control will also

identify when special variations occur that need to be identified and corrective and preventive actions implemented. Continuous improvement is a set of activities that the applicant carries out in order to enhance its ability to meet requirements [4,89]. Continual improvements typically have five phases as follows [9,96]:

- Define the problem and the project goals, specifically & Measure key aspects of the current process and collect relevant data and analyse the data to investigate and verify cause-and-effect relationships.
- Determine what the relationships are, and attempt to ensure that all factors have been considered.
- Seek out incitement of the defect if any.
- Improve or optimize the current process based upon data analysis using techniques such as design of experiments (DoE) to create a new, future state process.
- Set up pilot runs to establish process capability.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects.
- Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

3. TOOLS OF QbD

The concept of QbD has two components; (1) The science underlying the design and (2) The science of manufacturing. Upon understanding the elements of QbD and the steps for QbD implementation, it is important to be familiar with the commonly used tools for comprehending the aspects of QbD in the industrial paradigm, the implementation of successful QbD methods is essential, which includes the following [8,17,97-98]:

1. Risk assessment,
2. Design of Experiment (DoE), and
3. Process Analytical Technology (PAT)

3.1. Risk assessment

Risk can be commonly defined as the combination of the probability of occurrence of any harm and the severity of that harm. The assessment of risk helps in increasing the quality of process or method, in determining how the input variable affects a process or method. By carrying out the risk assessment, the CQA can be recognized which may affect the final quality of the product. It also helps in communicating effectively between FDA and research/development unit, whole industry and manufacturing unit as a whole and among various manufacturing sites within the company. The various principles involved in quality risk assessment include [89,99]:

- Risk assessment is a joint responsibility of business development unit, quality unit, regulatory affairs unit, engineering unit, sales and marketing, production operations, statistics unit, legal and clinical departments.
- Assessment of the risk based on scientific knowledge in order to confirm patient safety.

There are three essential elements in risk assessment [1,4,51, 97,100]:

a) Risk identification: systematically use of information to identify potential sources of hazard from historical data, theoretical analysis, and stakeholders' concerns;
b) Risk analysis: the evaluation of risk associated with the identified hazards; and
c) Risk evaluation: to compare the estimated risks using quantitative or qualitative scale to determine their significance.

Risk assessment is a methodology of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. It is the first step of quality risk management process; the other two steps are risk control and risk review. Risk control comprise of decision making to reduce and/or accept risks. The aim of risk control is to reduce the risk to an acceptable level. At the final stage, the output/results of the risk management process must be reviewed in order to gain new knowledge and experience. Throughout the risk management process, risk communication, the sharing of information about risk and risk management between the parties (including regulators and industry, industry and the patient, within a company, industry or regulatory

authority, etc.), should be ongoing at any stage of the risk management process. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality [97,101].

ICH Q9 provides a non-exhaustive list of 9 common risk management tools as follows [97,101]:

(1) Basic risk management facilitation methods (Ishikawa fishbone diagram, flowcharts, check sheets, etc.);
(2) Fault Tree Analysis (FTA);
(3) Risk ranking and filtering;
(4) Preliminary Hazard Analysis (PHA);
(5) Hazard Analysis and Critical Control Points (HACCP);
(6) Failure mode and effects analysis (FMEA);
(7) Failure mode, effects, and criticality analysis (FMECA);
(8) Hazard Operability Analysis (HAZOP);
(9) Supporting statistical tools.

According to the implementation of QbD, risk assessment has the priority over DoE. Among the tools, Ishikawa fishbone diagram and FMEA are widely used approaches for risk assessment, either separately or in combination [97,101-104].

