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AN OVERVIEW ON QUALITY BY DESIGN IN PHARMACEUTICAL PRODUCT DEVELOPMENT

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Keywords:

QbD, quality by design, International Conference on Harmonization (ICH), Risk assessment, Design space, Control Strategy, DoE

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ABSTRACT: The concept of Quality by Design reflects current global regulatory thinking related to pharmaceutical products. The pharmaceutical industry needs to improve its performance. Newer technologies need to be implemented that can effectively reduce the cost and, at the same time, improves product quality. Quality by design (QbD) is the best solution to build quality in all pharmaceutical products. The main objective of QbD is to ensure the quality product resulting from a combination of prior knowledge and new estimation during development. QbD is being widely promoted by the food and drug administration (FDA) and the international conference on Harmony (ICH). Quality by design (QbD) in the pharmacy field is mainly based on the understanding of how materials and process parameters affect the quality profile of final products. In this article, the key elements of QbD *viz.*, Target product quality profile, Critical quality attributes, Risk assessment, Design space, and Control strategy are discussed to understand the performance of dosage forms within the design space. Tools of QbD (DoE, Quality risk management, and process analytical technology) are also discussed in QbD. These reviews underline the importance of QbD in inculcating a science-based approach in pharmaceutical product development.

INTRODUCTION: Pharmaceutical development aims to design a quality product and its manufacturing process to consistently deliver the product's intended performance. It is important to recognize that quality cannot be tested in products. Quality should be built into the process design rather than tested into the final analytical process results [1]. The pharmaceutical market has been considered one of the highly regulated sectors, continuously providing quality drug products for human use to provide pharmacotherapeutic effects for the treatment of diverse ailments.

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In 2002, the US Food and Drug Administration [FDA] published a guidance document for pharmaceutical companies. Companies should build Quality, Safety, and Efficacy into their product. This concept is now known as Quality by Design. In a 2004 paper, Janet woodcock (Director for the Center for Drug Evaluation and Research) defined pharmaceutical quality as a product that is free of contamination. They reproducibly delivered the therapeutic benefit promised on the label to the consumer. The QbD approach is a recent trend in analytical method development, and it helps a lot if it gets properly implemented [2].

Pharmaceutical Quality: Pharmaceutical Quality = f (Drug substances, excipients manufacturing, packaging). For quality to increase, it must be built into the product. To do this required understanding how formulation and manufacturing process variables influence product quality; this is the

function f in the equation above. RP-HPLC / LC methods were developed and validated by applying the Analytical and Quality by Design approach [3]. Quality means customer satisfaction in terms of service, product, and process. Customer demands perfection in quality, reliability, low cost, and timely performances [4]. Quality, Productivity, cost, cycle, time, and value are interrelated terms. The quality has to be built in the product and service through proper planning [5]. With the development of the concept QbD "there will be a significant transformation in pharmaceutical quality regulation, from an empirical process to a more scientific and risk-based approach [6]. QbD also helps create the approach and common language needed to develop the bond necessary for successful outsourcing [7]. Initially, the concept of QbD was introduced for manufacturing processes, described in four steps [8]:

- Determination of patient requirements, namely, the Quality Target Product Profile (QTPP).
- Design and development of the manufacturing process.
- Risk assessment and definition of the manufacturing Design Space (DS).
- Implementation of a Control Strategy.

Formulation parameters (independent variables) affect the product's characteristics and are useful in optimizing independent variables to monitor the behavior of dependent variables in producing the optimized product under the given set of conditions. Thus, variables are included in QbD to ease the final best formulation of drug [9]. QbD is applied to optimize experimental conditions to ascertain the best suitable conditions with limited numbers of experiments [10].

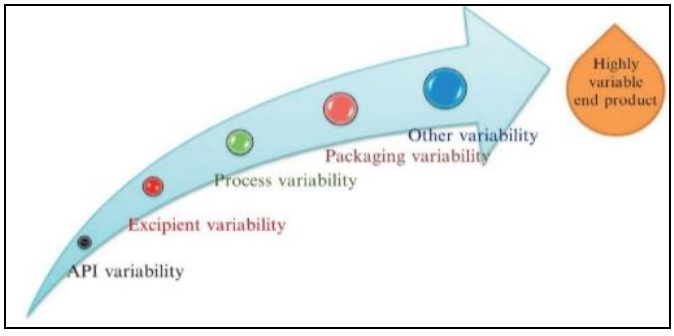


FIG. 1: SOURCES OF VARIABILITY IN DRUG PRODUCT QUALITY [9]

Understanding Pharmaceutical QbD:

Quality: Quality by Design (QbD) is defined in the ICH Q8 guideline as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on Sound Science and Quality risk management [11].