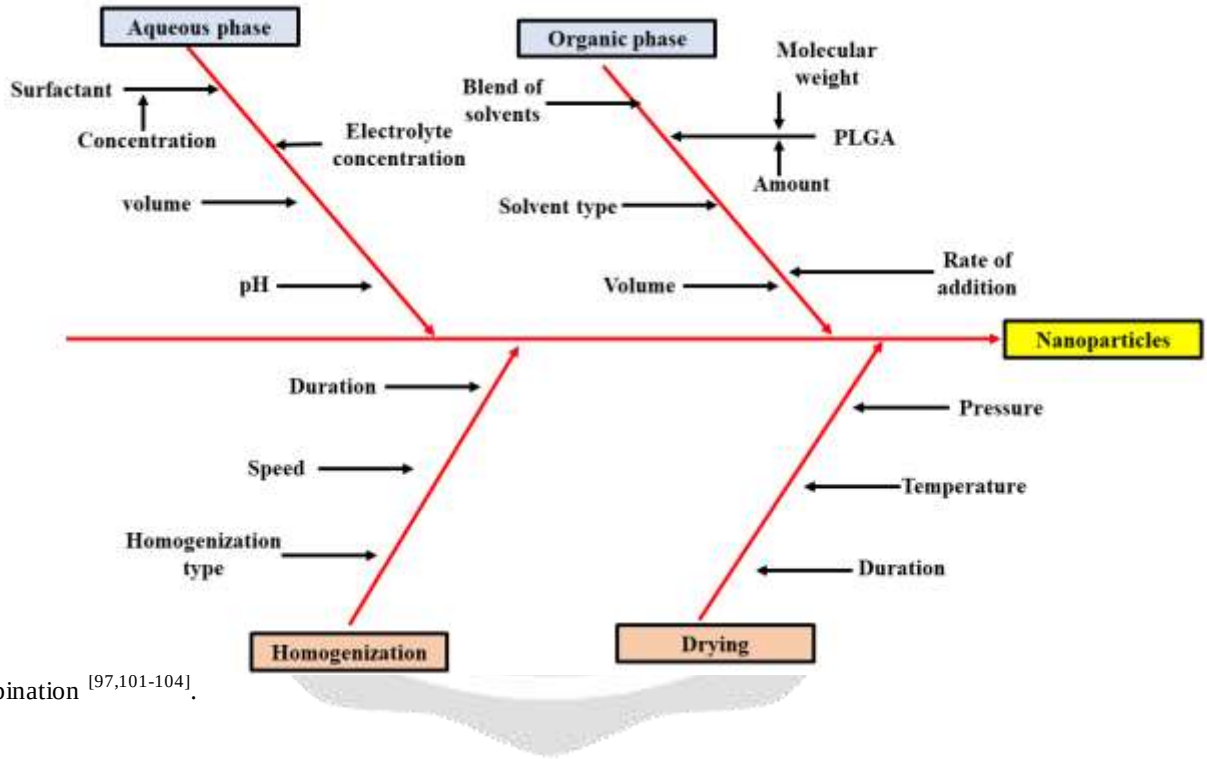


Figure-5(a): The Fishbone/Ishikawa diagram example for Nanoparticles [105]

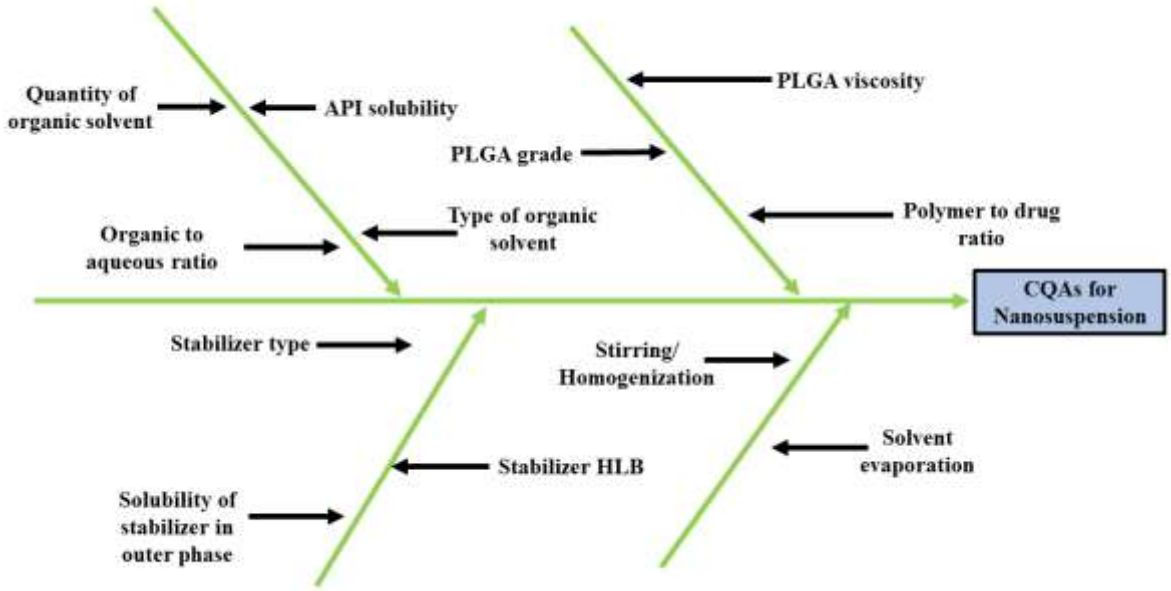


Figure-5(b): The Fishbone/Ishikawa diagram example for Nano-suspension [106]

3.2. Design of Experiment (DoE)

A risk-based assessment will be performed in addition to developing a research methodology. To carry out the design of experiment, the risk assessment should be taken into function first [97-98]. Testing design is an analytical, structured process to determine the relationship between process-related variables and DoE. An organised, structured method for determining the relationship between factors affecting a process and the output/result of that process is known as "Design of Experiments" (DoE). DoE is a magnificent tool that allows pharmaceutical scientists to systematically manipulate factors according to a pre-specified design. A good design is based on sound cognition of product and effective management of whole process during manufacturing. DoE studies works along with mechanism-based studies to achieve better product and process understanding. DoE is a rational method to determine the relationship between the inputs and outputs of a process. It can help identify optimal conditions, CMAs, CPPs, and, ultimately, the Design Space. It is wise to establish a Design Space through DoE for multivariate experiments. ICH Q8 defines the Design Space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality". It has been reported that there is no need to hand over supplements to revise (e.g., widen) the acceptance criteria to FDA if the changes are within the Design Space [8-9]. Classification of Design of Experiments (DoE) techniques are as follow [98]:

a) Fractional factorial design (FFD)
b) Placket-Burman design
c) Taguchi orthogonal array design
d) Box-Behnken design (BBD)
e) Central Composite design (CCD)
f) Factorial design

DoE is a computational method being used to design and implement research and interpret the information generated from the experimental work. It is a type of computational modeling used to perform statistical analysis of a model, method, and material that controlled input parameters to analyse its influence on the calculated response variable. This is a wonderful tool that allows researchers to inspect variables according to a predetermined design. DoE is a practical technique for establishing relationships among process inputs and outputs in order to acquire a deeper knowledge of products and processes. It could assist in determining the ideal setting, CPPs, CMAs, and design space. This is recommended to build a design space by DoE for nonparametric exploration. DoE was shown to be effective in developing different pharmacological therapies and operational

conditions, and it can be used more extensively in the future years to ensure strong research performance with improved results [9,98]. Product and process understanding is a key element of QbD. To best achieve these objectives, in addition to mechanistic models, DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a pre-specified design. The DoE also shows relationships between input factors and output responses. A series of structured tests are designed in which designed changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed. The strength of DoE over the traditional univariate approach to development studies is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be merged with mechanism-based studies to maximize product and process understanding. When DoE is used in the formulation or process development, input variables including the material attributes (e.g., particle size) of raw material or excipients and process parameters (e.g., press speed or spray rate), while outputs/results are the Critical Quality Attributes (CQAs) of the in-process materials or final drug product (e.g., blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release) [9,107-113].

Advantages of Design of Experiment (DoE) [98]:

1. Cost and time effective.
2. Less batch failure.
3. More efficient technology transfers to manufacturing.
4. Better innovation due to ability to improve processes.
5. Innovative process validation approaches.
6. Risk-based approach and identification.
7. Greater regulator confidence of robust products.

3.3. Process Analytical Technology (PAT)

FDA defined PAT as "a system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." The main aim of PAT is to support principles of QbD that draw attention to the fundamental process understanding and control focus to maximize process efficiency. The process includes the identification of scientific and engineering principles and variables that affect product quality. PAT is useful process in the reduction of cycle times, prevention of reject product and waste, real-time product release, large usage of automation and facilitation of continuous processing. This will produce a systematic process which consistently produce quality products. The knowledge of drug characteristics and other components of the drug product is essential to design such a process. unrecognised variability of raw materials may be displayed in the final product if certain critical attributes of pharmaceutical ingredients are not well-understood or taken into consideration during a manufacturing process. Therefore, a comprehensive identification and understanding of these attributes should be carried out [114-115]. ICH Q8 identifies the use of PAT to ensure that the process remains within an established Design Space [8]. The concept derived from the desire of the regulators to shift control of product quality toward a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing based on knowledge of the process. From a PAT viewpoint, a process is considered well understood when [97,102,116]:

a) All critical sources of variability are recognised and explained;
b) Variability is managed by the process; and
c) Product quality attributes can be accurately and reliably prognosticated.

A system is considered developed from a PAT perspective when all important causes of variability are defined and described; the system handles variance; product equity's performance can be calculated effectively and accurately. There is a three-step method of optimization of pharmaceutical preparations and production processes, which includes monitoring, study, and design, which is often used to compile literary works. In the monitoring stage, a performance measurement program allows real-time monitoring of all CPPs and CQAs by directly or indirectly systematic techniques and suitable analysis processes to investigate the identified quality

attribute, required product attributes, and processing methods. During the design stage, experiments are carried out to determine which key variables are connected to a material's role, and the process conditions and input material properties may have a major effect on finished product quality. This data is being used to identify the CQA, CPP, and QTPP requirements for establishing a PAT-based process control system [98,102,117-120].

As defined by FDA's PAT guidance document, whether to remove the sample or not, process analysis can be divided into three categories, namely at-line, on-line and in-line [97,88]:

1) At-line: Measurement where the sample is removed, separated from, and analysed in close surrounding to the process stream;
2) On-line: Measurement where the sample is diverted from the manufacturing process, and can be returned to the process stream;
3) In-line: Measurement where the sample is not removed from the process stream and can be invasive or non-invasive.

For the understanding of scientific, risk-managed pharmaceutical development, manufacture, and quality assurance, many tools are available in the PAT substructure. They can be divided into four classes according to the PAT guidance [97,88]:

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

Multivariate data acquisition and analysis are used for building scientific understanding about a process and identifying Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that affect product quality and merging this knowledge into the process control, which is essentially the same as the process knowledge in the context of QbD. Process analytical chemistry tools gives a real-time and *in situ* data about the status of the process. Multivariate data analysis reads the raw information from the PAT tools and connects it to Critical Quality Attributes (CQAs). Based on the outcome/result of the data analysis, process controls adjust critical variables to assure that CQAs are met [9,121-124].

4. STAGES AND STEPS INVOLVED FOR THE IMPLEMENTATION OF QbD

There are stages which took places in the initial QbD-based product development. Additional investment in accordance to time, money, and resources will be required, but it protects against variability later on; it also minimizes risk, reduces waste, and saves time in the long run [61].

Stages involved in QbD are shown in the below figure [125]:

Figure-6: Stages involved in Quality by Design (QbD)

There are three key stages in implementing a QbD approach to pharmaceutical development and production [61]:

- Initial product profiling, risk analysis, and Critical Quality Attributes (CQAs) / Critical Process Parameters (CPPs) determination during early development
- The design of experiments (DoE) and the definition of meaningful design spaces during the formulation/manufacturing development phase.
- The establishment of a manufacturing and control strategy during scale-up and routine production. Manufacturing is also supported by ongoing process verification to guarantee continued operation within the defined parameters.