The US Food and Drug Administration initiative to ensure product quality over the whole procedures established in pharmaceutical development of different dosage forms [12]. It is important for all products, including Generics and Biotech.

Purpose and Objectives: QbD encourages process and product understanding to support innovation and efficiency in product development. Moreover, the application of a QbD approach helps to meet FDA.

The benefits of QbD can be translated into an acceleration of product development and a reduction of costs and waste. The quality by Design (QbD) approach to custom 3D printed prostheses can help to ensure that products are designed and manufactured correctly from the beginning without errors [13].

The FDA publication defined QbD as:

1. Developing a product to meet predefined product quality, safety, and efficacy.
2. Designing a manufacturing process to meet predefined product quality, safety and efficacy.

FDA accepted this concept in 2004 and detailed description was given in pharmaceutical cGMPs for the 21st century-

- **A Risk-Based:** The FDA has taken the initiative to guide the pharmaceutical industry on implementing the concept of QbD into its process.
- **FDA's Process Validation:** Guidance in Jan 2011 is for companies to continue benefiting from knowledge gained and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are addressed.

- **International Conference on Harmonization (ICH):** Relevant documents from the international conference on harmonization of the technical requirement for registration of pharmaceuticals for human use. (ICH). US FDA / EMA refers to ICH guidelines Q8, Q9, Q10, Q11 & Q12 for QbD implementation.

- Pharmaceutical Development Q8 (R2).
- Quality Risk Management Q9.
- Pharmaceutical Quality System Q10.

ICH Q8: In the previous decade, the US FDA announced a new pharmaceutical regulatory concept, quality by design (QbD), which has challenged the pharmaceutical industry to design the quality of the final product instead of testing the product. The ICH guideline Q8 definition for QbD is "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [14].

Components of Drug Product Given by ICH Q8 [15]:

1. Drug Substances: The physicochemical and biological properties of the drug substances that can influence the performance of the drug product and its manufacturability".

Example of physicochemical and biological properties includes:

- Solubility.
- Water content.
- Particle size.
- Excipients.

The compatibility of the drug substances with excipients should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2. Formulation Development: The formulation's development includes identifying those attributes that are critical to the quality of the drug product and highlighting the formulation design's evolution from the initial concept up to the final design. Comparative *in-vitro* studies *e.g*., Dissolution (or) *in-vivo* studies, *e.g*., BE, link clinical formulations to the proposed commercial formulation.

3. Container and Closure System

- ✓ The choice of materials for primary packaging and secondary packaging should be justified.
- ✓ A possible interaction between product and container or label should be considered.

ICH Q9: Provides general guidance and references for some of the primary tools used in Risk assessment. Examples are provided for industry and regulators to evaluate the risk to quality based on scientific knowledge and risk to patient [16].

Quality risk management, a part of an effective quality system, helps in identifying the probability of occurrence and severity of the risk. It provides a non-exhaustive list of common risk management tools as follows [17]:

Basic risk management facilitation methods (Ishikawa fishbone diagram, flowchart, check sheets, *etc.*

- ❖ Fault tree analysis.
- ❖ Risk ranking and filtering.
- ❖ Preliminary hazard analysis.
- ❖ Hazard analysis and critical control points.
- ❖ Failure mode and effects analysis.

ICH Q10: Pharmaceutical Quality Systems, indicate on an abstract level how Quality by Design acts to ensure drug product quality. Especially for ANDA sponsors, who were not actively involved in the ICH processes [18].

These guideline applies in the process that help in design, development and preparation of drug substances such as API and drug products which includes biotechnology and biological products, throughout the lifecycle of product [19].