Implementation of QbD in the development of new pharmaceutical products can go through the following steps [9,81, 97,125-127]:

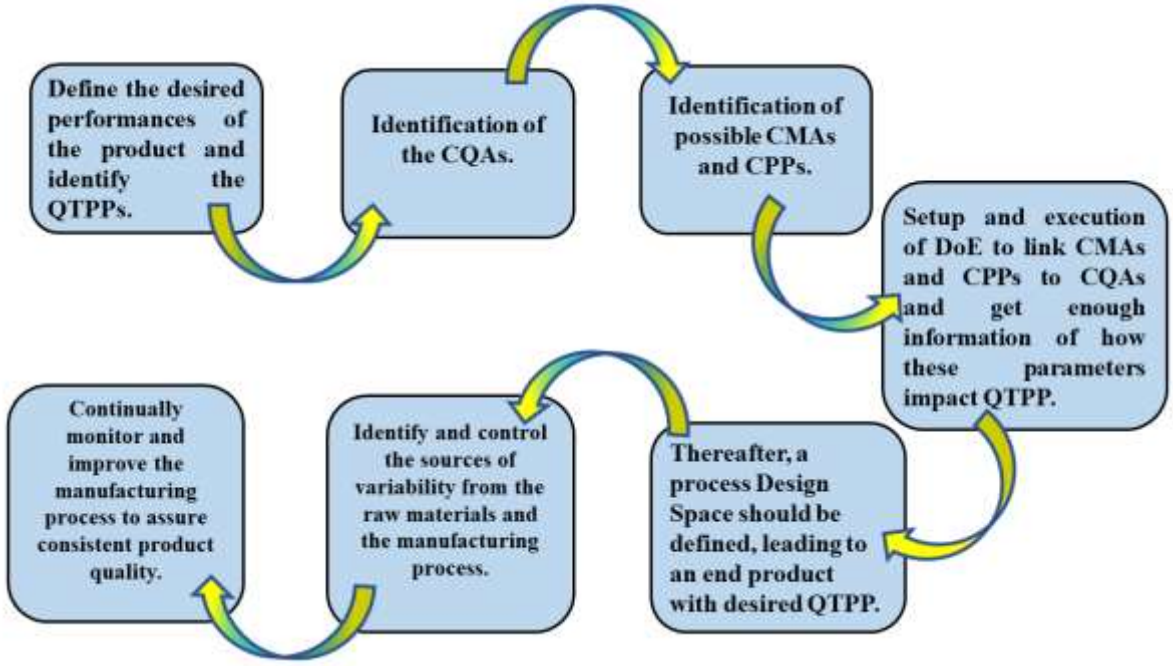


Figure-7: Steps involved in implementation of Quality by Design (QbD) approach to product development.

5. REGULATORY ROLE IN QbD

The common dossier is accepted worldwide by regulatory agencies. The FDA assisted the QbD submissions through regulatory flexibility which allows post-approval changes within pre-defined design space. According to Anastasia and Rathore, the regulatory burden is less in QbD application because there are wider ranges and limits based on product and process understanding. FDA is working on the effective pathway for risk-based assessment to ease post-approval change requirements. They also want to establish clinically relevant specifications, especially for bioavailability. And, the most obvious efforts are alignment of old ICH guidelines with new quality paradigm. The upcoming guideline Q12 of technical and regulatory considerations for pharmaceutical product lifecycle management will further refine the development process [86, 127-132].

5.1. FDA role in QbD

In 2005 USFDA asked participating firms to submit chemistry manufacturing control (CMC) details demonstrating application of QbD as part of New Drug Application. QbD involves thorough understanding of process; a goal or objective is defined before actual start of process. Design space and real time release risk assessment are other parameters for implementation of QbD [4,131]. In FDA's Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was built based on the application of product and process understanding. ONDQA's Chemistry, Manufacturing and Controls (CMC) Pilot Program was initiated in July 2005 with the main objective to provide participating firms an opportunity to submit CMC information demonstrating QbD and to enable FDA to implement new QbD concepts [86]. FDA also states the importance of quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance [4,132]. The regulatory body developed the internal guidelines on review considerations for QbD aspects. ONDQA has established QbD steering committee along with internal searchable database for tracking QbD elements in submitted applications. Extensive QbD training is also provided to small and large group of FDAs. Training for internal technical courses (e.g., DoE, statistics and chemometrics) and internal regulatory discussions (e.g., regulatory briefings, QbD Liaisons bi-monthly meeting) arranged along with hands-on analytical and unit operations or conference attendance. In the Office of Biotechnology Products (OBP) mock case studies are developed for proper reviewing the applications. The Office of Generic Drugs (OGD) also drafts case studies and published some of them like immediate release tablets, modified release tablets. The FDA Safety and Innovation Act (FDASIA) of 2012 contains several provisions that can aid regulators to enhance quality and efficiency. In summary, FDA has increased efforts to work collaboratively across review offices [86,129]. FDA's view of QbD is ''QbD is a systematic approach to product and process design and development''. This concept was accepted by FDA in 2004 and detailed description was given in 'pharmaceutical cGMPs for 21st century–a risk-based approach' [4,131].

In brief [4];

- Product quality and performance can be assured by designing efficient manufacturing processes.
- Product and process specifications are based on a scientific understanding of how process factors affect product performance.
- Risk-based regulatory approaches are for scientific understanding and control related process for product quality and performance.
- Related regulatory policies and measures are modified to assist the real time scientific knowledge.
- Quality assurance is continuous process.