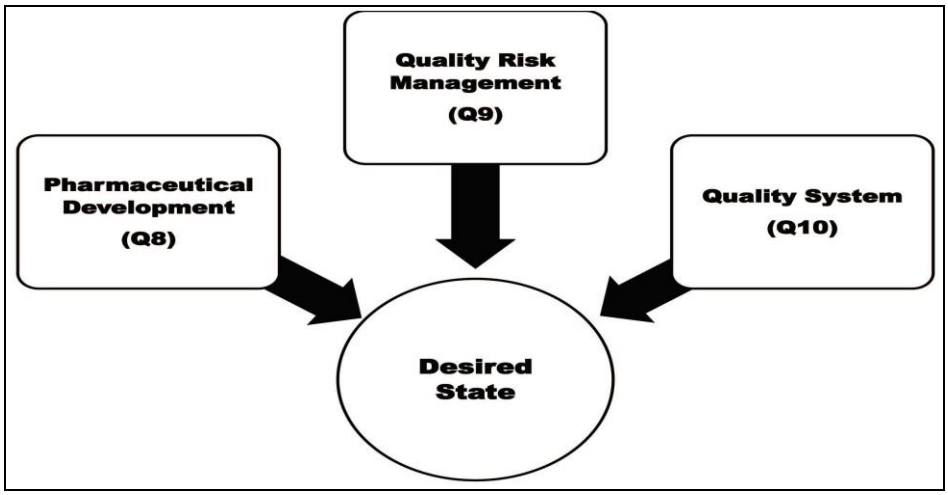
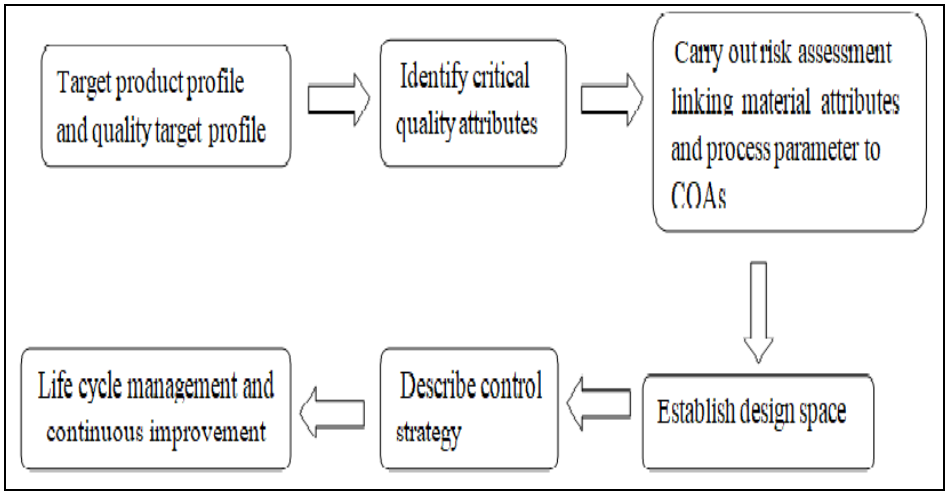


FIG. 2: QUALITY ATTRIBUTES GOVERNING QUALITY OF DESIRED PRODUCT [19]

Flow of Quality by Design [20]



Regulatory Challenges and Inspection: In a QbD concept, the regulatory burden is less because there are wider ranges and limits based on product and process understanding. Changes within these ranges and limits do not require prior approval. Traditionally, inspections have been conducted using the FDA system-based approach and in accordance with CDER's compliance program" Inspection of licensed Bio-logical Therapeutical Drug Product [21]. During prelicense and preapproval inspections under a QbD concept, the FDA inspection team will assess the implementation and effectiveness of the process design. The inspection will evaluate the quality system and its effectiveness regarding consistent product quality, change in control procedures, and process improvement. Companies Wanted Clarification from the FDA on QbD terminologies, acceptable methods, criteria to select and deselect Critical Quality Attributes, standards to guide adequacy of controls and criteria for analytical method substitution [22].

Benefits of Implementing QbD for FDA [23]:

- Increase Manufacturing efficiency, reduce cost, and project rejections and waste.
- Implementation of a Question-based review (QbD) process has occurred in CDER's office of generic drugs.
- Implementation of QbD for a biological license application (BLA) is progressing.
- Optimization Design performed using Quality by Design as 2^3 full factorial design [24]
- Organization learning is an investment in the future [25].