5.2. New Drug Application (NDA)

The brief understanding about drug, in-process and final product are essentials for the QbD approach. In FDA, ONDQA deals with the New Drug Application (NDA). It deals with the application on the science based with organized and talented staff. For pre and post market staffs are reorganized for implementation. The most important challenge to deal with was the inconsistency in quality and understanding of the NDA application within and across the FDA departments. Lack of international harmonization was another main cited challenge. The time lag to file QbD outside the USA is also significant, which may affect the business case negatively. Internal alignment across the company is a huge problem for many new drug producing companies [39,86,132].

5.3. Abbreviated New Drug Application (ANDA)

For ANDAs, the Target Product Profile (TPP) should be defined early in development based on the properties of the drug substance, characterization of the Reference Listed Drug (RLD) product and consideration of the RLD label and intended patient population. All quality attributes (CQA) are target elements of the drug product and should be achieved through a good quality management system, appropriate formulation design and development. Although, common business model of generic industry is based on papers first and learn later strategy. The foremost amendments occur during review process and if batch stability fails the formulation need to be revised. Therefore, all these factors result in longer approval time or post approval changes or worst would be approved product may not be marketed. The main challenge faced by generics manufacturers was a lack of belief in the business case [28,39,86,132-133].

5.4. ICH role in QbD

Underlying principles of QbD i.e., science- and risk-based product development, risk assessment, lifecycle approach and method design are explained in the quality guidelines of international conference on harmonization. International conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system gives stringent requirements regarding quality of product [4,134-136].

5.5. Pharmaceutical industries scenario for implementation of QbD

QbD has been adopted by industries in various fields including clinical trials, analytical methods, process validation, etc. "QbD does not indicate less analytical testing" rather, it is the right analysis carried out at the right time, including knowledge of science and risk assessment. By implementing QbD, a robust and rugged method complying with ICH guideline can be developed which can be helpful in improving the methods continuously [3,89]. The regulatory agencies promised various benefits but current status does not inspire confidence. It is unclear how much regulatory flexibility will actually be given. Without clear benefits, proponents of QbD in industry have expressed difficulty in promoting the idea within their companies, increasing scepticism and reliance on the internal business case. Additionally, a couple of companies expressed disappointment that they had not received as much flexibility as they thought should be granted in their previous QbD filings [86,132]. Traditionally, inspections have been conducted using the FDA system-based approach and in agreement with CDER's compliance program. But as now query arises that how the inspection will take place in the present scenario where QbD is mandated. During pre-license or pre-approval inspections under a QbD concept, the FDA inspection team will assess the implementation and effectiveness of the process design as described in the application and whether knowledge and risk management have been transferred successfully from development to manufacturing step. The inspection will check the quality system and its effectiveness regarding compatible product quality, change in control procedures, process improvements, deviation management, and knowledge and risk management during the product lifecycle. Inspection of facility and equipment qualification and maintenance, in addition with the raw material screening and supplier management will be same as it was performed earlier. But design, testing, and monitoring programmes that demonstrate robustness and consistency would be highlighted [4,129]. The understanding and practice of QbD is evolving, gaining momentum and passion throughout the industry. Although QbD application is facing considerable challenges while implementation in different products and processes. The scope of QbD approach for new drug application and biotechnologically derived products would be different. So, the QbD approach could be valuable for the product development and potential scientific challenges for these products. There is need to address the technical and regulatory gap. Apart from this, there are many additional efforts the FDA should consider in order to facilitate the QbD implementation. It is important to note that QbD didn't and was not expected to solve all pre-QbD quality challenges [4,86,129].

6. QbD IN DIFFERENT CONTINENT OF WORLD

6.1. Asia

Asia has presented itself as a major engine of global economic growth. The industries in this region especially pharmaceutical and biotechnology are likely to experience increased competition. The emergent biopharmaceutical business capacity presents an exclusive chance for the execution of new concepts in manufacturing like QbD. Due to low manufacturing costs in Asia as compared to the US and Europe, the interest of international biotechnology firms has increased in setting up the capacities in the field of manufacturing there. Though regulations may seem like an interference in the path of transfer of technology to

Asia, it is required that the companies here should standardize themselves with the standards for international compliance established by the USFDA, also the requirements for compliance and approvals of products according to the Asian authorities. The biotechnology industries in Asia are currently stressing on education in process control, while on the other hand in some other countries, experience and detailed knowledge with the compliance of current Good Manufacturing Practices (cGMP) are restricted to manufacturers who are well established. Having inadequate experience in bioprocessing, the Asian R&D experts can implement QbD to confirm successful technology transfer and process comparability. Process automation is considered as one of the pillars of QbD. The more automated process and modifications applied to the process based on experience and scientific data, make the transfer of a certain technology easier across geographical regions. Luckily, for newer markets such as Asia, experience can be achieved in the form of data sets. The total R&D can be less expensive and time efficient in Asian companies if QbD process used is automated and data-driven. QbD application will prove to be dynamic for Asia in the future as personalized therapies and drugs become more noticeable in the biopharmaceutical industry. It is easy for companies to get adapted to the changing environment with QbD, as it relies on real-time data based continuous improvements [89,137-138].

6.1.1. India

Among the developing countries, Indian pharmaceutical industry and companies is one of the most highly developed and biggest industries. The Indian pharmaceutical regulatory bodies have come out with main changes to compete with the international regulatory, it will play an essential role to place India on the peak of the pharmaceutical map of the world. By the USFDA, QbD is a concept that is introduced with an aim to recognize the pharmaceutical formulations design and development and manufacturing processes to assist the end product quality. At this moment, the International Pharmaceutical Excipients Council (IPEC) has urged all the manufacturers from India who export to the US to prepare and update themselves on the technical necessities so that they will not be taken by issues while filing any NDA applications. The major disturbance in the path of pharmaceutical industries towards QbD are to reduce the slow response, grey zones of responsibility, late calls for help when problems occur and move towards an environment where problems are immediately identified, shared and resolved across the plant [89,139-141].

6.2. Europe

QbD implementation in the Europe is ongoing. The European PAT team is working to ensure a harmonized approach described in ICH Q8 to 11 for assessment and inspection of QbD or PAT applications. EMA has prepared a harmonized approach within Europe on assessment of applications and performing GMP inspections of systems for PAT, including QbD principles and manufacturing science in the context of PAT for Human and Veterinary products. Applications including QbD and PAT elements have been already authorized both in the centralized procedure and within the work-sharing project (variations to nationally authorized products). The design space concept is now included in the Europe Legislation [86,142-143]. The European Medicines Agency (EMA) welcomes applications that include quality by design (QbD). Quality by design is an approach that aims to ensure the quality of medicines by using statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines. One of the objectives of quality by design is to ensure that all sources of variability affecting a process are identified/recognised, explained and managed by appropriate measures. This enables the finished medicine to consistently meet its predefined characteristics from the start-so that it is 'right first time'. Quality by design emphasizes on the use of multivariate analysis, often in combination with modern process-analytical chemistry methods and knowledge-management tools to increase the identification and understanding of critical attributes of materials and critical parameters of the manufacturing process. This enhanced understanding of product and process is used to build quality into manufacturing and provide the basis for continuous improvement of products and processes. The concepts behind quality by design were introduced in international guidelines intended for the pharmaceutical industry between 2009 and 2012 [89,144].

6.3. North America

6.3.1. USA

USA market is considered as the largest pharmaceutical market around the world. Around 80% of total research and development (R & D) in the field of biotechnology conducted globally is owned by US firms. This market also holds the most intellectual property rights to new medicines. In 2010, about 272,000 people were employed in the pharmaceutical sector, and according to the data shown by Pharmaceutical Research and Manufacturers of

America (PhRMA), these manufacturers spent $67.4 billion on research and development in the same year. The evolution that was conducted in the US marketplace for the current drug regulatory system is acknowledged worldwide as the gold standard for the efficacy and safety of the drug. As the implementation made by FDA and according to the Office of New Drug Quality Assessment (ONDQA), QbD has enhanced the quality assurance in the US pharmaceutical market along with the concession in the quality of all the information submitted to the FDA during any application including CMC, drug master files and supplements. Implementation of PAT has been estimated to increase the market by more than US$ 4.0 billion by the year 2023. Implementation of QbD in the US pharmaceutical industry has increased the innovation with reduced timeline and pressure [89,145-149].

7. ANALYTICAL QUALITY BY DESIGN (AQbD)

Analytical approaches are used throughout the biopharmaceutical and vaccines companies/industries to carry out exploration, research and development, and to help control manufacturing inputs and outputs. Similar to the materials they measure, analytical methods should be fit for use. At the abecedarian level, analytical methods are used to give data, or more broadly details, to make decisions. The decision-making process requires the concession of the risk of making the wrong decision. This acknowledgment of risk, and more precisely the control of risk, brings analytical methods into the state of risk-based development and highlights the need for the application of Quality by Design (QbD) to analytical methods (AQbD) [150]. One key element of the AQbD process is that the steps, tools, and approaches developed for application of QbD for manufacturing processes (as described in ICH Q8, Q9, and Q10) have similar operation to the development and use of analytical methods. This also involves the concept of an analytical target profile (ATP), which is seen "as having the eventuality to reduce the burden of post-approval variations." In fact, the ATP should be line up with the decision rule (acceptance criterion) associated with a use of a method to meet the anticipated Critical Quality Attribute (CQA) range, and thereby linking analytical dimensional conditions, system performance, and CQA requirements. Frequently, numerous method conditions may be suitable to meet the requirements set forth in the ATP and occasionally multiple ways, thereby allowing flexibility to choose or indeed switch methods if warranted [15,17,150,152]. An analytical method produces reportable values which must likewise be "fit for use." The scripted value must meet the requirements of the customer and balance risk from residual measurement uncertainty with the decision that is taken made on the basis of the data. The unusuality is related to the Total Analytical Error (TAE, combining accuracy, and precision) of the reportable value whereas the risk is related to the impact of an inaccurate decision grounded on the measurement data. Acceptable residual risk from data uncertainty to make decisions is the driver to define method performance requirements in the ATP. In addition to the TAE (or accuracy and precision separately), the ATP defines other critical method performance characteristics that are essential to the test similar as range, sensitivity, and particularly. In some cases, business drivers may be captured in the ATP as well. Different technologies might be able to support ATP requirements, while business drivers such as cost, maintenance, or throughput could drive the choice. For illustration, protein concentration measured by fixed pathlength UV absorbance could easily be implemented in any laboratory worldwide whereas variable pathlength UV absorbance or refractive index measures might be more limited [151,154-155]. The mindset and testament for implementation of AQbD and associated life cycle management of an analytical method can be deduced from approaches and requirements for pharmaceutical processes and products The progress of AQbD in small- and large-molecule companies was reported from the IQ Analytical Leadership Group. AQbD system confirmation approach is that the validation of analytical method over a range of different API batches. It uses both DoE and MODR knowledge for designing method validation for all kind of API manufacturing changes without revalidation. The approach provides the needed ICH confirmation rudiments as well as information on interactions, measurement query, control strategy, and continuous improvement. This approach requires fewer resources than the traditional validation approach without compromising quality [150, 155-162].