Benefits to Industry:

- ❖ Ensure better design of the product with less problems in manufacturing.
- ❖ Improve interaction with the FDA deal on a science level instead of a process level.
- ❖ Nanocellulose prepared by the QbD approach had better flow property and compatibility [26].

Seven Steps of QbD [27]: The best way to assess how to implement QbD in your organization in a simple seven-step process:

Hire an independent Quality design expert.

Audit your organization and processes with the expert conducting a gap analysis.

- ❖ Hold a basic QbD workshop with all your personnel – the expert should lead this and design it to speak to multiple levels, from the factory floor to the board room.
- ❖ Review the expert's report and recommendations.
- ❖ Draft an implementation plan, timelines, and estimated costs.
- ❖ Assign the resources.
- ❖ Retain the independence expert as your project assurance advisor.

Elements of Pharmaceutical Development: QbD comprises all elements of pharmaceutical development mentioned in the given guideline Q8-

Quality Target Product Profile (QTPP): ICH Q8 defines QTPP as "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 [28].

Necessary element [29]

1. Quality characteristic – Sterility, purity.
2. Pharmacokinetic characteristic – Dissolution
3. Therapeutic effect
4. Target patient population neonates, clinical diagnosis.
5. Shelf life temperature, light conditions, *etc*.

Desired Elements:

1. Dosage form liquid for injection, solid tablet.
2. Route of administration oral, IV, IM, SC.
3. Clinical setting self or clinic administration.

QTPP leads → **CQA definition**

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as a physical, chemical, biological or microbiological property or characteristic within an appropriate limit, range, or distribution to ensure the desired product quality [30]. The successful execution of a product development exercise to meet the end objectives always depends on the holistic identification of the QTPP [31].

Critical Quality Attributes [CQAs] are identified by Quality risk management and experimentation to determine the effect of variation on product quality. The framework for the product design and process understanding is achieved by identifying the CQA [32].

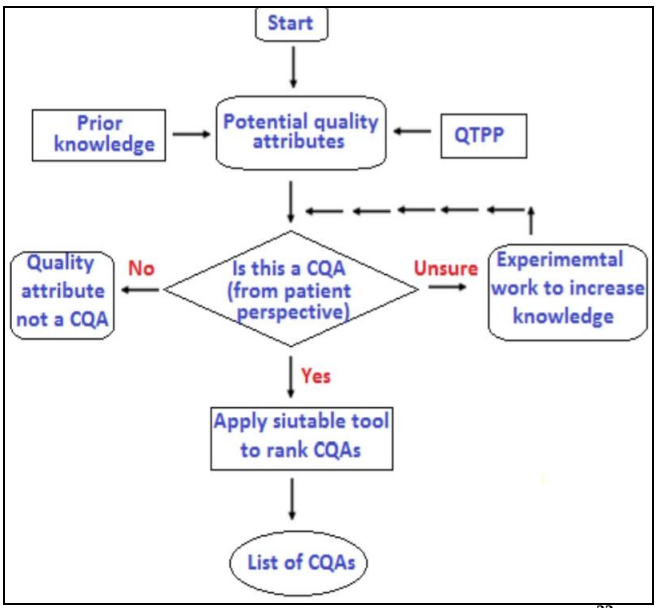


FIG. 3: DECISION TREE TO DECIDE CQAs [33]

Target Product Profile (TPP): FDA gives guidelines for defining Target Product Profile (TPP) [34]. As per these guidelines. The TPP is totally correlated to drug development program that provides knowledge of drug during development. Generally, the TPP is useful for developing a link between drug labeling and drug development activities. According to ICH-Q8 (pharmaceutical development), pharmaceutical development should include "Recognition of critical quality attributes of the drug product with consideration of its intended use as well as the route of administration hence it becomes essential to consider the intended usage and route of administration [35].

Critical Material Attributes (CMA): As per ICH, CQA is defined as a quality attribute that comprises physical, chemical, biological, or microbiological characteristics, and it is desired that these attributes should be controlled (directly or indirectly) to give assurance that the product obtained will attain desired safety, efficacy, stability and performance [36]. 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 [37]. In determining product performance, CQA observes the mechanistic variables such as particle size and hardness. Hence, both the aspects *i.e.*, product performance and product performance determinants, could be explained by using TPQP [38].