Thus, AQbD represents a methodical frame to align method requirements with product requirements to balance decision and patient risk with method performance. While AQbD is not the only approach to achieve this goal, the systematic framework allows integrating efforts more efficiently across the entire system life cycle [150].

Terminology involved in AQbD	Definition
Analytical Target Profile (ATP)	Prospective summary of objectives of tests/methods and quality condition
Potential Method Attributes (PMAs)	Characteristics of an analytical method that should be within an appropriate limit or range, to ensure the desired method performance, e.g., system suitability criteria

Critical Method Attributes (CMAs)	Potential method attributes which are influenced by critical method variables and have the probability to go beyond appropriate limit or range
Potential Method Variables (PMVs)	All the possible variables involved in an analytical method
Critical Method Variables (CMVs)	Potential analytical variables which have influence on critical method attributes
Experimental Runs or Trials	Analytical experiments carried out under defined situations, i.e., combinations of factors at varied levels for each of the to be measured
Method Operable Design Region (MODR) or Analytical Design Space	Multidimensional explorable space enclosed by upper and lower levels of the enciphered variables demonstrated to give assurance of method performance
Analytical Control Space (ACS) or Normal Operating Range (NOR)	Part of the design space generally employed for setting in-house specifications within the working terrain of the company
Control Strategy	A schematic set of different controls to master all possible sources of variability to meet ATP demand during analytical method transfer

Table-3: Understanding of Terminology involved in AQbD [1,151]

7.1. Steps involved in the implementation of AQbD

An analytical method development in an AQbD framework implementation take place in following five steps [59]:

1. Defines Analytical Target Profile (ATP) where the method requirement and performance criteria are shown. Based upon the requirement of the method, a suitable instrument technique can be chosen which will allow the method to provide the carry forward the performance.
2. After selecting an acceptable analytical technique, systematic method will be developed for the sample preparation and for analysis through variety of experiments. The objectives of activity experiment are to roughly gain knowledge of robustness and set the method condition.
3. The knowledge earned from the method development will then be implemented in risk assessment. The objective of risk assessment is to spot risk factors that should be experimentally evaluated in a design of experiment (DOE).
4. The DOEs help for establishment of Method Operable Design Region (MODR) and a control strategy. The concept MODR suggested by Reid et al is synonymous to Design Space. Any place in the MODR will be consider as the Normal Operating Condition (NOC) for the method, and the MODR & NOC will be verified and validated.
5. The final but continuous step in AQbD involves knowledge management i.e., knowledge acquired from method optimization, development, verification, and use should be collected utilized and transferred thorough the life cycle of the method.

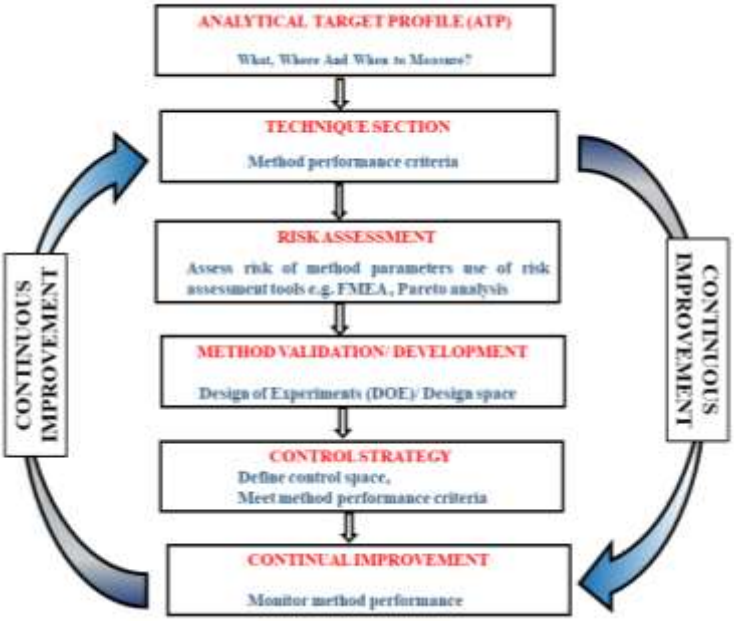


Figure-8: Flowchart of AQbD development process

7.2. Advantages of implementing AQbD

Advantages of implementing AQbD are as follows [1].:

1) Increased understanding and control;
2) Beyond traditional ICH procedure of method validation;
3) Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biologic al samples;
4) Reduction in variability in analytical attributes for improving the method robustness;
5) To keep the values of analytical attributes within the pharmacopeial monographs, and away from Out of Specification (OOS) limits;
6) Smooth process of method transfers to the production level;
7) No requirement of re-validation within MODR.