Design Space: Design space may be defined as the set of all combinations of a method's input variables that have been proven to assure the quality of the data produced by the method [39]. Design space may be constructed for a single unit operation, multiple, or the entire process.

The risk assessment, prior experimentations, and multivariate factor screening methods are used for identifying the criticality of factors and their ranges for establishing a design space. There could be more than one design space in a pharmaceutical product. Ideally, design space is generated using experimental design at lab/pilot scale and extrapolated to exhibit/commercial scale by establishing a correlation with the help of scale-independent parameters [40].

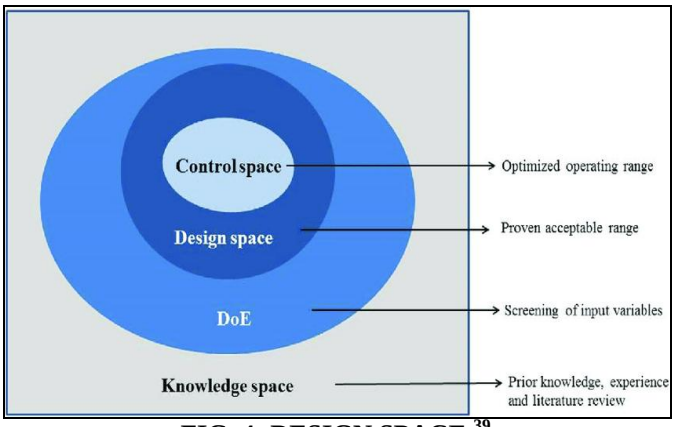


FIG. 4: DESIGN SPACE [39]

Control Strategy: A control strategy based on extensive knowledge of the process and the product includes control over the CMA of the input materials and intermediates, control of the process parameters, final drug product quality, and final packaging. All these components of control strategy are covered under process analytical technology (PAT) [41].

Control space should be within the design space; it is an upper and lower limit for raw material (or) a process within which parameters and material are regularly controlled, which assures the quality of the product. Every process has a control strategy right now. **Fig 5** shows a simplified quality assurances diagram under the current regulatory evaluation system.

In this system, product quality is ensured by fixing the process to produce the active ingredient, raw material testing, performing the drug product manufacturing process as described in a fixed batch record, in-process material testing, and end-product testing. A factor identified to have risk has to be controlled [42].

Control strategy includes the following elements:

- Input material attributes (*e.g.*, drug substances, excipients).
- Equipment operating conditions.
- In-process controls.
- Finished product specifications.

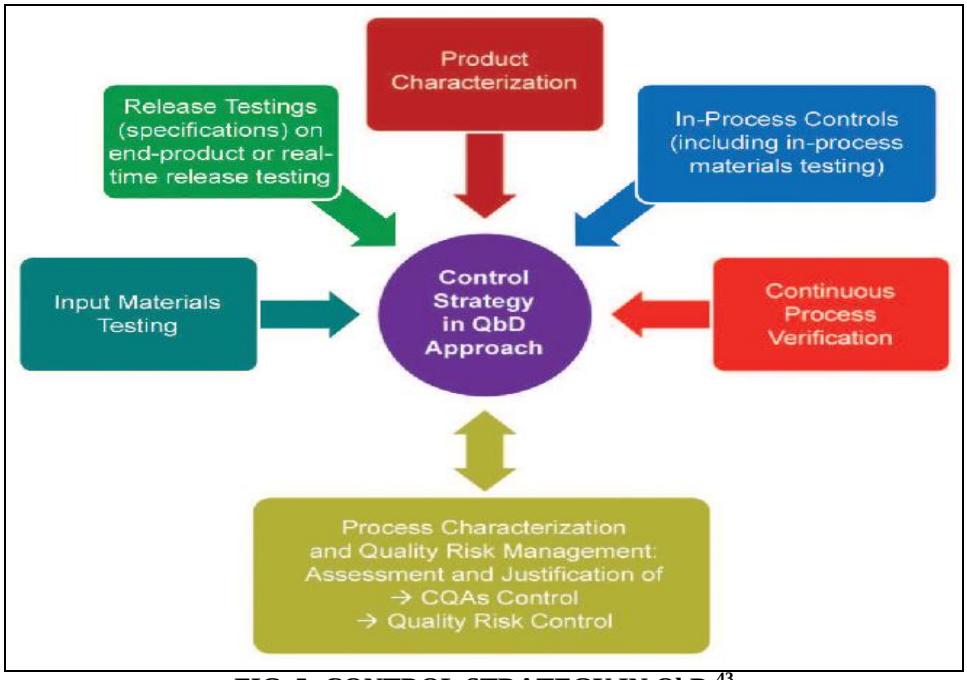


FIG. 5: CONTROL STRATEGY IN QbD [43]

Tools of QbD:

Quality risk management (QRM): FDA defines risk management as a strategic safety program that decreases product risk by using intervention (or) tools. It is a systematic process for the assessment, control, and communication review of risk to the quality of drug across the product life cycle [44]. Risk management is the joint responsibility of the quality unit, regulatory affairs, production operations, sales and marketing, and clinical department. Two important principles were highlighted in this document for the use of Quality Risk Management [45]:

1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
2. The level of efforts, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

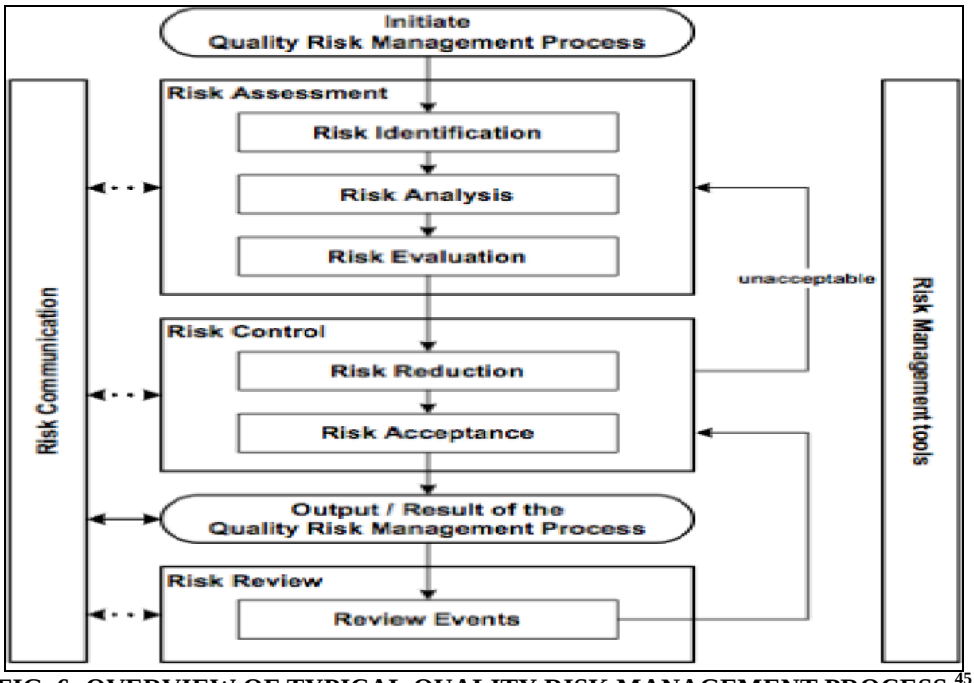


FIG. 6: OVERVIEW OF TYPICAL QUALITY RISK MANAGEMENT PROCESS [45]

Design of experiment (DoE): A structured, organized method for determining the relationship between factors affecting a process and the output of that process is known as" Design of Experiments" (DoE). With the help of DoE, We can define many factors, create designs, construct models, define responses, evaluate the models, interpret results and hence reach a decision. Traditionally we are used to single variant study DoE help to do multivariate analysis *e.g.*, wavelength, flow rate, concentration in case of HPLC and its impact on retention time, resolution, *etc.* [46]. Design of experiment (DoE) is one such structured method that considers the effects of the CMAs and CPPs on the CQAs of the final dosage form [47 9, 10].

It has gained tremendous attention with the introduction of QbD by the FDA in the formulation development of pharmaceutical products [48].

PAT as an Important Tool of QbD: PAT is defined as "Tools and systems that utilize real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce a final product that consistently conforms to established quality and performance standards [49]. PAT forms a part of the quality by design (QbD) concept, which provides tools to facilitate the quality.