8. OPPORTUNITIES OF IMPLEMENTING QbD AND AQbD

Opportunities to obtain the following benefits from QbD and AQbD are [67]:

1. Reduced batch failure rates, reduced final product testing and lower batch release costs;
2. Lower operating costs from fewer failures and deviation investigations;
3. Increased predictability of manufacturing output and quality;
4. Reduced raw material and finished product inventory costs;
5. Faster technology transfers between development and manufacturing;
6. Faster regulatory approval of new product applications and process changes;
7. Fewer and shorter regulatory inspections of manufacturing site;
8. Provides for better coordination across review, compliance and inspection;
9. Provides for better consistency; Improves quality of review;
10. Provides more flexibility in decision making;
11. Ensures that decisions are based on scientific rather than empirical information;
12. Involves various disciplines in decision making;
13. Uses maximum resources to address higher risks;
14. Ensures better design of the products with fewer problems in manufacturing;
15. Allows for the implementation of new technology to improve manufacturing without regulatory scrutiny;

16. Ensures less complication during review, so that reduced deficiencies and quicker approval is possible;
17. Improves interaction with regulatory authorities at a scientific level instead of a process level;
18. Allows for a better understanding of how active pharmaceutical ingredients and excipients affect manufacturing;
19. Relates manufacturing to clinical during design;
20. Provides a better overall business model.

9. CONCLUSION

This article gives a brief overview about Quality by Design (QbD), generalities of Quality by Design (QbD), perpetration of Quality by Design (QbD) approach and Analytical Quality by Design (AQbD). QbD has earned huge significance in the area of medicinal processes like medicine development, phrasings, logical system and biopharmaceuticals. The end of enforcing pharmaceutical QbD are to reduce product variability and blights, thus, enhancing product development and manufacturing edge and post-approval change operation. It's gained by designing a robust expression and manufacturing process and establishing clinically applicable specifications. The crucial rudiments of pharmaceutical QbD may involves the part of QTPP, product design and understanding, process design and understanding, and gauge up, control strategy, and continual enhancement. The main reason behind relinquishment of QbD is the nonsupervisory conditions. Pharmaceutical assiduity needs a nonsupervisory compliance so as to get their product approved for marketing also QbD approach gives quality product with cost effective procedures and that's the introductory need. QbD replaces Quality by Testing (QbT) approach of process development by furnishing a design space conception. A successful product development strategy requires thorough understanding of QbD principles and the tools for establishing the QbD strategy. Science and threat- grounded product development strategy is carried out with the help of QbD. Design of trials, threat assessment tools, and PAT are the major tools for the establishment of QbD principles. Establishment of a design space by QbD provides an occasion for inflexibility in constructing a more meaningful design space. The changes in product and process can be managed better with the help of QbD. The thing of a well- characterized system development trouble is to develop a dependable system that can be enforced with a high degree of assurance to constantly produce data meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of logical styles. AQbD tools are as follows ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk assessment, system confirmation and Continuous Method Monitoring (CMM) and nonstop enhancement. Manufacturers can execute certain changes without filing previous blessing supplements and can simply notify nonsupervisory authority in periodic reports. The profitable and resource void due to total confirmation conditions can significantly be minimized. The perpetration of QbD principles can change the chemistry, manufacturing, and control nonsupervisory process into a wisdom and threat- grounded assessment. Analytical system development and confirmation with QbD plays an important part in the pharmaceutical assiduity for securing the product quality. The result of AQbD is the understanding from product development to marketable product. Scientist can effectively identify the threat originally so that quality can be increased. Hence, QbD is implement to solve the challenges of medicine development and manufacturing.

List of Abbreviation

QbD	Quality by Design
ICH	International Conference of Harmonization
cGMP	current Good Manufacturing Procedures
FDA	Food and Drug Administration
CMC	Chemistry, Manufacturing, and Controls
ONDQA	Office of New Drug Quality Assessment
NDA	New Drug Applications
QbT	Quality by Testing
QTPP	Quality Target Product Profile

CQA	Critical Quality Attributes
CMA	Critical material attributes
CPP	Critical Process Parameters
TPQP	Target Product Quality Profile
DoE	Design of Experiment
PAT	Process Analytical Technology
FTA	Fault Tree Analysis
PHA	Preliminary Hazard Analysis
HACCP	Hazard Analysis and Critical Control Points
FMEA	Failure Mode and Effects Analysis
FMECA	Failure Mode, Effects, and Criticality Analysis
HAZOP	Hazard Operability Analysis
FFD	Fractional Factorial design
BBD	Box-Behnken design
CCD	Central Composite Design
OGD	Office of Generic Drugs
OBP	Office of Biotechnology Products
FDASIA	FDA Safety and Innovation Act
ANDA	New Drug Application
TPP	Target Product Profile
RLD	Reference Listed Drug
PhRMA	Pharmaceutical Research and Manufacturers of America
EMA	European Medicines Agency
AQbD	Analytical Quality by Design
ATP	Analytical Target Profile
PMA	Potential Method Attributes
CMA	Critical Method Attributes
PMV	Potential Method Variables
CMV	Critical Method Variables
MODR	Method Operable Design Region
ACS	Analytical Control Space
NOR	Normal Operating Range
OOS	Out of Specification
CMM	Continuous Method Monitoring

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