TABLE 1: APPLICATION OF QbD IN PHARMACEUTICAL PRODUCT DEVELOPMENT

Experimental Design	Pharmaceutical product	Critical process parameter(CPP)	Critical quality attributes(CQA)
Factorial Design	Solid lipid nanoparticles (SLN) [50]	Homogenization time	Size, PDI, entrapment efficiency
2-Level factorial design	Nanoemulsion [51] Pellets [52] Lipid [53] Micelles [54]	Amount of oil (Capmul MCM), amount of surfactant (Tween 80), and amount of cosolvent (Transcutol HP) Kneading temperature, impeller speed, liquid addition, extrusion speed, Spheronizer speed and time Surfactant concentration, solid/liquid lipid ration and ultrasonication time Hydration temperature, stirring speed and stirring time	Globule size, equilibrium solubility of cilostazol, zeta potential and dissolution efficiency at 30min of lipid-based nanoemulsifying Cilostazol Activity, hardness and roundness of pellets for oral lysozyme delivery. Particle size and particle size distribution of nanostructured lipid carriers containing salicylic acid for dermal use. Polydispersity index of miltefosine-loaded polymeric micelles
3-level factorial design	Emulsion [55] Lipidnanoparticle [56] Microemulsion[57]	Span 60: Sodium lauryl sulfate ratio, organic: aqueous phase volume ratio, and polymer concentration Poloxamer 188 and acetone to methanol ratio. Oil to surfactant/cosurfactant ratio and concentration of Gellan gum	Emulsion phase stability, viscosity, and conductivity. Particle size and entrapment efficiency of efavirenz loaded solid lipid nanoparticles. *In-vitro* drug release and viscosity at physiological pH of a microemulsion of lorazepam via the intranasal route
Full factorial Design	Solid nanocrystalline dry powder [58]	Inlet temperature, flow rate, aspiration rate	Particle size, moisture content, percent yield, crystallinity
Fractional factorial design	Tablets [59]	API flow rate, lubricant flow rate, pre-compression pressure	Tablet weight, tablet dissolution, hardness, ribbon density
Fractional factorial design and Central composite design	Granules [60]	Inlet air temperature, airflow rate, and binder spray rate during the sprying phase	Moisture of granules and flow through an orifice of the granules obtained by fluid bed granulation
Central composite	Oral dispersible films [61]	Drying temperature. Combination ratio of Eudragit®FS-30D /	Tensile strength, elongation at break, Young's modulus, disintegration time Size of

design	Microspheres [62]	Eudragit® RS-PO, PVA and NaCl concentration on external phase	microspheres, encapsulation efficiency of enoxaparin sodium, percentages released over 24h in gastric, duodenal and colonic media
Box-Behnken Design Plackett-Burman(PB)	Beads [63] Lipid [64] Nanoemulsion [65] Nanoparticles [66] Controlled release tablets [67] Nanoparticles [68]	Sodium alginate percentage, chitosan percentage, and calcium chloride percentage. Lipid, lipid oil, and surfactant phase. Amount of surfactant/cosurfactant mixture, processing pressure, and number of homogenization cycles. Homogenization rate. Preparation technique. Stirring rate	Maximum drug encapsulation, particle size, and drug release of cefpodoxime proxetil chitosan alginate beads. Particle size, entrapment, permeation flux, and percentage release of aceclofenac loaded-nano structured lipid carriers. Globule size, size distribution (PDI), percentage transmittance, and drug release of silymarin nanoemulsion. Average particle size, zeta potential, encapsulation efficiency. Maximum solubility after 30 min, equilibrium solubility after 24h, dissolution efficiency. Encapsulation efficiency, particle size, zeta potential, burst release and dissolution efficiency

CONCLUSION: Quality by Design (QbD) is increasingly becoming an important and widely used technique in pharmaceutical product development. Provides quality medicines to patients and production improvement. Quality by Design (QbD) and its tools indicate the demands of the modern manufacturing process. Quality by design is a cost and time-efficient approach in design and manufacturing. QbD also has wide scope in biotechnological products such as- vaccines, enzymes, monoclonal antibodies, *etc*. This new Quality by Design (QbD) process provides the opportunity for much greater regulatory flexibility in the future. Moreover, Quality by Design has become a broadly applicable manufacturing model and is going far beyond pharmaceuticals.

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CONFLICTS OF INTEREST: Nil

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